AEC Symposium Series **27**

clinical uses of radionuclides: critical comparison with other techniques

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clinical uses of radionuclides:

critical comparison with other techniques

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PREFACE

The clinical uses of radionuclides invade many medical specialties and are frequently changing; to keep abreast of them is a constant challenge to investigators and clinicians. Every now and then we must take stock of what has been learned and reexamine selectively those contributions of greatest significance and promise. These proceedings review the achievements and disappointments of recent years. They assess the value, limitations, and failures of radioisotopic procedures and compare them with other diagnostic procedures. Many laboratory tests using radionuclides are being developed; these are adding enormous costs to the care of the sick and may be confusing to many practitioners since their applications are sometimes ill defined.

In many instances comparatively simple laboratory tests and radiographic procedures will adequately supplement the history and physical examination and will supply the additional data required for diagnosis and effective management. However, in the past decade a wide variety of more sophisticated, costly, and potentially risky diagnostic procedures have become available. The papers in this symposium have been selected as a representative cross section of diagnostic techniques that are of proven value in radiology, nuclear medicine, and, in some instances, clinical pathology. The authors have had extensive experience in these procedures and in interpreting their results. Only enough technical detail is included to allow the reader an appreciation of the complexity and the potential for error inherent in the tests. The primary emphasis is on their practical usefulness in clinical practice. An effort has been made to evaluate the costs, potential risks, and side effects in relation to the value of the information obtained.

In planning the publication of the symposium proceedings, we again sought the cooperation of the U. S. Atomic Energy Commission's Office of Information Services (OIS). Although this program represents the 13th symposium of the Oak Ridge Associated Universities (ORAU) Medical Division, our first association with OIS in the publication of the proceedings of a

symposium was not until 1962, when *Progress in Medical Radioisotope Scanning*, the first publication in a new series of AEC symposia, was published. Others followed, of course, with numbers 3, 6, 11, 13, and 20 of the series representing the outcome of meetings held by the Medical Division of ORAU. (The AEC Symposium Series is listed on the back cover of this volume.)

For the first time in the series of ORAU Symposia on Nuclear Medicine, we have had the sponsorship of the American College of Physicians as well as the AEC Division of Biomedical and Environmental Research. The College has been most helpful in advertising the program, which was included in its 1971-1972 series of postgraduate courses. Its staff aided in processing applications, and their participation has relieved us of many administrative duties.

In planning the program, we thought it logical to devote each series of presentations to a specific organ system, presenting papers on radiographic and radioisotopic approaches and then a summary and critical appraisal of both.

The final group of papers includes two on the diagnosis of cancer followed by three that emanated from a panel discussion: "When Should Radioisotopes or Roentgenograms Be Used in the Diagnostic Work-Up, and Why?"

We felt that we should not discuss radioisotopes in the treatment of patients. Instead the symposium tries to be more comprehensive in covering the diagnostic applications.

The published discussions represent our efforts to record the most significant of the informal comments made at the meeting. We hope that our editing, performed in the interests of brevity and clarity, has not done injustice to any speaker's intentions.

Contributing to the publication of these proceedings are the efforts and skills of the staffs of the ORAU Medical Division, the ORAU Library, and the Editorial Branch of the USAEC Technical Information Center, especially Jean Smith. Carolyn Houston prepared the index. The editors gratefully acknowledge this support. Finally, we thank Marion Garber, technical editor, ORAU Medical Division, for her major contribution to the publication.

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Moderator:
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BRAIN

RADIOLOGIC EXAMINATION OF THE BRAIN

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ABSTRACT

This paper is concerned with the technique, interpretation, and complications of neuroradiologic studies, particularly angiography and pneumoencephalography-ventriculography. The discussion is focused on six areas of neurologic disease: traumatic lesions of the brain, tumors of the brain, subarachnoid hemorrhage, occlusive disease, inflammatory disease of the brain, and hydrocephalus. The paper includes the role of brain scanning in the diagnosis of lesions in these categories.

As we discuss the radiologic examination of the brain, the special techniques that we will consider in detail are angiography, pneumoencephalography, and ventriculography. However, we want to emphasize that isotopic techniques, such as brain scanning, radioiodinated serum albumin encephalography, cisternography, and cerebral-blood-flow studies, are indeed radiologic techniques for these studies utilize radiation sources. More importantly, many neuroradiologists are directly involved with the performance and interpretation of isotopic studies. Thus, from our "neuroradiologic" point of view, isotopic studies are one important methodologic approach that we use daily along with angiography and air studies. We see these studies not as competitive techniques, but as complementary techniques.

Before we compare isotopic studies with angiography and air studies in certain specific neurologic disease states, we will review some historical and technical aspects of air studies and angiography.

The first radiographic demonstration of the ventricular system took place early in this century (1912). The patient was a man who had sustained a trauma, and, because of a fracture in the posterior wall of his frontal sinus, air had entered his ventricular system. Dr. Lockett in New York obtained radiographs that demonstrated the air-filled ventricles. It was not until 1918-1919, however,

that Walter Dandy deliberately introduced air into the ventricles and into the subarachnoid space of the spinal canal to demonstrate the ventricular system.

Cerebral angiography appeared on the scene approximately a decade later. In 1927, Egas Moniz published a report of his first attempt at cerebral angiography in human patients. Because his complication rate was high, and he was not always successful in the timing of the radiography, his films did not always show the contrast material (strontium bromide) in transit in the cerebral vessels. Moniz later abandoned the bromides for the iodides because of toxicity problems. We have gradually moved toward increasingly safe contrast materials; thus today complications of angiography can more often be attributed to the technique of the angiography rather than to the contrast material itself.

Angiographic techniques cause relatively little alteration in intracranial pressure; thus cerebral angiography has largely supplanted pneumography in the investigation of intracranial neurologic disease. This is especially important in the investigation of the patient who is suspected of having a mass lesion. The replacement of cerebrospinal fluid with air or even the addition of air to the cerebrospinal fluid spaces without removal of spinal fluid in a patient with a mass lesion is the first in a series of events that may lead to shifts in the position of the brain, which may jeopardize the patient's condition. However, there are various lesions that are best diagnosed by air studies. Advances in our knowledge of the arteriographic and venographic anatomy as it relates to the ventricular and cisternal anatomy now permit well-informed statements about the exact location and state of most parts of the ventricular system. The complete demonstration of all parts of the ventricular system and cisterns is possible only with the replacement of spinal fluid with contrast material, which is either opaque or nonopaque. Thus certain tumors that are large enough only to protrude into the subarachnoid cisterns, intraventricular lesions, juxtaventricular lesions, certain congenital anomalies (Fig. 1), and conditions associated with atrophy of the brain are best studied in this manner.

In most centers pneumoencephalography is performed when an air study is indicated in a patient with no evidence of increased intracranial pressure, and ventriculography is reserved for patients with increased intracranial pressure. Whether we do pneumoencephalography or ventriculography on a patient with a mass lesion, we should be prepared to operate immediately after the air study since profound changes may follow the air study and lead to further deterioration of the patient.

A full discussion of the techniques involved in the performance of air studies and of angiographic studies is beyond the scope of this presentation. It is germane, however, that we consider the complications of these procedures, for this will lay the groundwork for a better appreciation of the benignity of the isotopic studies.

Considering air studies first, we must mention that encephalography is a most uncomfortable type of diagnostic test. Headache of varying degree of

Fig. 1 Lateral ventriculogram of a patient with aqueductal stenosis. The white arrow points to the stenotic aqueduct, which is carrying a small amount of oily contrast material from the third ventricle to the fourth ventricle. The collection of oily contrast material labeled S represents a spontaneous ventriculostomy rupture of the posterior third ventricle. These diagnoses could not have been made angiographically.

severity is common, and it occasionally lasts for more than a few days. The risk of herniation in a patient with a mass lesion is ever present. This occurs more commonly when the lesion is supratentorial than when it is in the posterior fossa. There are other serious possible complications that are uncommon, including meningitis (bacterial), extracerebral hematoma, and air embolism.

Although reaction to contrast material may cause complications in angiography, more commonly the complications are related to local factors, such as the production of emboli either by dislodging atheromatous material from a plaque or by injecting a fibrin clot or bubble of air. Other complications due to local factors include partial obstruction of the vessel into whose wall the contrast material is injected (subintimal injections are especially hazardous), hematoma formation from bleeding after the needle is withdrawn, and, finally, injuries to structures, such as nerves that lie adjacent to the vessel injected. There are complications associated with the selection of each of the particular arteries we might choose to study the brain.

Another factor in the equation is that certain patient groups are more prone to complications than others. Patients with occlusive disease, for example, have a higher rate of complications than patients from a younger age group.¹

Complications can be minimized with experience, by using a catheter technique rather than a pure needle technique, and by using on occasion an indirect technique when the direct approach to a diseased vessel is apt to be hazardous. Mastery of techniques of angiography and acquisition of the judgment as to when to proceed and when to cease all efforts comes with long experience. Complication rates varying from 0 to 5% reflect different degrees of competence as well as varying degrees of frankness in reporting complications.

We will proceed to consider the role of various neuroradiologic procedures in the following disease states:

1. Traumatic disease.
2. Tumors.
3. Subarachnoid hemorrhage.
4. Occlusive disease.
5. Inflammatory disease.
6. Hydrocephalus.

TRAUMATIC DISEASE

Although angiography and occasionally encephalography may be used effectively for the diagnosis of a number of traumatic lesions of the brain, the commonest indication for angiography in this area is to demonstrate or exclude the presence of an extracerebral hematoma. Such lesions are simply and effectively handled with surgical techniques. The extracerebral hematomas include both epidural hematomas and subdural hematomas. An epidural hematoma is usually a result of a laceration of the middle meningeal artery. The presentation of the patient classically follows (one-third of the time) a lucid interval which succeeds a state of unconsciousness associated with the trauma.

A subdural hematoma may be classified as acute, subacute, or chronic. The clinical setting in each category is different, relating to the stage of the evolution of the pathological process involved. The patient with an acute subdural hematoma usually is seen soon after the trauma. Underlying brain injury generally is present, and its significance is greater and more ominous than the presence of a thin layer of blood in the subdural space. At times, however, the thin subdural clot may be an important factor in the clinical course of the patient, contributing to an increase in intracranial pressure. In contrast, the symptoms of subacute subdural hematoma begin several days after injury, and the degree of injury may be slight. The associated brain damage is not usually severe. Early organization is present on the surface of the clot. Chronic subdural hematoma may not become apparent clinically until after a number of weeks or

months. The trauma frequently is slight in this type of lesion. The neurologic symptoms and signs may be focal or ill-defined.

Subdural hematomas are frequently bilateral. They occur high over the convexity in children and lower in adults. They may at times be confined to an area of the middle fossa, largely below the temporal lobe. Other less common locations include the area between the cerebral hemispheres and the posterior fossa (Figs. 2a and 2b).

Angiography is close to 100% accurate in the diagnosis of these lesions. The key to angiographic diagnosis is the demonstration of a bare space. The bare space is between the vascularized brain and the inner table of the skull or, in the case of an interhemispheric hematoma, between a vascularized hemisphere and the falx² (Fig 3).*

Special angled views may at times have to be obtained to demonstrate a bare space in an unusual location. Angiography usually reveals large areas of intracerebral injury too when these are present acting as mass lesions.

Scanning is usually used as a screening test in the work-up of a patient with a traumatic lesion; i.e., scanning is carried out whenever we have the luxury of time sufficient to perform the scan. This is usually so when the patient is thought to have a chronic subdural hematoma.

Several factors determine how well a subdural hematoma can be demonstrated by scanning.³ These include the position of the lesion, the age of the lesion, the time at which the scan is performed relative to the injection of the radionuclide, and the radiopharmaceutical used. Posterior fossa lesions and lesions that are largely subtemporal or interhemispheric are at times difficult to demonstrate because of overlying normal vascular structures. The scan diagnosis of subdural hematoma is dependent on an asymmetry of the vascular rims (crescent sign). Bilateral lesions may be difficult to diagnose because the vascular rims of the brain, although abnormally "hot," may be bilaterally symmetrical.

Scanning permits the accurate detection of subdural hematomas in about 80% of cases, with false positives presenting almost as great a problem as false negatives. False positives are most common in the acute illness, but they may occur in the chronic disease. Scalp hematomas frequently cause false positive results (Figs. 4a to 4d). Cerebral contusions and hematomas may also occasionally give rise to positive scans mimicking subdural collections.

One other traumatic lesion that should be mentioned in a discussion of this sort is the fistula, which gives rise to cerebrospinal fluid otorrhea or rhinorrhea. A number of radiologic techniques are available for localizing such fistulas, including tomography and the introduction of Pantopaque into the subarachnoid space, but an isotope technique such as encephalography with radioiodinated serum albumin will usually give good localization if the leak is active.

* Figures 3, 4a-d, 6a-c, and 10a-b are from L. H. Zingesser, in *Clinical Scintillation Scanning*, L. M. Freeman and P. M. Johnson (Eds.), pp. 180-191, Hoeber Medical Division, Harper & Row, Publishers, New York, 1969.

Fig. 2a Brow-down ventriculogram. The white arrowhead points to a fracture. The white arrow points to the fourth ventricle, which is displaced to the left.

Fig. 2b Same patient as in Fig. 2a. Brow-up ventriculogram with oily contrast material indicating a kink in the aqueduct (black arrowhead). This patient had a subdural hematoma in the posterior fossa. Neuroradiologic contrast studies would be expected to be much more precise than scanning in defining such a lesion.

Fig. 3 Left-carotid angiogram with compression of the right-carotid artery; AP Towne view. The black arrows indicate displaced cortical vessels bilaterally. There was no shift of the midline. The "bare areas" bilaterally between the inner table of the skull and the displaced cortical veins are the angiographic representation of bilateral chronic subdural hematomas.

(Credit cited on page 6.)

TUMORS

Angiography may help not only in determining the presence and site of an expanding neoplasm, but also in elucidating the nature of the mass. This information depends on two factors: (1) displacement of arteries and veins from their normal course and (2) the angioarchitecture of the tumor.

The displacement of vessels will depend on the size and situation of the tumor and on whether the growth is displacing or infiltrating. Displacements may also reflect secondary changes, such as edema or swelling around the tumor and obstruction of cerebrospinal pathways with ventricular dilatation.

Some tumors are highly vascular, much more than normal brain, whereas others may have a poor blood supply. Tumor vessels, with their irregular lumina and shapes, differ from normal vessels. They are more tortuous than normal

vessels, and connections may be present between arteries and veins. Malignant tumors may have numerous arteriovenous shunts within their substance and may undergo necrosis, cystic changes, and even hemorrhage, causing areas of avascularity which are recognized in the angiogram. Meningiomas may have a dual supply derived from both internal and external carotid arteries (Figs. 5a and 5b).

The circulation rate through a tumor may suggest the pathologic condition present. Glioblastomas containing numerous arteriovenous shunts may show the tumor vessels filling during the arterial phase only, followed by the early disappearance of the contrast medium; thus very little of the tumor may retain medium during the venous phase. Meningiomas with a more homogenous angio-architecture consisting of numerous capillaries usually retain the contrast medium for a longer period, and the tumor opacification will still be present during the venous phase. Metastatic deposits have a circulation rate that usually lies between those of glioblastomas and meningiomas. Swelling of brain tissue may delay circulation time, and this will become manifest where the opacification of the tumor occurs later than that of the normal brain tissue.

Large avascular space-occupying masses, such as cysts and abscesses, may displace and crowd vascular channels on the periphery of a mass. These crowded normal cerebral vessels must be distinguished from the tumor vessels forming a halo or ring shadow on the surface of a glioblastoma.

Angiography is over 90% reliable in the demonstration of a brain tumor, and the combination of angiography and encephalography is still more reliable.

Results of scanning in the evaluation of patients with suspected neoplasms must be divided into results with infratentorial neoplasms and supratentorial neoplasms. Although a number of authors have claimed that results with posterior fossa tumors are as good as results with supratentorial tumors, the consensus is otherwise.⁴ Routine and special (angled) views of the posterior fossa may at times demonstrate a lesion well. We have had cases where tumors and brain-stem tumors were not demonstrated on scans, probably mainly because of the overlying, normally high concentration of circulating radioisotope. Reports indicate that the accuracy of scanning in the detection of neoplasms in the supratentorial area is over 85%. The commonest tumors—meningiomas, glioblastomas, and metastatic lesions—are demonstrated in a high percentage of patients. Some meningiomas are missed, but not many; this statement is true of glioblastomas also.⁵ Metastatic tumors are not missed unless they are small or deep or both. Less common lesions, such as low-grade gliomas, colloid cysts of the third ventricle, chromophobe adenomas, and craniopharyngiomas, frequently are associated with negative scans. A few explanatory words are in order here.

Sellar and suprasellar lesions are strategically located and may first be noticed clinically when they cause visual disturbances or signs of pituitary dysfunction, even though the lesions are of relatively small size. Furthermore,

Fig. 4a Scan (supine position) of a patient who sustained trauma to the head 4 weeks previously. The black arrow indicates an area of abnormal activity. The nasion is indicated by the black triangle. (Credit for Figs. 4a-d cited on page 6.)

Fig. 4b Right-lateral scan of patient in Fig. 4a. The area of abnormal activity is indicated by the black arrow. The black triangle labels the nasion, and the black rectangle indicates the external auditory meatus.

Fig. 4c Right-carotid angiogram, AP Towne projection. There is neither a shift of the midline nor an avascular space indicative of an extracerebral hematoma.

Fig. 4d Right-carotid angiogram, lateral projection. No displacement of the vessels is demonstrated. Pneumoencephalography was also negative. The white arrowheads point to the subgaleal hematoma, which was responsible for the positive scan. Several months later brain scans were repeated and were negative.

Fig. 5a Lateral internal carotid angiogram of a patient with a meningeoma arising from the falx. The black arrowhead indicates a displaced branch of the anterior cerebral artery. Note the tumor stain above the arrowhead.

Fig. 5b Same patient as in Fig. 5a. Selective external carotid angiogram. Note the supply from the external carotid and the dense homogenous stain in the tumor. These features are typical of a meningeoma.

lesions in this area are hidden to some extent by pools of circulating isotope. There is nothing about the intrinsic nature of these tumors which renders them less susceptible to detection by scanning than other lesions less strategically located. This can be surmised from the fact that these lesions, when moderately large or large, can be detected by the usual scanning procedure.

The low-grade gliomas, however, even when large and located in areas not obscured by circulating isotope, may not be associated with a large enough leak in the blood-brain barrier to be detected. Some of these tumors are solid and some are cystic. Low-grade astrocytomas occasionally show a reduced counting rate compared with normal brain tissue.⁶ Since not all cystic tumors are associated with negative scans, the cyst itself is not responsible for a low concentration of isotope. Cysts, on the contrary, have at times been found to contain fluid with a relatively high level of radioisotope.

Very rarely is a meningioma associated with a negative brain scan. Scanning may therefore be of use in the differential diagnosis of lesions of the skull. An osteolytic lesion of the skull resulting from the growth of a meningioma would be associated with a positive brain scan, for example, whereas an osteolytic defect resulting from fibrous dysplasia might or might not be associated with a positive brain scan. An area of hyperostosis resulting from the growth of a meningioma would be associated with a positive brain scan, whereas the increase in bony density due to involvement of the skull by an osteoma would be associated with a negative brain scan.

Glioblastomas and metastatic lesions larger than 2 cm are seldom missed on scans. Scanning has a special role in these cases. It may delineate extension of a malignant lesion across the corpus callosum better than conventional neuroradiologic methods, and it is usually superior to conventional neuroradiologic methods in demonstrating multiple lesions. For the detection of small vascular metastatic lesions, angiography has the edge over scanning, but otherwise scanning is superior; angiography, in the patient with lesions not associated with abnormal vasculature, reflects only vascular displacements, and it is seldom possible to distinguish multiple lesions in the same area (Figs. 6a to 6c). Furthermore, scanning often depicts the location of avascular lesions much more accurately than angiography and pneumoencephalography, which demonstrate displacements of normal intracranial structures due to a combination of tumor and edema surrounding the tumor. Thus angiography may demonstrate marked displacements of vessels near and at a distance from a small metastatic lesion, whereas the conventional scan performed a short time after injection of radioisotope will show the tumor itself. Later scans will show a larger lesion because there is often more isotope in the area of edema surrounding the lesion several hours after injection.

The evaluation of a patient with a known malignant disease for single or multiple brain lesions is a common and important indication for brain scanning. There is a pitfall here which we encountered on one occasion. In one of our

Fig. 6a Left-lateral brain scan. The nasion is labeled with the black triangle, and the black rectangle labels the external auditory meatus. There are three metastatic deposits indicated by the black arrows.

(Credit for Figs. 6a-c cited on page 6.)

Fig. 6b Same patient as in Fig. 6a. Left-carotid angiogram, arterial phase, lateral projection. The black arrowheads indicate depressed insular-opercular branches of the middle cerebral artery.

Fig. 6c Later phase of angiographic series. Only the largest metastatic deposit (incomplete ring of abnormal vessels, indicated by the black arrowheads) is well demonstrated. Thus scanning much more accurately reflects the extent of the disease here.

patients with a glioblastoma, the scan showed two distinct areas of abnormal concentration of isotope separated by a few centimeters of low activity. Surgery was performed on this patient, and a single large tumor was found which contained areas of cyst formation, hemorrhage, and necrosis between areas of viable tumor. Presumably the concentration of isotope in the degenerated areas of this particular tumor was much less than the concentration in the viable tumor. This is not true in general, however. Necrotic tumor often is responsible for a greater concentration of isotope than is viable tumor.

SUBARACHNOID HEMORRHAGE

The most common cause of subarachnoid hemorrhage is rupture of an aneurysm involving a cerebral artery. These aneurysms are usually found in the circle of Willis at sites of branching. Aneurysms are frequently multiple. Signs that localize and lateralize an aneurysm are not uncommonly present, but, because of the tendency to multiplicity, both carotid and vertebral trees should be studied angiographically if surgery is to be considered. Angiography is over 96% accurate in the diagnosis of cerebral aneurysm.⁷ Because of the graveness of the disease and because medical management in most centers is not as efficacious as surgical therapy, angiography is usually carried out to locate the aneurysm, to rule out other aneurysms, and to indicate preoperatively what surgical technique would appear to have the best chance of success (Fig. 7).

Scanning has very little place in the management of an aneurysm. However, approximately 15% of subarachnoid hemorrhage is due to rupture of an arteriovenous malformation, and these lesions may be demonstrated on scans and/or isotope angiograms over 80% of the time. Clinically there may be an indication that the subarachnoid hemorrhage is from an arteriovenous malformation rather than from an aneurysm. A history of seizures for many years before the ictal episode would be such a clue. In such instances isotope angiography or brain scans could have a place in the management of the patient, but even so angiography would probably be required to indicate whether or not an associated intracerebral hematoma was present and whether or not the lesion could be treated surgically. This would be a function of its location and the complexity of the feeding arteries. Isotope studies would do well in localizing the lesion, but the resolution inherent in such studies could not demonstrate the feeders and drainage well enough to plan surgery.

OCCLUSIVE DISEASE

Ischemic lesions of the brain may result from occlusive disease anywhere along the arterial tree leading to the brain. Recent publications have stressed the high incidence of extracranial vascular disease as a localized entity.

The best figures available to the incidence of radiologically demonstrable lesions in patients with symptomatic occlusive disease have been acquired in the Cooperative Study of Extracranial Arterial Occlusion.¹ In an analysis of the angiographic findings in 3788 patients with 4 vessels studied:

- 67.3% had multiple lesions that were surgically accessible.
- 33.3% had a combination of accessible and inaccessible lesions.
- 41.2% had accessible lesions only.
- 6.1% had inaccessible lesions only.
- 19.4% had no lesions demonstrated.

In assessing structural disease in the neck vessels, we look not only for occlusion and stenosis, but also for evidence of ulceration into an atheromatous plaque (Fig. 8). Such lesions have been shown to be related to embolic disease.

Angiography also allows assessment of collateral pathways when there is occlusive disease. Both intracranial and extracranial disease may lead to function of such collateral channels (Figs. 9a and 9b).

Finally, the speed and direction of flow may be of significance in the "subclavian steal" syndrome, for example.

Intracranial occlusive disease may be recognized if a main cerebral artery or branch artery can be seen to be occluded. Collateral circulation may assist in the diagnosis.

Fig. 7 Carotid angiogram, periorbital view. The black arrow points to the neck of an aneurysm arising from the middle cerebral artery at its trifurcation. Information as to the exact site of an aneurysm and the delineation of a neck, if one is present, are required if surgical therapy is a consideration.

Fig. 8 Lateral carotid angiogram of a patient with an occluded internal carotid (black arrowhead). There is narrowing of the proximal portion of the external carotid as well.

Fig. 9a Lateral carotid angiogram. Multiple small branches of the middle cerebral have not filled (black arrowhead).

Fig. 9b Same patient as in Fig. 9a. Note the collateral in the area previously void of vessels. These branches have filled in a retrograde fashion.

Angiography may disclose infarction without demonstrable occlusion, showing increased perfusion around infarction with veins in the area filling early. When the infarct produces a mass effect and differentiation from a tumor is difficult, serial scans may be of great assistance in the diagnosis.

Since angiography is not without complications, it should not be undertaken lightly. The complication rates reported in the Cooperative Study of Extracranial Arterial Occlusion¹ are unremarkable, however, indicating the infrequency of serious complications of angiography in this patient population. With all techniques of angiography (carotid, subclavian, brachial, and retrograde aortic angiography), complications were more frequent with patients who had severe deficits to begin with, but even here severe complications ranged from 1 to 3%.

As indicated, isotope studies may be of assistance in the differential diagnosis of problem cases. To determine the frequency of positive brain scan in patients with hemispheric occlusive disease, a prospective study was undertaken at the Albert Einstein College of Medicine.⁸ Fifty consecutive patients with occlusive disease were studied with angiography and with serial brain scans.

Of the 50 patients 24% had a positive initial scan, 62% had a negative initial scan, and 14% had an equivocal scan (Figs. 10a and 10b). A surprisingly large proportion of the positive scans were in patients with hemorrhagic lesions (Table 1). Patients with middle or anterior cerebral occlusions had a higher percentage of positive scans than patients with carotid occlusions (Table 2). Fifty percent of the second scans were positive (Table 3); 43% of patients with initially negative scans had positive follow-up scans. Important conclusions relative to patient management may be drawn. Patients with suspected cerebrovascular accidents should be scanned shortly after the onset of their acute symptoms if the study is to be used as a screening procedure. Only 17% of patients with acute ischemic infarction have abnormal initial scans, whereas over 80% of hemispheric tumors are associated with positive scans.

In addition to brain scanning, other isotopic tests are used in this area of disease, some as screening tests, others as research methods. Isotope angiography, as carried out in a more or less sophisticated fashion, is probably a useful screening procedure. Scans of the distribution of an intracarotid injection of microaggregates of albumin are occasionally used in this area. These might be helpful in the differentiation of tumor and infarction. Cerebral-blood-flow measurements with isotopes are performed in many centers around the country in this patient population, but these methods are best classified at this time as research methods rather than clinical methods.

INFLAMMATORY DISEASE

We will consider two categories of inflammatory disease: (1) subdural empyema and (2) cerebral abscess. Subdural empyema, in our experience, is most often a result of untreated sinusitis or middle-ear disease. The patient

Fig. 10a Left-lateral brain scan obtained 11 days after the patient's ictus. The black arrow points to an area of abnormal activity. The scans were negative on the 1st postictal day. Scans on the 55th postictal day were also negative. The nasion is labeled with the black triangle, and the black rectangle labels the external auditory meatus.

(Credit for Figs. 10a-b cited on page 6.)

Fig. 10b Left-carotid angiogram, lateral projection, of patient in Fig. 10a. Angiography was carried out on the 4th postictal day. This angiogram demonstrates absence of filling (black arrow) of the frontal branches of the middle cerebral artery.

TABLE 1
RESULTS OF SCANS IN HEMORRHAGIC
AND ISCHEMIC LESIONS

Lesion	No. of patients	Positive scan, %	Negative or equivocal scan, %
Ischemic	41	17	83
Hemorrhagic	9	55	45

TABLE 2
RESULTS OF SCANS IN PATIENTS WITH
DIFFERENT TYPES OF ARTERIAL DISEASE

Disease	No. of patients	Positive scan, %	Negative or equivocal scan, %
Middle or anterior cerebral artery disease	5	40	60
Carotid artery disease	14	7	93
No angiographic abnormality	18	16	84

TABLE 3
RESULTS OF SECOND SCANS MADE 3 TO 8 WEEKS
AFTER FIRST SCANS IN 32 PATIENTS

Time after initial scan, weeks	No. of patients	Positive scan, %	Negative or equivocal scan, %
3 to 4	26	54	46
5 to 8	6	40	60
Total	32	50	50

usually has had a brain scan before being referred for angiography. On the brain scan, a "crescent" sign is seen, the same sort of abnormality as found in patients with subdural hematomas. Or, if the collection of pus is localized to the front of the cranial cavity in the form of a loculation behind the frontal sinuses, for example, the scan may suggest a localized cerebral lesion, such as a tumor or abscess. Angiography in this situation will demonstrate a bare area between the vascularized brain and the inner table of the skull. If the collection is not well demonstrated on conventional views, oblique views may be necessary.

Cerebral abscesses are demonstrated angiographically as avascular mass lesions. Around the avascular center of the lesion, a ring of vascularized brain may be noted. In this area the vessels of the brain surrounding the lesion are compressed so that there appears to be a condensation of contrast in the area. Early filling of veins in the area of an abscess may be noted. Often the "ripple" sign or "onion peel" sign is present. This describes the gyral-sulcal pattern forming concentric circles around the lesion. The sign is not specific for an abscess. Air studies demonstrate a mass effect when the abscess acts as a mass lesion. When the abscess communicates with the ventricle or subarachnoid space, air may enter the abscess cavity (Fig. 11).

The abscess in evolution passes through a stage of cerebritis. This is a stage of early necrosis, and no capsule is present at this time. Angiography and air studies performed at this stage in the illness do not usually show a mass lesion. The brain scan at this stage of the illness may be positive. The brain scan, thus, may well be useful in following the development of an abscess. Although it would seem from this fact that the brain scan is more sensitive than angiography and air studies, this is not always true. Sizable abscesses may be missed on brain scans, and some of these abscesses can be noted angiographically, even when they are negative on scans.

HYDROCEPHALUS

A discussion of hydrocephalus should include not only the communicating and noncommunicating varieties, usually thought of as diseases of infancy and childhood, but also the "low or normal pressure" variety of hydrocephalus seen in adult life.

Traditionally, pneumoencephalography and ventriculography using air and sometimes oily contrast medium have been used for the diagnosis of hydrocephalus and for the localization of the point of obstruction to the ventricular system, if such an obstruction is present. These studies also serve to distinguish hydrocephalus from the other causes of a big head, such as hydranencephaly and megalencephaly and subdural hematomas. In skilled hands angiography can yield about the same information, sometimes less, sometimes more, even to the point of distinguishing varieties of hydrocephalus, aqueductal stenosis from communicating hydrocephalus, for example. Vessels outlining the lateral and third

Fig. 11 Air in an abscess adjacent to the frontal sinus. The abscess arose from infection in the sinus. The posterior displacement of the anterior cerebral artery (black arrow) and its frontal-polar branches further delineates the abscess.

ventricles, the brain stem, the limits of the fourth ventricle, and the position of the venous sinuses around the posterior fossa are important in this sort of analysis. In the Arnold—Chiari malformation and in aqueductal stenosis, the lateral sinuses define a small posterior fossa, whereas in the Dandy—Walker malformation, the lateral sinuses are in a higher position than normal because of distention of the fourth ventricle.

Brain scanning, keyed to an assessment of these vascular structures, may allow differentiation of several forms of hydrocephalus. For example, brain scanning may demonstrate the high transverse sinuses of a Dandy—Walker syndrome. Isotope may be injected into the ventricles for delineation of the ventricular system, but again the inferiority of isotope imaging devices compared to the resolution of X-ray films limits the usefulness of this technique. An isotope study would not distinguish a congenital aqueductal stenosis from an

aqueduct obstructed by a mass lesion, but this differentiation could most always be made using angiography and/or pneumoencephalography—ventriculography.

An important area of usefulness of both angiography—pneumoencephalography and isotope encephalography is the differentiation of various causes of dementia. The degenerative diseases, such as Alzheimer's disease, Pick's disease, and Jakob-Creutzfeldt disease, are one important cause of dementia. Low- or normal-pressure hydrocephalus is another cause of dementia, making up a group that is numerically small compared to the first group but unlike the first group responds to shunting procedures. Pneumoencephalography is performed in demented patients to rule out midline ventricular tumors, to indicate whether or not air is able to pass through the subarachnoid cisterns to reach the convexity, and to indicate whether or not sulci of the hemispheres are dilated as would be the case if atrophy of the gray matter were present. Lack of passage of air through the tentorial notch would indicate adhesions in the area. Such adhesions might be caused by old inflammatory disease or might be the residua of hemorrhage into the subarachnoid space. These adhesions might lead to ventricular dilatation by compromising the absorption of ventriculo-spinal fluid.

Radioiodinated serum albumin encephalography yields similar and additional information about the flow of ventriculo-spinal fluid. Both studies should be performed for the evaluation of the patient with dementia.

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BRAIN SCANNING

IN THE NEURODIAGNOSTIC WORK-UP

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ABSTRACT

The brain scan using $^{99m}\text{TcO}_4^-$ is a valuable clinical test that aids in the detection and localization of a wide range of focal brain pathology. It should be available to every clinician responsible for diagnosis of neurological disease. Scanning displays lesions having either a defective blood-brain barrier or a regional blood volume significantly different from surrounding brain. Although its major application has been in the detection and localization of cerebral tumors, it is also of value in detecting subdural hematomas, infarction, and most other focal lesions resulting in a gross histologic deviation from healthy brain tissue. Lesions near the base of the skull and in the posterior fossa are poorly seen by scanning because they blend in with subcranial tissue isotope. Most symptomatic brain tumors are detected about as dependably by scanning as by angiography. A positive scan usually leads to cerebral angiography, which is more definitive but substantially more hazardous. Despite its limitations, scanning is a valuable adjunct to other neurodiagnostic procedures such as skull radiography, electroencephalography, ultrasound echo, brain midline detection, pneumoencephalography, and angiography, each of which assesses some specific aspect of brain structure and/or function.

Before he can intervene sensibly in the natural course of the disease process, the physician must detect the nature of the patient's malfunction. Confronted by a sick patient, the clinician is starved for information. Out of the few scraps of physiological data available to him, he must construct a concept of the disease. The clinical confrontation is nowhere more starved for information than when evaluating central nervous system (CNS) dysfunction.

Until the past few decades, all our information about human CNS dysfunction resulted from watching its output (behavior) in response to the controlled input of the neurological examination. An experienced neurologist

TABLE 1

**SOME PRACTICAL CLINICAL FACTORS RELATED TO NEURODIAGNOSTIC PROCEDURES
COMMONLY PERFORMED ON PATIENTS HAVING BRAIN SCANS**

Procedure	Information supplied	Hazard	Discomfort	Patient cooperation required	General availability*	Cost, \$
Brain scan	Low-resolution display of blood—brain barrier and regional blood volume	None	None	Moderate	Restricted	100 to 150
Skull radiography	Calcium distribution	None	None	Minimal	Widely	50 to 100
Electroencephalography	General indicator of brain activity	None	None	Moderate	Widely	25 to 50
Echoencephalography	Brain midline displacement	None	None	Minimal	Widely	15 to 25
Pneumoencephalography	Cranial location of cerebrospinal fluid	Slight	Moderately severe	Total†	Restricted	150 to 300
Angiography	High-resolution blood distribution and rate of flow	Occasional hemiplegia	Moderately severe	Total†	Restricted	200 to 400
Neurologic consultation	Overview	None	None	Minimal	Restricted	50 to 100

*General availability refers to the access of a patient in smaller communities not having equipment or professional skills available in major medical centers.

†Total cooperation required unless done under general anesthesia.

can often arrive at valuable decisions on management of the patient from the clinical history and neurological examination, but his need for more diverse input for decision making has forced the development of a number of ancillary diagnostic procedures (Table 1).

These procedures will be discussed in terms of the information they provide, the harm they might do, their cost, and their degree of applicability. Emphasis is placed here on brain scanning, and discussion of the other tests must necessarily be brief. It is important to recognize that the skilled clinical impression viewed as a "test" ranks foremost among all diagnostic procedures. The impression of a trained neurologist, when available, is totally atraumatic, provides a wide range of information, and is relatively inexpensive. Neurological consultation costs the patient less than several of the specific laboratory tests described here. Because of these virtues the clinical neurologist is not likely to become obsolete in the foreseeable future.

Radioisotope scanning will be compared here with other diagnostic methods commonly used in the same patient (skull radiography, electroencephalography, echoencephalography, pneumoencephalography, and angiography). Each procedure provides information about a different aspect of brain structure and function. Some are almost wholly structural, and pathophysiology must be inferred; others are almost entirely functional and provide minimal localization.

An ideal test would define structural and several physiological parameters, be harmless, painless, inexpensive, and be carried out by relatively unskilled personnel. Patients under neurological evaluation are commonly unable to cooperate and may even resist any form of manipulation; therefore, a test that requires little cooperation is more easily applied. Isotopic scanning holds the promise of approaching these ideals in the foreseeable future.

With each test the parameter of brain structure or function under assessment will be noted, and the hazard, discomfort, cost, and general availability will be discussed. Since each test has produced many monographs, only a few practical clinical points can be presented.

BRAIN SCANNING

Brain scanning refers here to the mapping of the cranial distribution of gamma-emitting radionuclides subsequent to their intravenous (I.V.) injection.^{1,2} The aspect of brain pathophysiology defined by scanning is regional alteration of the blood-brain barrier (BBB) and, to a lesser degree, regional tissue blood volume.

Although many gamma-emitting nuclides can be used for brain scanning, the well-recognized merits of the physical decay and tissue distribution of $^{99m}\text{TcO}_4$ (hereafter referred to as Tc) are such that only the clinical use of this agent will be considered here.

Clinical Indications

Current scanning techniques are designed to show relative regional increases in isotope content of tissue and not absolute isotope levels; therefore only focal diseases are defined. This excludes a large number of disease processes where more general abnormalities are produced. Essentially all focal brain disease results either in some changes of BBB or of regional blood volume; thus many suspected diseases can be detected and crudely localized by scanning. These disease categories include neoplasia, infarction, hemorrhage, trauma, and infection. Since the scan can help in detecting a wide range of diseases, it should be thought of not only as an elective procedure but also as one which should be available on an emergency basis whenever the clinical indication arises.

Brain scanning is atraumatic. Those of us working in nuclear medicine are confident of this fact, but we must recognize that tissue irradiation from internal radioactive isotopes generally is viewed with more alarm than similar irradiation from diagnostic radiographic procedures. This alarm is justified in pregnancy and in children. Scans of these patients should be considered only as specific diagnostic tests and seldom for screening purposes.

For several reasons brain scanning does not occupy now the prominence it deserves in neurology departments. The technology is alien to most clinical neurologists since it has not been emphasized by most past medical curricula. Traditional neurological training provides a good background for the ready acceptance of structural studies by radiography because these are applied gross neuroanatomy. Similarly, classical electrophysiology sets the stage for clinical electroencephalogram (EEG) acceptance. Histology prepares for neurological pathology. Despite the resistance of the neurologists to take on scanning, this field is probably as important to master as that of neuroradiology or electroencephalography.

Useful brain scanning can be done with a rectilinear scanner, which currently costs little more than an EEG machine and considerably less than a radiography machine. There is no discomfort associated with scanning, and it is only moderately expensive (\$100 to \$150). Because brain scanning is so safe, inexpensive, painless, and informative, it is applicable both as a screening test and as a specific diagnostic technique.

The basis for the usefulness of brain scanning is shown in Fig. 1. This figure shows Tc levels in rat plasma, scalp, and brain after I.V. injection. The blood level falls rapidly. Immediately after injection the blood level was about 2500 on the ordinate of Fig. 1, and it is evident that even by 1 min the Tc has largely left the blood, distributing to extracellular fluid and other extravascular compartments. The distribution in humans will be somewhat slower than that shown here in the rat. The scalp is representative of most nonneural tissues, and its content rises with the fall in blood level. This extravascular distribution is possible because a substantial fraction (20 to 30%) of plasma Tc is unbound to protein. Because Tc is both bound and unbound to plasma protein, its

Fig.1 Distribution of Tc in rat plasma, scalp, and brain after I.V. injection. The very low tissue levels achieved in brain relative to scalp and plasma cause the brain to appear essentially free of isotope. Initially, the high blood-plasma level causes the nuclide to map primarily blood-pool distribution. Early scans emphasize lesions such as aneurysms which are predominantly blood. After the first few minutes, the blood level has fallen and the scalp concentration has risen sufficiently that delayed scans display predominantly the extracellular space of scalp and to a lesser extent of skull. After the first few minutes, the blood contributes relatively little to the halo that appears about the head on the brain scan. Because the BBB prevents healthy brain from achieving any significant tissue concentration of isotope, lesions containing a defective BBB cause regional "hot spots" to appear. Tissue concentrations in most lesions with BBB defects will approximate those shown here for scalp. Rarely a "cold spot" is seen in the presence of cystic lesions which do not contain blood and do not exchange freely with plasma. The persisting blood level causes Tc to be both an extracellular fluid and a blood marker.

distribution resembles both vascular markers, like radioiodinated albumin, and extracellular markers, like EDTA complexes. The Tc in healthy brain is confined to the blood compartment, and the total tissue content remains very low because of the BBB. The arachnoid membrane on the inner surface of the dura is

Fig. 2 Lateral and frontal views of the Tc brain scan revealing an empty cavity representing the cranial tissues inside the dura. The ability to see a lesion is at its maximum when the lesion is not superimposed on extracranial tissue uptake. The dashed line on the lateral view represents the region within which maximal detection sensitivity is achieved. Outside this line lesions of the cerebral hemisphere tend to fuse with extracranial tissues, particularly below the floor of the cranial cavity. TS represents largely plasma protein-bound Tc within an ill-defined transverse sinus. The poorly defined empty space inferior to this represents the posterior fossa (PF), and this is not well differentiated from the rather thick, overlying extracranial tissues. On the AP scan the cranial halo is seen to be roughly symmetrical, and considerable blood is seen in the sagittal sinus and in other central cortical vessels. This prominent isotope concentration is seen because the sagittal sinus is viewed longitudinally, and a considerable depth of blood is seen by the elongated sensitivity pattern of focal collimators. This isotope in the region of the sagittal sinus gradually fades, particularly after the first few minutes.

the outer limit of the nervous-system compartment not exchanging freely with blood plasma. The dura and all tissues exterior to it do exchange.

Current thinking on the anatomic basis of BBB is that it represents a fusion of capillary-endothelial cells to adjacent cells forming tight, impermeable junctions. The intercellular clefts accounting for the small-molecule permeability of general capillaries are thus obliterated, and any capillary exchange in brain must take place directly through the two plasma membranes of the capillary cell. Pinocytosis is also absent in brain capillary cells, whereas this process is quite active in nonneural capillaries. How these changes in brain capillary cells are brought about is unknown, but it is useful to consider that one function of healthy brain (possibly a function of the astrocyte) is to keep its capillaries shut off. When sufficient pathology exists, the brain cannot carry out this function and the brain capillaries come to resemble capillaries elsewhere. The time-course of distribution of Tc in most brain lesions will resemble that shown for scalp in Fig. 1.

Here it is sufficient to indicate that many forms of brain pathology result in a loss of BBB, and, when this focal loss is large enough, current techniques for external scanning can detect it. The BBB creates a unique restriction of exchange between tissue extracellular fluid and plasma, causing the normal cranial cavity to appear essentially empty in the scan. This, together with its isolation from other major organs, makes it an attractive organ for scanning.

How big must a lesion be to be seen? Even with a near-ideal nuclide like Tc, collimator imperfections, Compton scatter, and movement of the patient create a limit of about 1 cm on practical spatial resolution. Most brain lesions must have dimensions greater than about 2 cm to be clearly seen, although this depends on the lesion shape and how much the Tc concentration in the lesion exceeds the surrounding brain.

In what location are lesions best seen? Lesions surrounded by tissue with intact BBB are best seen (Fig. 2). On the scan image those near the floor of the cranial cavity are difficult to separate from the extradural tissues below the cranial cavity. With Tc, the parotid gland and nasal mucosa tend to create unusually dense subcranial tissue uptake. Thus, to be recognized, pituitary, sphenoid-ridge, and olfactory-groove tumors must protrude into brain tissue and be relatively larger than if they were located away from the floor of the cranial cavity (Fig. 3). This also applies to lesions in the posterior fossa where there is not much room for them to get very large without serious symptoms because of the medullary vital centers. The presence of the overlying transverse sinus (Fig. 2), the occipital bone (seen obliquely), and thick, subcutaneous, soft tissues obscure the small "empty" space and make the posterior fossa a difficult region for interpretation. Some larger lesions can be seen, though, particularly in the reverse Towne projection. This is an area where high resolution and a meticulous technique can be of value. Section scanning can improve the

Fig. 3 Right-lateral scan showing pituitary tumor. Although pituitary tumors are poorly located to be seen on the lateral or AP scan because they blend in with the subcranial tissues, a large chromophobe adenoma may project sufficiently out into brain tissue to be seen as a clearly defined regional uptake. Such a lesion must be quite large, however, to be seen with routine rectilinear scanning. Section scanning just above the floor of the cranial cavity can better define these lesions. EAM is the external auditory meatus, I theinion, and N the nasion.

visualization of lesions near the floor of the cranial cavity and in the posterior fossa.

Lesions more rostral in the brain and clearly separated from the floor of the cranial cavity are much better seen on the scan image. Small parasagittal lesions are not as well seen as those entirely within brain substance because of their fusion with the cranial "halo" surrounding the brain (Fig. 4). With Tc scanning this is due to tangentially-seen extracellular scalp and bone and, to a lesser extent, sagittal sinus and cerebral-venous blood. For suspected parasagittal lesions, a vertex view is sometimes useful because the scalp and skull in this region are seen at right angles rather than tangentially, as on the lateral view, and the halo does not obscure the lesion.

Although lesions entirely within the cerebral hemispheres are most favorably located for external scanning, the occasionally visible choroid-plexus uptake of Tc must be recognized. The basis of this occasional uptake is problematic since presumably all choroids concentrate Tc yet few are visible on the scan. This uptake can be prevented by oral administration of 200 to 300 mg of NaClO_4 1 to 2 hr before scanning and this should be routine.

What classes of lesions are best seen? Scanning is of particular value in the recognition of tumors, subdural hematomas, and brain infarction. A detailed

Fig. 4 Small lesions near the vertex (V) tend to blend in with the cranial halo, but usually parasagittal meningiomas such as in this case are seen provided they are more than about 2 cm in diameter. In this case the scan was performed after the common carotid angiogram, which was initially read as negative. In retrospect, in the light of this scan, the lesion could be recognized on the angiogram. The lesion was confirmed angiographically by demonstrating filling from the external carotid artery and was successfully removed surgically.

consideration of all conditions in which scanning can be of value is impractical here, but the frequency with which tumors, subdural hematomas, and infarctions are visualized justifies a brief discussion.

Tumors

How does the brain scan fit into a tumor work-up? Supratentorial brain tumors are best suited to detection and localization by scanning. These tumors commonly present with some combination of the following modes of onset: (1) progressive focal neurological deficits, (2) focal or generalized seizure activity, (3) elevated intracranial pressure, (4) elevated cerebrospinal fluid (CSF) protein, (5) focal EEG abnormality, (6) midline brain shift, (7) personality change, and (8) persistent headache. Any of these symptoms or signs is an indication for scanning. Most symptomatic cerebral tumors eventually will have positive Tc scans. The exact incidence of positive scans cannot be readily determined because the time of scanning in the evolution of the tumor is so variable. A positive scan showing a single lesion is indication for angiography, a procedure more definitive in showing location, feeding vessels, rapidity of blood transit, and vascular architecture.

The effects of various types of tumor in different locations at different stages of evolution are highly variable. They produce so many clinical pictures that it is impossible to generalize on likely results of the various tests. They may (rarely) all be negative or all positive. The angiogram usually is required for tumor diagnosis. Most neurosurgeons insist on this procedure before craniotomy is undertaken. Occasionally tumors seen by scanning are not demonstrated by angiography.

If a patient has a negative scan, other clinical considerations may still demand an angiogram and/or an air study. A negative scan in the presence of a lesion is due to (1) the unfavorable location of the lesion near the floor of the cranial cavity or in posterior fossa, (2) the BBB or blood volume of the lesion is not very different from the surrounding brain, (3) the lesion is too small to be seen, or (4) the scan is technically unsatisfactory. These occasional false negatives occur with scanning as with all techniques.

Technically inadequate scans are most often due to patient movement. Even though each of the four projections usually taken requires only about 10 min, the patient must remain motionless during these periods. Movement is a serious limitation of this technique in many neurologically ill patients. Minor repetitive movements may degrade the resolution of the scan and yet not be recognized.

False-positive scans can be due to skull defects or scalp abnormalities, such as those produced by trauma or previous craniotomy. Since most of the Tc seen over the brain in the cranial scan is in scalp, changes in scalp thickness or unusual capillary permeability may create "hot spots." Simple artifacts, such as scalp or hair contamination by isotope, may be quite elusive.

Fig. 5 Multiple areas of regional uptake in the presence of evidence of an intracranial tumor are virtually pathognomonic of metastatic brain tumors. Multiple primary brain tumors are exceedingly rare, and virtually all multiple neoplasms are metastatic. This left lateral scan, in itself, could not be clearly differentiated from that produced by multiple cerebral infarction caused by embolization from atrial fibrillation. The time-course on serial scans would tend to improve over a course of weeks with infarctions, but the multiple metastatic lesions will progressively worsen.

If a scan shows obvious multiple cerebral lesions (Fig. 5) and a malignancy is established elsewhere in the body, it may justifiably be decided to spare the patient an angiogram since multiple cerebral tumors are almost invariably metastatic and inoperable. Even this is not a hard-and-fast rule since multiple embolic infarcts may produce a similar scan.

The safety of the scan is a very important consideration in tumor work-up since many patients with a negative scan can be spared an angiogram. A common clinical situation is the appearance of one or a few grand mal seizures in an adult. This may be due to many factors, but one important possibility is a cerebral tumor. Some neurologists almost routinely in the past subjected such patients to angiography. The ability of scanning to detect the presence of a cerebral tumor is approximately as good as angiography, but less useful information is provided. The addition of brain scanning to the battery of atraumatic tests applied in such cases does the patient a great service.

The brain scan is particularly important in the management of the elderly. Patients over 70 tolerate angiography and subsequent craniotomy poorly. The atraumatic scan greatly facilitates management of such cases.

The scan may be less valuable in children because of less cooperation, frequent movement, concern about radiation, and the subtentorial location of most pediatric brain tumors. These are not prohibitive factors, however, and the obviously ill child may be scanned usefully and ethically. Before 15 years of age, most brain tumors are in the brain stem or cerebellum and do not achieve a great size because of the restricted volume they can occupy. High-resolution technique

can demonstrate such lesions, however. If immobility can be achieved, cerebral lesions such as abscesses and subdural hematomas can be seen, much as in adults.

Meningiomas constitute only 10 to 15% of brain tumors, but they are very important tumors to diagnose since there is, with good surgical technique, an excellent chance for a long-term recovery. Most meningiomas large enough to be clinically significant are detectable by scan unless they are small, at the base of the skull, or in the posterior fossa. Because these tumors usually are supplied by the external carotid, selective angiography is usually diagnostic preoperatively.

The commonest brain tumors, metastases and malignant gliomas, are not treatable in the sense that a long-range cure can be expected, but patients can be managed more intelligently with a firm diagnosis. Palliative measures, such as radiation, chemotherapy, and steroids, can be instituted. Thus, even though the long-range outlook in most brain tumors is bleak, this should not generate diagnostic nihilism. A definite diagnosis is worthwhile. As noted, most cerebral tumors are either metastatic or of glial origin (gliomas). Brain metastatic tumors are usually multiple and commonly are near the surface of the hemispheres. They are well shown by scanning provided they are individually large enough or form a detectable cluster of lesions.

Gliomas comprise about half of all brain tumors and exhibit a wide range of histology and malignancy. The glioblastoma is the commonest and most malignant and presents as a rapidly progressive, disruptive tumor that almost invariably produces a markedly positive scan (Fig. 6). Gliomas of lesser malignancy are less disruptive of cerebral function, and their histology is less strikingly abnormal. Some very slowly growing gliomas histologically look very much like adjacent brain. Their BBB is correspondingly undisturbed, the scan is less abnormal, and current routine scanning technique commonly misses them.

Arteriovenous malformations are rare tumors and exhibit such strikingly abnormal hemodynamics with very active arteriovenous shunting that they are detectable by many techniques. Because the veins of these tumors are subjected to the arterial pressure head, they are greatly distended, and a large proportion of the tumor mass is blood. On the scan they can be particularly well seen early after injection when regional blood volume is being displayed. Since Tc distribution displays both blood compartment and extracellular fluid, these lesions are usually visible even in the routine scan done 30 to 60 min after injection.

Subdural Hematoma

The detection of subdural hematoma is very important because the lesion is common and is treatable by trephination if identified early. It almost invariably is accompanied by a persistent headache and may or may not be related to a history of head trauma. There is usually progressive headache, cortical deficit, somnolence, coma, and ultimately death from brain-stem herniation. Subdurals are occasionally missed, and resultant death is always viewed with great concern

because they usually are treatable and there is an excellent chance of permanent recovery if discovery is early. The lesion is most definitively diagnosed by angiography. The hematoma depresses the hemisphere away from the inner table of the skull; this is visualized when surface cortical vessels appear in the late arterial phase of the angiogram (Fig. 7). There is a gap between skull and brain resembling the gap between chest wall and lung in the radiogram of the pneumothorax.

This lesion enters into the differential diagnosis of many chronic, subacute, and acute cerebral deficits. It is important to have a reliable screening test to rule it out. Some surgeons place cranial burr holes when the lesion is suspected, but, if modern angiography is readily available, the burr holes are best deferred until after the angiogram if the patient's condition permits the delay. In less acute cases where more time is available, a scan can be very helpful in diagnosing a hematoma. Most subdural hematomas large enough to be symptomatic can be detected by scan.³ They are seen as a considerable thickening of the cranial halo on the AP or PA projection (Fig. 7), sometimes referred to as the crescent sign because of its crescentic shape.⁴ Usually the hematomas are parasagittal at first, but they spread laterally over the cortex from the region of the vertex. The bleeding is usually attributed to tears in the cerebral veins at entry into the dural sinuses. The arachnoid-dural interface is normally freely separable, and even venous blood under low pressure dissects and accumulates between the dura and the arachnoid. The venous source of the blood explains the usual slow progression of the hematoma, but why bleeding occurs at all is not entirely clear. Probably there is in most cases some minor head trauma that is forgotten by the patient. These lesions are not as well seen on the lateral projection because their thickness in this direction is minimal, but they are rather large in the plane of the scan. They are not prone to produce a clear local increase in isotope concentration in this projection.

The isotope probably enters the subdural fluid from the extracellular fluid of the dura. The dura constitutes the lateral wall of the hematoma, and, since the dura does not have a BBB, the dural extracellular fluid rapidly equilibrates with plasma.

The patient may manifest simply an intractable headache and few local neurological deficits. Commonly the patient is brought in comatose, or intermittently in and out of coma. Since the brain fluid dynamics may change quickly and the ability of brain to adapt to the extracortical mass is already taxed when the patient is seen, these cases must be handled smoothly or fatal temporal-lobe herniation through the incisural opening in the tentorium and herniation of the cerebellar tonsils through the foramen magnum may occur quickly. These hematomas occur much more often in the chronically ill from any cause and particularly in alcoholics, but no one is immune. They must be suspected in any persistent headache or unexplained coma, and provision for work-up must be available around the clock. Even though an angiogram usually

Fig. 6 A very dense uptake of isotope is seen in the presence of a malignant glioma (glioblastoma), and the lesion is solitary. The BBB is highly defective in such lesions, and they are almost invariably visible.

Fig. 7 In the case of a subdural hematoma, a much thicker cranial halo is seen on the side of the lesion. In seriously suspect cases AP scans should be carried out both at about 1 hr and 4 to 5 hr after injection. The angiogram better defines this lesion showing an avascular area beneath the inner table and herniation of the brain away from the lesion. Unilateral subdurals are usually easily detected on the scan, but bilateral subdurals, which are reasonably common, may be more difficult to assess because the "crescent" sign may be quite symmetrical.

best settles the question, it is impractical and, indeed, unwise to subject all suspect cases to angiography, or cranial burr holes, particularly in the chronically debilitated.

The high incidence of positive scans in subdural cases suggests that this test should be available and applied on an emergency basis. There are occasions when the clinical picture is sufficiently clear and the patient so near death that immediate burr holes are indicated to decompress the brain. Although burr holes are technically simple and safe, this direct blind approach should be reserved for use by those with extensive clinical experience. Sometimes these lesions are bilateral, making it more difficult to assess asymmetry of cerebral surface uptake of the isotope. A unilateral lesion is simpler to detect because of its asymmetry, and, with good technique, it is almost always seen by the scan. When subdural hematoma is suspected on the scan, angiography should be carried out before craniotomy if time permits.

Cerebral Infarction

Cerebral infarction is signaled by the relatively rapid onset of a neurologic deficit within the course of minutes to a few hours, usually without severe headache or loss of consciousness. Usually the scan is not immediately positive, but it becomes positive after a few days and remains so for months. Since cerebral tumors commonly have a clinical picture resembling infarction, the scan is not of immediate help in differentiating tumor from simple infarction. Infarction is much more common. The shape of the scan defect may be helpful since it tends to fan outward peripherally and remain superficially on the surface of the hemisphere. The clinical course is different with the infarct generally tending toward improvement and tumors toward deterioration. The scan abnormality improves some weeks after an infarction and usually progressively worsens in the tumor. The angiogram frequently settles the issue showing immediate nonfilling of the infarcted area early in the arterial phase and retrograde arterial filling later. The tumor commonly shows early or delayed filling and emptying, a tumor "stain," abnormal vessels, and regional-vessel displacement.

Even though tumors, subdural hematomas, and infarcts are the lesions most commonly diagnosed by brain scanning, it is important to recognize that cerebral infections,⁵ head trauma,⁶ extradural hematoma, intracerebral hematoma,⁷ and many other lesions¹ are also demonstrable.

Scanning Technique

In the light of the previous discussion of clinical application, various aspects of technique can be considered. These are scanning agent, time of scanning, equipment, and future developments.

The previous discussion of scanning has assumed the use of Tc. This agent is distributed both as a blood-compartment label and an extracellular space

label, making it useful to demonstrate both BBB and blood-volume abnormalities in brain. Probably its affinity for blood protein explains its slow disappearance from blood. It would be desirable to have an agent that would leave the blood 1 to 3 hr after injection. For brain scanning its affinity for parotid, nasal mucosa, and choroid plexus is a disadvantage. Another major disadvantage is its short-lived parent, which limits the useful life of a generator to about 10 days. The generator thus requires frequent replacement and is correspondingly costly.

Indium-113m is also an excellent scanning agent produced from a long-lived ^{113}Sn parent ($t_{1/2}$, 118 days) and is correspondingly less expensive, particularly for laboratories doing few scans. It is more easily chelated than Tc and in the chelated form is a better extracellular fluid marker and thus a better demonstrator of BBB defects. It is also an excellent blood-pool marker when injected directly in the dilute HCl eluate from the generator.

Many other nuclides can and have been used. Any polar, lipid-insoluble compound tagged with a gamma emitter will work as a brain-scanning agent since no specific metabolic characteristic is required. The current nuclides were chosen for their physical-decay characteristics rather than for their specific tissue distributions.

The amount of nuclide that accumulates in a lesion is a function of the integrity of the regional BBB and the distribution space of the nuclide in the tissue. This distribution space is largely the extracellular space of the tissue with most scanning agents now common. This is probably not more than 20 to 30% of the total tissue space in most brain lesions. If the agent is actively taken up by the cells of the brain once it penetrates the abnormal BBB, very high concentrations accumulate in the brain lesions. An ideal agent would circulate in free solution in blood unbound to plasma protein and would disappear rapidly from the blood to minimize blood background. It would be of small molecular size to leak readily through a minimally defective BBB, but it should not pass through the normal barrier. In contact with brain tissue, it should be actively taken up. The compound with these properties would be ideal. If glycine were labeled with a gamma-emitting nuclide, such as ^{11}C , it should make a good tumor-scanning agent. This is impractical at present because of the cyclotron origin and short half-life of ^{11}C , but such biologically active specific molecules will be used in the future and should be much more efficient brain-scanning agents than Tc.

Commonly, Tc is given intravenously, and scanning is carried out 15 to 45 min later. This is a compromise, demonstrating both blood-compartment and BBB abnormalities. Ideally two scans should be carried out, one immediately after injection and another about 2 hr later to demonstrate blood distribution and extracellular fluid distribution, respectively. It is difficult to say what should be routine. In view of Fig. 1, it would seem reasonable to laterally scan the clinically suspect hemisphere in the 5 min or so immediately after injection to

map blood distribution and then do a full scan series (AP, PA, and both laterals) 2 hr later to see extracellular fluid.

A dual-probe rectilinear scanner is probably the best routine instrument for current scanning techniques. A single probe is useful, but it takes more than twice as long as the dual because of the need to reposition the probe. The dual probe more precisely compares opposing views of tissues containing the same levels of isotope. The single probe sees each projection at a different time with slightly different views and different isotope levels. Gamma cameras are expensive and are best suited to dynamic studies that require many sequential views. Their resolution is poor as one goes away from the collimator, and they do not offer sufficient advantages in brain scanning to warrant their routine use.

The future course of brain scanning will be directed at correcting its current limitations, most important of which are low spatial resolution, prolonged scanning time, and nonspecificity of the positive scan.

Currently resolution is limited to about 1 cm, and it is not likely to get better because of Compton scatter, patient movement, and collimator imperfections. Thus we cannot hope for the fine structural detail provided by radiography. Since truly fine structural detail seems precluded, future evolution of brain scanning will probably pursue the distribution of labeled, physiologically active compounds rather than the current nonspecific tracers. Some additional information could be gained simply by comparing the distribution of blood compartment and extracellular space markers. The prolonged scan times now make it difficult to study many uncomfortable or otherwise uncooperative patients who fail to remain immobile. Many of these limitations would be overcome if greater quantum utilization could be achieved. Now only an infinitesimally small fraction of the total number of gamma rays leaving the patient's head is actually used to form an image.

Future instrumentation breakthroughs will undoubtedly correct some of these limitations, but one improvement that could immediately enhance our ability to see subtle concentration differences in brain would be the removal of scalp and skull isotope contributions to the head scan. Over half of the cranial counts originate external to the arachnoid membrane. One method of subtracting these superficial counts has been suggested.⁸ The characteristic X ray of nuclides such as ^{113m}In or ^{123}I penetrate skull inefficiently; those seen by external detectors largely originate superficially in the skull and the scalp. These X rays could be used to subtract the gamma rays, which also originate superficially.

SCINTILLATION ANGIOGRAPHY

Serial camera monitoring of the brain during the initial pass of a bolus of Tc through the brain circulation can be done at no additional cost or risk. Scans delayed more than 10 min after injection are only slightly influenced

by regional tissue blood volume. In the very early serial films, regional blood volume (and rate of filling) alone is shown, and ischemic or highly vascular regions can be seen. Increased statistical noise makes the inherently low resolution of gamma imaging systems even worse in the short-exposure scintillation angiogram, but we can often gain additional useful information about the distribution of blood to and within the brain.⁹

The dose to brain on this initial pass could probably be increased by a brief occlusion of arterial supply of the noninjected arm and both legs for about 15 sec after release of the I.V. bolus. I have not seen this done, but it would probably be of interest here and in other regional studies, such as pancreas and kidney, where much of the organ uptake occurs in the first 1 to 2 min. Currently most of the isotope is allowed to distribute to tissues of no interest whatever, wasting isotope and irradiating tissues unnecessarily.

It is unlikely that I.V. scintillation angiography will replace radiographic angiography in the foreseeable future because of its inherently poor spatial resolution. Even if similar resolution could be realized, it would be of limited value because the I.V. bolus would visualize all the brain vessels, making interpretation highly complex.

SKULL RADIOGRAPHY

This test shows only bone or intracranial calcification; soft tissues are not shown. Since we are interested usually in the intracranial soft tissues, we must infer structural abnormality of brain tissue from whatever changes are seen in cranial calcium distribution. An example of this would be the effects of chronically elevated intracranial pressure on resorption of the inner table of the skull and dorsum sellae and the enlargement of the sella. Some tumors may partially calcify and become visible. To go into greater detail on the numerous subtle skull changes reported in the literature is beyond our scope here, but let it suffice to say that many of the changes observed are seen only late in the disease process and only indirectly are related to the brain disease.

Of all the physiological changes accompanying brain disease, changes in calcium distribution in the head must be very minor but assume clinical significance because they happen to be easily assessable by skull radiography. The same X-ray equipment and technique used for radiography of other systems are used without modification or special skills for skull films. Radiography accordingly is so widely available, atraumatic, inexpensive, and well accepted that it is very widely practiced. Even subtle, indirect relations to brain disease thus become important in patient management. Skull radiography requires only sufficient cooperation for the patient to remain in position for the brief exposure times.

ELECTROENCEPHALOGRAPHY

Electroencephalography is, like skull radiography, a very commonly performed ancillary neurologic diagnostic procedure. The test displays the electrical activity of the brain from about 0.2 to 100 Hz as observed from the scalp. The dominant frequency, wave forms, and location of the activity are defined. The test signifies CNS activity, and, from analysis of wave forms, some qualitative idea of the nature of the pathology can often be gained. The electrical changes accompanying CNS pathology are very easily monitored and thus become clinically important out of proportion to their fundamental role in brain function much as the ease of mapping of head calcium distribution makes the skull film of value in diagnosing brain disease even though it is only very indirectly related to the disease process.

Although the origins of many of the various wave forms remain obscure, a tremendous mass of empirical clinical correlations has been accumulated.¹⁰ The EEG is of greatest value in diagnosing and managing seizure disorders. It can detect cerebral tumors, residual effects of head trauma, many drug effects, disturbances in consciousness, and cerebral metabolic disorders. It is of value in establishing irreversible cerebral death. Many neurological diseases show no clinically useful correlation. The results are commonly nonspecific and in the management of any one case may be of restricted value even though statistically valid correlations can be shown in large groups of patients. The value of the EEG is enhanced by a conservative, informed interpretation. I have observed that the emphasis placed on the EEG in case management is less among those clinicians with extensive neurologic experience than those with limited experience. Medicolegal emphasis of the EEG interpretation is often particularly unrealistic.

The development of other diagnostic tests during the past two decades has caused the EEG to slip into a less dominant role in neurologic diagnosis. However, it will continue to be useful because it is atraumatic, causes minimal discomfort, is not very expensive, and is available in most medical facilities. It is gradually being replaced by other tests more directly related to brain disease. For the present, however, it serves a very important screening function. For this purpose it need not be highly specific but should only indicate the presence of an abnormality and a need for other studies more specifically demonstrating altered structure and function.

The EEG requires only moderate cooperation to allow placement of leads and immobility for brief intervals during the test. Since the equipment is expensive (\$6,000 to \$10,000) and a specialized technician is required, only centers doing a sufficient level of neurodiagnosis can justify a shielded room and the high cost of an EEG laboratory. Small hospitals in some areas are now serviced by mobile EEG laboratories.

ULTRASOUND ECHOENCEPHALOGRAPHY

To be clinically useful, ultrasound echoing must identify and localize structures of interest. Most echoes returning from the body are not identifiable with any definite structure, and only a few of the identifiable structures are of great clinical interest. In the head the identification of the third ventricle (Fig. 8) is of clinical value because its echo is related to the brain midline, and the position of this structure is thus of great clinical interest.

Why is the echo demonstration of brain midline of such great interest? The brain is quite fluid at body temperature and is constrained by the skull, tentorium, and falx. These are nonyielding structures and create three rigid compartments interconnected by the opening in the falx and the incisural opening in the tentorium (Fig. 9). Brain nearly fills these compartments, and any local increase in brain-tissue volume in one compartment results in displacement into the others in response to local pressure gradients. The right cerebral hemisphere, for example, moves into the left cranial compartment through the opening in the falx in the presence of an increased right hemisphere volume. This opening has an area much less than the medial surface of the cerebral hemisphere. The brain distorts and must be extruded through this rather broad orifice, resulting in an exaggerated lateral midline displacement. Thus the position of the brain midline becomes a sensitive indicator of changes in the relative volumes of the cerebral hemispheres. A disparity of hemispheric volumes is found in many conditions, such as subdural hematoma, any intrahemispheric mass, or asymmetrical hemisphere edema.

At present this midline detection is the only generally accepted use of echoing in brain. It is so simple, inexpensive, and atraumatic that it merits wide application as a screening test for hemispheric masses. One point of caution should be raised concerning the simplicity of midline detection. In the usual A-scan echo ranging of the third ventricle (Fig. 8), the midline is easily detectable by the skilled interpreter, but it requires critical probe positioning and gain settings. When the midline is displaced, interpretation often becomes more difficult. There is now on the market a small computerized echoing system that interprets the echoes via a solid-state logic system. This probably is more reliable than oscilloscopic interpretation¹¹ and should make it much more widely applicable since unskilled operators can use it profitably.

The cost of A-scan equipment is \$3500 to \$7000, and a user skilled and interested in its application is required. Because of its specificity of usefulness, it probably is not economical for most small medical installations. There is no sensation associated with the procedure; it is totally harmless, well tolerated, and the cost is small (\$15 to \$25).

Fig. 8 Ultrasound echoencephalography (A-scanning). In this technique the pulse is injected transversely into the head just above the ear and the pulse probe positioned to produce a visible echo from the near and far walls of the skull and from the third ventricle and noting the position of this midline echo complex relative to the near and far skull. A displacement of third ventricle from the cranial midline of more than 3 to 4 mm can usually be detected.

Fig. 9 Brain distortion from an expanding mass in the right cerebrum. The cranial cavity is rigidly compartmentalized by the midline falx cerebri and the tentorium cerebelli. When an inequality of cerebral hemisphere volume is produced in disease, the brain must herniate through the opening in the falx. Since this is a smaller cross-sectional area than the medial surface of the hemisphere, an exaggerated lateral displacement takes place. This same mechanism may allow displaced midline vasculature to be seen on high-resolution AP isotope scans. Herniation of the medial side of the temporal lobe can also take place downward through the incisural opening causing angulation of the third and sixth cranial nerves (3N and 6N) and displacement of the pineal gland (X). SR is the sphenoid ridge.

PNEUMOENCEPHALOGRAPHY

Pneumoencephalography renders visible the intracranial compartments containing CSF by replacing CSF with gas, usually air. It thus defines the ventricles and subarachnoid spaces.^{1,2} The ventricles are visualized better than the subarachnoid spaces because they accumulate larger confluent volumes of gas. The CNS is not directly visualized, and changes in its volume and position must be inferred from changes induced in CSF compartments. Thus the pneumoencephalogram (PEG) is of value in those conditions causing a change in brain volume or a displacement of brain structures. It is commonly performed in

seizure disorders to demonstrate regional atrophy and is often used to give an overall structural assessment.

Even though planigraphic apparatus and special chairs for positioning the patient are commonly used to provide greater information, a useful PEG can be carried out with no special apparatus beyond an ordinary medical X-ray machine. A skilled pneumoencephalographer is required to inject the air and immediately interpret where it is going, how much is needed, and what views are required.

Even fractional pneumoencephalography (small injected air volumes) causes some degree of discomfort, usually headache, which may persist from hours to several days. If cases for pneumoencephalography are properly chosen for tolerance of stress, it is not a very dangerous test despite its immediate discomfort. Patients seriously considered to have an intracranial mass should not have a PEG since brain-stem and cerebellar herniation may occur. It has been shown that PEG is not as dangerous in the presence of a mass as had been previously thought, but conservatism dictates that as little manipulation as possible should be carried out with a known brain mass. If a mass is suspected, angiography and radioisotope scan are indicated since they cause no tissue displacement in the head. If a supratentorial mass is suspected and visualization of the cerebral ventricles is desired, usually air is injected directly into the ventricles (ventriculography) to decompress the brain from above the tentorium and foramen magnum and thus minimize herniation, distortion, and compression of vital midbrain and medullary centers.

Since a skilled physician and at least 10 films are required, pneumoencephalography is rather expensive (\$150 to \$300). The PEG provides almost purely structural information, but in certain circumstances altered function may be suggested. One example is the failure to fill the cortical subarachnoid spaces, indicating that CSF is not circulating normally over the hemispheres. The demonstration of the failure of labeled albumin to circulate over the hemispheres during cisternography more directly exhibits this altered physiology despite its inherently poor spatial resolution.

ANGIOGRAPHY

Angiography refers here to serial skull films after the rapid injection of a bolus of iodinated contrast medium into either the carotid or the vertebral arterial supply of the brain. Cerebral angiography is best thought of as an opacification of the blood passing through the injected artery during 1 sec. Thinking of the test as visualizing the moving bloodstream rather than static vessels aids in understanding many of the dynamic phenomena seen in rapid-sequence films.¹³ This opacified bolus passes through the brain compartment in 6 to 10 sec. Rapid serial films add a time dimension to the structural

data of single-shot films and allow an estimate of regional and overall brain-blood flow.

Because of the variety of conditions in which it can provide information, angiography is of great clinical usefulness, so useful that there is a tendency, after some proficiency in its performance is achieved, to apply the technique too freely. Even in the best of hands, angiography is too hazardous, time-consuming, and expensive to be used as a screening test. Because of these drawbacks in the integration of angiography into total patient management, we should use the test judiciously and only when less hazardous screening tests point to its need.

Of all the ancillary tests under consideration here, the indications for cerebral angiography most closely parallel those for isotopic scanning. Because of this overlap and because it is potentially hazardous, the clinical indications will be briefly discussed, and some of the technical sources of complication will be considered in detail.

Clinical Indications

Since cerebral angiography demonstrates the passage of a bolus of opacified blood through the brain, it is useful in those suspected conditions where the location and rate of transit of opacified blood would be of interest. These are (1) abnormalities of the vascular lumen (stenosis, occlusion, and aneurysm); (2) abnormalities of vascular architectural patterns (tumor); (3) displacement of vessels (tumor, local edema, and hematoma); and (4) abnormalities of timing of regional transit (tumor and infarction).

Ordinarily angiography is not considered until all the available information from less hazardous tests has been obtained. This includes the clinical evaluation, skull films, echoencephalography, and scan. A preliminary chest film is also mandatory to rule out lung malignancy. Known elevated intracranial pressure is no contraindication to angiography, and indeed there are very few specific contraindications other than an established allergy to iodinated compounds.

Complications

How hazardous is cerebral angiography? The published incidence of serious complication is highly variable (0 to 4%). Published reports of complications probably reflect an unrealistically low incidence since such occurrences are not usually reported. Carotid angiography rarely results in death, but sometimes it causes a persistent hemiplegia. The possibility of serious morbidity is probably greater here than in any other common diagnostic test. Most complications are probably due to operative technical factors¹⁴ and not to direct adverse effects of the contrast agent. Sensitivity reactions to contrast media are now quite unusual. Some sources of complication are (1) dissection of obliterating intimal flap by the jet stream of injected medium, (2) discharge of clot from needle or catheter, (3) mural thrombus with embolization from

Fig. 10 Some of the common causes of complications resulting from common carotid-artery angiography. These factors are discussed in the text.

puncture site, (4) obliteration of arterial lumen by needle pressure, (5) hyperosmolarity of contrast medium, (6) injection into some extraarterial compartment, (7) injection of wrong material, and (8) postwithdrawal hematoma. The first four factors are sources of serious complications and are diagrammatically illustrated in Fig. 10. The last four factors, although sources of concern, seldom cause permanent effects.

It is difficult to estimate the relative importance of these various technical factors, but one source of complications is the production of an intimal flap as shown in Fig. 10(a). The intima on the back wall of the artery is traumatized during cannulation, and, when the high-velocity injection takes place, fluid dissects under the intima creating a flap that obstructs the forward passage of blood. This probably results more often when a sharp needle is used for the angiogram, and for this reason only a blunt catheter or cannula should be threaded up the artery before injection to minimize intimal trauma. The discharge of a clot from the needle or catheter produces an embolus that is stopped somewhere in the cerebral hemisphere [Fig. 10(b)]. Unlike the lung, which is more tolerant of such small emboli from intravenous injection, the brain, if a vital region is infarcted, may be permanently damaged.

There may be substantial damage to the arterial wall from puncturing, particularly if inexpert multiple passes are made through the artery. The traumatized intima can become a site for mural thrombus formation with

possible subsequent embolization from the puncture site [Fig. 10(c)]. Such emboli pass directly into the brain and create a hazard in the same way as the clot discharged from the needle or catheter. The mural thrombus, however, may be much larger.

When the artery is being punctured, the only guide the angiographer has is to palpate the pulsating common carotid and to use this pulsation for directing the puncturing cannula. When a needle large enough to do a satisfactory angiogram approaches the artery, it first collapses the wall, bringing the top and bottom surfaces into apposition [Fig. 10(d)]. This obliterates the pulse distal to the point of compression and presumably stops the common carotid flow. If the inexperienced angiographer is uncertain of what he is doing, it is possible that the artery may be held obliterated for prolonged periods during the attempted arteriopuncture. Although unilateral compression of the common carotid for a brief period is well tolerated by most younger people, some older people do not tolerate even brief carotid compression, particularly if the opposite carotid system is inadequate.

Because a highly specialized physician is required and between 20 and 40 films are usually taken with expensive specialized apparatus, the cost of cerebral angiography is high (commonly \$200 to \$400). Cerebral angiography is a highly valuable but potentially hazardous and costly procedure. If maximum information is to be derived, it is a highly complex, specialized procedure and is not widely available. Because it requires specialized skills and apparatus, the occasional angiographer should be discouraged and referral made, when possible, to centers where the procedure is routine. Angiography is the logical sequel to a positive brain scan, but whether or not it is warranted is up to the managing physician.

In conclusion, brain scanning is a valuable clinical test to which every neurologist should have access. It constitutes about half the work load of most general departments of nuclear medicine. It is of use in the detection of focal lesions resulting in increases of permeability of BBB or of regional blood volume. This includes most classes of focal pathology. It is useful as a diagnostic test in its own right, but it is particularly good as a screening test for angiography, to which an abnormal scan will usually lead. Its limited spatial resolution requires supplementation by radiographic techniques.

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ISOTOPE CISTERNOGRAPHY

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ABSTRACT

The use of radiopharmaceuticals in studying cerebrospinal fluid dynamics provides physiologic data heretofore unobtainable. In combination with the anatomic information obtained by pneumoencephalography, a more scientific evaluation of hydrocephalics for neurosurgical treatment is possible.

Quantification of scan or camera imaging, the use of newer radionuclides, such as ^{111}In and ^{123}I , and greater experience collating present criteria with postshunt results will improve patient selection even further.

The use of radioactive pharmaceuticals in tracing cerebrospinal fluid (CSF) dynamics has gained widespread use in a variety of clinical situations as a complementary neurodiagnostic procedure. The major applications of this technique have been in the investigation of (1) CSF leaks, (2) CSF dynamics in patients with hydrocephalus, (3) CSF dynamics after surgical shunt procedures, and (4) in the evaluation of posterior fossa tumors.¹⁻⁴ This technique has also been used to investigate patients with possible subarachnoid blocks in the cervical, thoracic, or lumbar-spine regions.⁵ The term "isotope cisternography" encompasses (1) radionuclide ventriculography, in which the ventricles and cerebral subarachnoid spaces are imaged; and (2) myeloscintigraphy, in which only the spinal subarachnoid space is investigated. This paper will deal mainly with the applications of isotope cisternography in the evaluation of patients with hydrocephalus for possible surgical shunt procedures and will attempt to put the isotope cisternogram in its proper perspective in relation to other neuroradiologic diagnostic techniques.

NORMAL CSF DYNAMICS

Most workers believe that CSF is formed mainly by the choroid plexus within the ventricles and that it flows into the subarachnoid spaces, circulating freely until it is finally absorbed partly or completely at the arachnoid villi.⁶ Also, it is believed that a smaller fraction of CSF is formed by the subarachnoid lining. When the ventricles enlarge, it is thought that there is also reabsorption of the CSF through the subarachnoid lining itself. Normally the reabsorption by the Pacchionian granulations of the CSF, including its protein content, plus the molecular diffusion of the fluid through the subarachnoid lining, creates a bulk flow from within the ventricles out and over the convexities of the brain. When the ventricles enlarge, as in communicating hydrocephalus, it is believed that there is a net increase of protein flow into them by way of their increased reabsorptive surface, and this reverses the normal flow, causing increased ventricular filling and stasis of the radioactive tracer. There are thought to be intermediate stages when, during the period of compensation, the initial flow may be directed into the ventricles but then reversed, moving the tracer out of the ventricles and distributing it over the cerebral hemispheres. The length of time during which a radiopharmaceutical stays within the ventricles is critical in the interpretation of derangements of CSF dynamics.

RADIOPHARMACEUTICALS

Many agents have been used for radionuclide cisternography. Studies in dogs have shown that a variety of agents (Table 1) have a two-compartment

TABLE 1
CLEARANCE RATES OF RADIOPHARMACEUTICALS
USED IN ISOTOPE CISTERNOGRAPHY

Agent	Nuclide	Clearance time
Ions (TcO_4^-)	^{99m}Tc	Too rapid
Chelates (DTPA)	^{99m}Tc , ^{169}Yb , ^{67}Ga	Intermediate
Inulin	^{99m}Tc , ^{51}Cr	Intermediate
Albumin	^{99m}Tc , ^{131}I	Intermediate
Colloids	^{99m}Tc , ^{67}Ga	Too slow

exponential clearance pattern.⁷ The half-time of the first clearance component was 18 to 25 min except for pertechnetate, which was 0.9 min. The clearance half-time of the second component was 5 to 10 hr except for colloids, which were slower. Therefore the ions and the colloids are unsatisfactory because of

TABLE 2
RADIONUCLIDES USED IN ISOTOPE
CISTERNOGRAPHY

Radionuclide	Physical $t_{1/2}$	Most useful gamma emission, keV
^{123}I	13.3 hr	159
^{131}I	8.05 days	364
^{99m}Tc	6.05 hr	140
^{113m}In	1.7 hr	393
^{111}In	2.81 days	173, 247
^{51}Cr	27.8 days	320
^{169}Yb	31.8 days	177, 198

their clearance rates, but the chelates, inulin, and albumin preparations are more or less the same and, on the basis of clearance, seem equally suitable for CSF studies. Because of their physical characteristics (Table 2), ^{111}In (Ref. 8) and ^{123}I appear to be the most nearly ideal nuclides presently available for isotope cisternography, whether tagged to chelates, inulin, or albumin. Since cases of aseptic meningitis have been reported as a result of the use of albumin with low specific activity, even though the amount injected has been as low as $375\text{ }\mu\text{g}$, it seems reasonable to avoid this potential hazard by using chelate or inulin preparations if at all possible. The approximate radiation doses to the spinal cord under normal and obstructive conditions⁹ are listed in Table 3.

ISOTOPE CISTERNOGRAPHY IN HYDROCEPHALUS

A simplified classification of hydrocephalus is listed in Table 4. The one condition that has caused such recent interest because of the dramatic improvement after shunting is a communicating hydrocephalus with CSF pressure, frequently referred to as "occult" hydrocephalus. The syndrome associated with this condition was first described in 1965.¹⁰ It consists of progressive dementia, psychomotor retardation, unsteadiness of gait, and urinary incontinence associated with communicating hydrocephalus and normal CSF pressure. There is some confusion in the literature because, in addition to the occult communicating hydrocephalus, there is probably an even larger group of patients with "overt" communicating hydrocephalus secondary to trauma, hemorrhage, meningitis, or surgery; these patients may also improve dramatically after shunting. They frequently have normal CSF pressure at the time they are discovered, the intraventricular pressure having been initially increased but having become normal as the ventricles enlarged.

TABLE 3*
LUMBAR SPINAL SURFACE DOSE (RADS)
FROM 100 μ Ci*

Nuclide	Condition		Cervical block
	Normal	Hydrocephalic	
^{131}I	7.24	12.3	58.7
^{123}I	1.1	1.93	2.59
^{99m}Tc	0.27	0.46	0.54
^{113m}In	0.75	1.27	1.96
$^{111}\text{In}^\dagger$	0.6	1.02	1.57

*Abstracted from Harbert et al.⁹

†Estimated from calculations used in Harbert et al.⁹ Tissue outside the range of the conversion electrons (>0.5 mm) receives a significantly lower dose; e.g., spinal cord, 0.04 rad/100 μ Ci.

TABLE 4
CLASSIFICATION OF HYDROCEPHALUS

Internal obstructive (noncommunicating):
Intraventricular obstruction at or above the level of the fourth ventricle.
External obstructive (communicating):
Block in the subarachnoid space.
Normal-pressure hydrocephalus.
1. Overt (macroscopic).
2. Occult (microscopic).
Atrophic:
1. Generalized.
2. Localized.

TECHNIQUES

The radiopharmaceutical is administered by lumbar or cisternal puncture or through an existing surgical shunt. This lumbar-puncture technique fails from 11 to 27% of the time,^{11,12} and in these failures the radioactive material is seen in recognizable patterns. These patterns are (1) epidural or Christmas tree; (2) subdural or railroad tracks; (3) spinal ligament or midline immobile collection; or (4) a combination, probably the most common. One of the probable reasons

for failure is that the bevel of the needle is positioned partially within the subarachnoid space. When injected the radiopharmaceutical as well as some CSF fill the potential subdural or epidural spaces. There appears to be no relation of these failures to lumbar punctures or pneumoencephalograms done 2 weeks, 1 week, or 2 days before the cisternogram attempt.¹¹ The patient should be kept prone for several hours after injection.

Immediately after the material is introduced, either scan or camera images should be obtained of the injection site and then of the head within the first 6 to 8 hr. Further views of the head are taken at 24 to 96 hr.

Although not normal, it is not unusual for the material to enter the ventricles within the first 8 hr. If it gets into the ventricles and persists there after 24 hr, this is definitely abnormal.

Normally the tracer reaches the basal cisterns by 3 hr, the frontal poles and Sylvian fissures by 6 hr (Fig. 1),* and is over the convexities of the brain and in the parasagittal regions by 12 to 24 hr (Fig. 2).

The scan findings in hydrocephalus have recently been summarized in two outstanding articles.^{3,13} Abnormal uptake (as in subarachnoid cysts, porencephalic cysts, fistulae, and surgical defects) as well as obstructions to normal tracer flow to any CSF space can be delineated by camera or scan images.

With obstructive, noncommunicating hydrocephalus, there is no ventricular filling, and tracer activity is seen over the convexity of the brain and in the parasagittal areas.

In the classic communicating occult hydrocephalus with normal pressure, the ventricles fill early (Fig. 3) and the tracer remains in them for at least 48 hr (Fig. 4). There are other patients with rapid intraventricular filling who have either absent or markedly diminished intraventricular activity by 24 hr. Some of these patients have had shunt operations in the past with no benefit. These are thought to represent a compensated variation of normal-pressure hydrocephalus and will not improve with shunting procedures. Because subjective interpretation of the images has been found wanting, several workers have described methods for quantification of tracer clearance in an effort to separate these groups with greater objectivity.

Curl and Harbert¹⁴ measured the counts coming from the whole head and subtracted a thigh count which they felt was equivalent to cranial vascular activity. Normal values at 24 hr were 40 to 80% of the 6- to 12-hr peak and 25 to 40% at 48 hr. The patients with communicating hydrocephalus had their peak delayed to 24 to 30 hr, and clearance of radioactivity in the head was also delayed. Interestingly, after shunting had been performed in this group, the peak as well as the clearance rate was faster than in the normal group.

*Figures 1 to 4 are from A. E. James, Jr., et al., Normal-Pressure Hydrocephalus: Role of Cisternography in Diagnosis, *J. Amer. Med. Ass.*, 213 (1970).

Fig. 1 Normal activity in basal cistern at 6 hr.

Fig. 2 Normal distribution of activity over convexities at 24 hr.

Fig. 3 Normal-pressure hydrocephalus with activity already seen in the ventricles at 1 hr.

Fig. 4 Normal-pressure hydrocephalus with continued intraventricular stasis at 24 hr.

DeBlanc et al.¹⁵ found that patients with a high ventricular activity at 6 hr had a greater probability of having residual intraventricular activity at 24 to 48 hr. These workers concluded that the quantitative clearance rate from the ventricles alone was superior to using whole head counts.

Sanders and Cohen¹² measured radioactivity in the entire head at intervals up to 5 days and found the normal clearance half-time to be 1.6 ± 0.2 days. These data were compiled without background subtraction. Five patients had transient intraventricular filling but with normal clearance times. Not all patients with prolonged clearances exhibited ventricular filling. One such patient, with a clearance half-time of 3.4 days, had a shunting procedure and improved.

ROLE OF PNEUMOENCEPHALOGRAPHY

Because of the difficulties frequently encountered in differentiating the occult normal-pressure hydrocephalus syndrome from brain atrophy, a review of the pneumoencephalographic findings has been made in the hope of establishing more precise criteria for diagnosis of this entity.

The pneumoencephalogram is not without morbidity to the patient. It is not always possible to differentiate clinically those patients with neurologic disturbances due to vascular insufficiency, unsuspected tumors, or subdural hematomas from those patients with the occult normal-pressure hydrocephalus syndrome. For this reason it is worth while to consider the use of the cerebral radioangiogram (CRAG) and the brain scan as the initial neurodiagnostic procedures in the evaluation of these patients. If these studies suggest tumor or subdural hematoma, cerebral angiography should be performed to better define the nature of the abnormality and to select patients for later pneumoencephalography with minimal risk. The following classification of pneumoencephalographic findings parallels that outlined in Table 4.

Internal Obstructive Hydrocephalus

Internal obstructive hydrocephalus indicates an obstruction to the flow of CSF at or above the outlet of the foramina of the fourth ventricle. In such cases the extent of filling of various portions of the ventricular system will depend on the site of block, and it may be necessary to perform ventriculography. In these patients there should be no obstruction to the passage of air over the convexity. However, we may see an unexplained decrease or absence of filling of the subarachnoid spaces over the convexity.¹⁶

External Obstructive Hydrocephalus

External obstructive hydrocephalus indicates an obstruction of the CSF pathways in the subarachnoid cisterns. In this group of hydrocephalics, the

various ventricular and subarachnoid abnormalities and their prognostic significance are:

1. Lateral ventricles and third ventricles. There is no consistent correlation between the degree of enlargement and the patient's clinical improvement.¹⁷⁻¹⁹ Indentation along the floor of the third ventricle by an ectatic basal artery has been described as another etiologic factor in normal-pressure hydrocephalus. Improvement in two patients with this finding has been reported,²⁰ but full understanding of its significance awaits further clinical correlation.

2. The area of indentation of the caudate nucleus into the lateral ventricle, which is normally convex medially, has been described as being either flattened or convex laterally in some patients. There appears to be a greater correlation with clinical improvement in these patients.¹⁷

3. The corpus callosal angle, representing the roof of the anterior horns as measured on the brow-up, AP view is normally between 130 and 140°. An angle of 120° or less has been described in patients with normal-pressure hydrocephalus. The response to ventricular shunting in these patients appears to be better than in those patients with a normal angle measurement.¹⁹

4. Temporal horn. It has been reported that in patients who have disproportionate dilatation of the temporal horns as compared with that of the lateral ventricle, there is a greater incidence of clinical improvement after shunting.^{17,21}

5. Fourth ventricle and aqueduct of Sylvius. Heinz, Davis, and Karp¹⁸ feel that patients with a disproportionately enlarged fourth ventricle and aqueduct have a good chance for clinical improvement after shunting.

6. Subarachnoid findings. Although the pneumoencephalogram may demonstrate an anatomic block at the incisura, this does not necessarily indicate a functional block at this level. The absence of air above the level of the incisura may occur with obstruction at sites between it and the sagittal sinus. Air may be present in the Sylvian and/or interhemispheric fissures or in the subfrontal sulci in a convexity block.^{17,18} These findings are more commonly seen in occult normal-pressure hydrocephalus than in a pure incisural block.

Atrophic Hydrocephalus

In atrophic hydrocephalus we may see enlargement of the ventricles. Associated with cortical atrophy, there may also be localized or generalized widening of the sulci of the convexity. We may gain greater information from the pneumoencephalograms if follow-up frontal and lateral films are obtained at 12, 24, and 48 hr, and even longer if necessary, to evaluate the rate of absorption of air.

Pneumoencephalography is valuable for demonstrating the anatomy of the ventricular system and the subarachnoid spaces; however, little information on the physiology of CSF flow is obtained.

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NEUROSURGEON'S VIEW OF THE DIAGNOSTIC ROLE OF RADIONUCLIDE IMAGING

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ABSTRACT

A rational approach to the use of scanning techniques in relation to nonisotopic methods is outlined. The risks of the various studies are pointed out and balanced against information to be provided. A neurosurgeon's view of the use of isotopes in the study of intracerebral neoplasms, inflammatory processes, vascular lesions, trauma, hydrocephalus, and ischemia is presented, and the various problems that he encounters are discussed.

The formulation of a rational approach to the evaluation of neurologic problems is difficult in many respects. Modern neurosurgical techniques necessitate a precision in localization that is not often afforded by even the best history and neurologic examination. In addition, many neurologic and neurosurgical patients are, because of their basic disease process, unable to relate a good history.

Fortunately, we have at our disposal radiologic and isotopic techniques which, when used alone or in combination, ordinarily result in correct diagnosis and localization. However, each procedure that affords more information may offer liability to the patient, in the form of increased anxiety, morbidity, and mortality, besides increased cost and expenditure of time. In assessing this liability and weighing it against information to be provided, the physician must exercise clinical judgment based on experience.

This paper will show the practicing clinician the value and limitations of radionuclide techniques compared to nonisotopic, radiographic studies.

A radioactive tracer for brain-tumor localization was first described in 1948, but radionuclide imaging of the brain did not become a widely used clinical tool until the late 1950's. At that time technical improvements had made it a safe, simple, and accurate diagnostic method, particularly for determining which patient should have further study, usually in the form of arteriography, pneumoencephalography, or ventriculography. There is essentially no morbidity

or mortality associated with brain imaging, and, in fact, its simplicity is such that it may be performed on an outpatient basis. A radionuclide imaging study costs \$140 in our institution and includes a blood-flow study plus any late views.

In contrast, the possibilities of vascular damage from the needle puncture (even with modern catheter techniques), allergic reaction to the contrast material, local hematoma, stroke, and death do exist during and after arteriography. Approximately 2% of cerebral arteriograms¹ involve a complication associated with morbidity. In addition, arteriograms are associated with substantial anxiety and discomfort, and the cost for a four-vessel study is \$300 to \$400 plus the expense of hospitalization. Pneumoencephalography and ventriculography involve considerable morbidity, and the latter requires an operative procedure for the introduction of air and contrast material. It is easy to understand why brain scanning, with its accuracy and lack of morbidity, has become a major tool in the diagnosis of neurologic disease. However, minor procedures such as imaging do not always obviate the need for the major procedures since the latter often offer significant additional information.

Radionuclide imaging provides invaluable information in a variety of neurologic disease processes. Imaging is useful in depicting the size and location of primary and metastatic brain neoplasms, inflammatory processes, vascular malformations, traumatic sequelae, including extracerebral collections and cerebrospinal fluid fistulas, and in evaluating hydrocephalus and shunt function. Of lesser interest to the neurosurgeon is the role of imaging in occlusive vascular disease.

Radionuclide techniques do not necessarily depend on indirect evidence afforded by displacement or deformity of vascular structures and air-filled spaces. Rather, they rely on changes in blood-brain permeability, and in some cases increased vascularity, to detect an abnormality. Frequently imaging accurately portrays the position and extent of the tumor because the tumor bed itself is visualized.² Generally, an abnormality on a radionuclide imaging study is manifested by an increased uptake; occasionally, as in the case of cystic lesions, decreased uptake may be significant.

BRAIN TUMORS

Maynard³ reported that brain scanning depicts from 65 to 95% of neoplasms. This large variation may be due to the relative percentage of different neoplasms in a series, to different techniques, or to different criteria for positivity. Accuracy may be improved by taking additional views, such as a vertex projection, and by utilizing chemical blocking agents, such as atropine and perchlorate. In the same chapter Maynard reported an accuracy in depicting neoplasms of 46.9% for plain skull films, 92.3% for arteriograms, and 93.9% for air studies.

Wang,⁴ reporting the diagnostic findings in 518 cases (44 histologically proven tumors), found that 86% of the scans were positive or questionably positive, and 74% of electroencephalograms, 45% of echoencephalograms, 33% of plain skull films, 83% of arteriograms, and 100% of pneumoencephalograms were positive. The combination of scan, electroencephalogram (EEG), and skull films failed to demonstrate the presence of a tumor in only 2 of 44 cases, paralleling the accuracy of arteriography.

The percentage of lesions demonstrated by radionuclide imaging of the brain will be more or less the same regardless of which radionuclide is used and what instrumentation is available. At the University of California, San Francisco, 12 mCi of ^{99m}Tc -labeled pertechnetate and a Nuclear Chicago Pho/Gamma Camera are generally used.

The variables that determine the percentage of lesions demonstrated depend principally on the type of tumor and its location. Also, the apparent high accuracy of pneumoencephalography and arteriography may be due, at least in part, to the prior use of imaging as a screening procedure.

Radioisotope images are more than 90% accurate in revealing meningiomas (Fig. 1), malignant glial tumors (Fig. 2), and metastases³ (Fig. 3). They are less accurate in revealing more benign and slow-growing tumors, such as low-grade astrocytomas, acoustic neuromas, pituitary adenomas, pinealomas, and cranio-pharyngiomas. Ninety-five percent of posterior-fossa neoplasms (Fig. 4) may be detected, although midline lesions smaller than 1.5 to 2 cm may be missed.

DeLand and Wagner⁵ reported 86% positive scans in a series of patients with eighth-nerve tumors. In the same series 16% of arteriograms, 60% of pneumoencephalograms, 67% of cisternal myelograms, and 38% of routine tomograms were positive. We have found posterior-fossa myelography with Pantopaque to be by far the most accurate test in delineating tumors along the eighth nerve.

False-positive findings for tumor may occur with craniotomy defects (Fig. 5), skull fracture, malignant skull or scalp tumors, hematomas and abrasions, and benign skull lesions, such as fibrous dysplasia, hemangiomas, and hyperostosis frontalis interna. They may also occur if the patient's saliva becomes contaminated with pertechnetate tracer.

Usually, radionuclide uptake has markedly diminished by 2 to 3 months after a craniotomy for tumor, and deep labeling (Figs. 3 and 4) thereafter generally indicates tumor recurrence.⁶ It is interesting that a positive finding on a radionuclide study believed to be secondary to an operative defect has been reported 22 years postcraniectomy.

We are especially interested in evaluating the response of brain neoplasms to systemic chemotherapy (Fig. 2), and we have used serial scintiphotographic studies⁷ for this purpose. In 64% of the cases to date, the scintiscans have agreed with our clinical evaluation of the patient; 21% of the studies have been indeterminate and 15% have disagreed with clinical findings. We have also found scintiphotography to be useful in repeated monitoring of the course of tumors and their response to radiotherapy.

Fig. 1 Meningioma. This patient, like most of those illustrated in this paper, was studied after ^{99m}Tc -pertechnetate had been injected as an intravenous bolus. Rapid-sequence anterior-view scintiphotos were obtained at 2-sec intervals by replay from a data storage system. Beginning 9 sec postinjection, filling of the carotid arteries, middle cerebral arteries, and eventually the venous drainage can be observed. In the 13- to 15-sec exposure, there is an area of abnormal filling parasagittally in the right hemisphere which becomes much brighter between 15 and 17 sec as this radioactivity is drained to the superior sagittal sinus. Static scintiphotos confirm that there is an abnormal area of capillary permeability parasagittally in the right posterior parietal area. It is better seen in the right lateral than in the left lateral because there is less intervening normal structure between the area with abnormal localization of the radiopharmaceutical and the surface. The mouth is brightly labeled by saliva that was secreted after uptake of pertechnetate by the salivary glands. Perchlorate, given soon after administration of the pertechnetate, caused a discharge of labeled saliva from the salivary glands and a discharge of pertechnetate from the choroid plexus where it might be difficult to distinguish from abnormal labeling within the brain.

This study is a typical demonstration of a meningioma to the timing of the abnormal vascular filling somewhat after filling of the middle cerebral system. The delay is related to the external carotid source of this tumor's vascular supply. An AVM would be expected to fill earlier than the middle cerebral arterial filling and possibly be associated with a steal from other intracranial vasculature. Gliomas and other primary brain tumors tend to be less vascular than meningiomas.

Angiography is especially valuable for selectively delineating the blood supply to certain intracranial tumors, particularly meningiomas. It is occasionally negative in patients with parietal tumors, and, in these, pneumoencephalography is necessary for definitive diagnosis.

Fig. 2 Astrocytoma: subtotally resected Sept. 6, 1969, progression after radiation therapy, bischloroethylnitrosylurea (BCNU) protocol, starting Dec. 2, 1969. This figure illustrates the response of an astrocytoma to chemotherapy during a 2-year period. Left lateral and posterior views are shown on each study date for comparison. On Dec. 2, 1969, the tumor was readily visible in the left parietal region with extension nearly to the midline. It subsequently became more difficult to distinguish in the studies in 1970 and disappeared completely in the study of October 1971. There was corresponding clinical improvement. Therapy was with BCNU given intravenously every 2 months.

ABSCCESS

Despite the introduction of numerous new antibiotics and their use in systemic and mastoid disease, the incidence of brain abscess has been unchanged for several decades. Davis and Potchen⁸ reported a series of 50 patients with brain abscess; 16 patients had brain scans, 100% of which were positive. Technically good imaging procedures will be positive in the great majority of brain abscesses (Fig. 5) except for very small lesions. However, the specific findings are few, and local areas of cerebritis or meningitis may produce radionuclide localization in the absence of a discrete abscess. A negative radionuclide imaging study in the work-up of an intracranial lesion militates strongly against an abscess.

TRAUMA

In the evaluation of trauma and its sequelae, radionuclide imaging has several uses. The crescent pattern of uptake associated with subdural hematoma⁹ is well

Fig. 3 Patient with metastatic melanoma on cischloroethylnitrosylurea (CCNU) and vincristine therapy. Rapid-sequence anterior-view scintiphotographs showing symmetrical filling of the carotids, middle cerebral arterial arborizations, and venous drainage. Midline vasculature is not definitely displaced. The superior sagittal sinus is well filled between 20 and 28 sec. Static scintiphotographs show several focal abnormalities in the left hemisphere in the anterior, posterior, and left lateral views. Abnormal deposition of the radioactive tracer is suggested also in the right hemisphere in the posterior view but is not as definite as the findings in the other hemisphere. Abnormal labeling near the vertex in the right lateral view may be a focal abnormality in the left hemisphere which is seen through the thickness of the head. The faint, stippled labeling abnormality seen in multiple areas here is typical of the findings in metastatic malignancy involving the cerebral hemispheres.

described. However, this pattern is characteristic not only of subdural hematoma but also of craniotomy defects, scalp contusions, metastatic lesions, cerebral vascular ischemia, granulomatous pachymeningitis, Paget's disease, and acute epidural hematomas.

We have made only limited use of brain imaging in acute head trauma. In the detection of chronic subdural hematoma,¹⁰ however, brain imaging is 80% accurate (Fig. 6), being positive more often in patients with older lesions. Lesions less than 10 days old are positive in 50% of patients, and lesions greater than 10 days old are positive in 91%. The presence of well-formed membranes correlates well with the finding of an image abnormality. Perfusion studies are of considerable additional benefit. Good arteriography is definitive in suspected fluid collections except for an occasional childhood case necessitating pneumoencephalography.

Cerebrospinal fluid (CSF) fistula¹¹ is an uncommon but troublesome and elusive sequel of head injury. Not only can it relate to head injury but it may also be spontaneous and associated with the empty sella syndrome.

Leaks of CSF occur in approximately 2% of head injuries; within a week 50% of these will have stopped spontaneously. However, if untreated, 25 to 50%

Fig. 4 Cystic cerebellar astrocytoma. Rapid-sequence posterior-view scintiphotographs after intravenous injection of the pharmaceutical demonstrate normal vascularity without evidence of vascular filling in the area of the posterior-fossa abnormality which is seen in the static photographs. The static scintiphotographs show a poorly defined midline abnormality located anteriorly in the posterior fossa. It is somewhat better seen in the left lateral than the right, but the posterior view definitely shows that its location is midline. This posterior view was obtained with the head slightly flexed so as to throw the posterior fossa into superimposition over normal anterior brain areas, allowing demonstration of any capillary permeability increase within the posterior fossa.

of the remainder will result eventually in meningitis. The site of the leak must be localized accurately to plan operative closure. In some cases it is difficult to ascertain if the leakage is truly CSF, and clinical localization of the exact site may be impossible. Pneumoencephalography and Pantopaque studies have proved to be unsatisfactory for this task, and tomograms of a fracture do not necessarily establish it as the site of dural and arachnoidal interruption. In an effort to correlate the site of leakage and intracranial anatomy, numerous techniques have been tried, such as dye methods, fluorescence studies, and, more recently, brain imaging and isotope cisternography.¹²

The favorite sites for CSF fistulae are the frontal sinus, the lamina cribrosa, the sphenoid sinus via the sella, and the petrous bone via the middle ear and Eustachian tube. Difficulty in localization may be caused by multiple leaks or distant routes of drainage. For instance, rhinorrhea has been known to occur secondary to a leak in the cerebellopontine angle.¹¹

One method of detecting these leaks is to place cotton pledgets in strategic places like the sphenoethmoidal recess, high in the olfactory sulcus, and in the middle meatus; to inject a tracer into the CSF; and to remove the pledgets after a short while and measure their radioactivity. However, this method fails to give morphologic information. With a routine cisternogram, on the other hand, the

Fig. 5 Brain abscess after meningioma resection (3 weeks postoperative). Same patient as illustrated in Fig. 1. Three weeks after resection of the meningioma mild left hemiparesis developed and a repeat examination was conducted. The rapid-sequence scintiphotos after peripheral intravenous injection of pertechnetate show some decrease in the distal arborization of the left middle cerebral artery in this posterior-view flow study. This is followed by a slight focal labeling increase in the same area, consistent with minimal prolongation of vascular transit times in this region. There is no bright focal labeling increase similar to that seen due to meningioma vascularity. Static scintiphotos show a focal abnormality deep in the right parietal lobe at the surgical site. Also clearly defined in the right lateral view is the margin of the previous surgical procedure. This is particularly well seen in the central region extending down from the superior sagittal area. This accumulation of radiopharmaceutical which is related to the recent surgery would be expected to diminish and perhaps disappear over the next 2 months.

site of the leak, and often the fistulous tract, is usually seen. The technique suggested by Di Chiro et al.¹² is ideal for detection and postoperative follow-up of these cases.

We have recently adapted an infusion technique to the cisternogram in an attempt to delineate occult leaks and have been successful in precipitating copious leakage and in obtaining diagnostic studies (Fig. 7).

Failure to identify the site of leakage before operation may subject the patient to an unsuccessful and extensive procedure. A cisternogram provides either positive information or none. It should never be misleading, and its only disadvantage is that it may require considerable time and patience on the part of both physician and patient.

Regardless of technique, the patient should be scanned or photographed while actively leaking. If necessary, he should be tilted or bent in various positions to afford maximum flow of CSF. We generally use (radioiodinated serum albumin) RISA for our CSF leakage studies; however, ^{99m}Tc-labeled

Fig. 6 Subdural hematoma. Rapid-sequence posterior-view scintiphotographs after peripheral intravenous injection of pertechnetate show symmetrical carotid filling with a marked asymmetry in the 15- to 18-sec and subsequent views of the intracranial areas. There is a curvilinear impression on the vessels in the arborization of the left middle cerebral artery in the 18- to 21-sec picture. This is followed by increasing filling of the scalp vessels via external carotid circulation. Static scintiphotographs show only a slight suggestion of the left hemispheric abnormality which is seen in the flow study. Late scintiphotographs taken 8 hr after injection show a clearly defined crescentic abnormality in the left lateral view. This crescent of abnormal labeling extends from the central area posteriorly around the dorsal surface of the left parietal lobe. The anterior view shows a patchy increased retention of radioactivity over the left hemisphere with one brightly labeled focus. This is somewhat less evident in the left lateral view unless this is compared directly with the right lateral view.

albumin is also satisfactory. With the scintillation camera it is possible to make rapid serial scans with the patient in any position.

ANEURYSMS AND ARTERIOVENOUS MALFORMATIONS

Although angiography is the most useful diagnostic study in patients with arteriovenous malformations (AVM) and aneurysms, the larger of these lesions

Fig. 7 Cerebrospinal fluid rhinorrhea from the cribriform area. After introduction of high-specific-activity (high radioactivity concentration for the amount of protein administered) ^{125}I -human serum albumin into the lumbar cerebrospinal fluid, the basilar cisterns are seen to fill well at 1 hr. At $2\frac{1}{2}$ hr there is early filling of the Sylvian cisterns as determined from the anterior view, and a suggestion of radioactive label is seen out over the hemispheric convexities. At $5\frac{1}{2}$ hr there is clear definition of abnormal labeling to the left of the midline below the level of the basilar cisterns in the anterior view, and this is seen faintly in the left lateral view at that time. At 26 hr there is a residual bright focus of abnormal labeling, indicating the site of deposition of the tracer after leaking from the cribriform area. There is a normal slight amount of activity out over the hemispheres, showing that there was absorption at normal sites.

may be detected with scintiangiography^{1,3} as well (Fig. 8). The Anger camera permits visualization of the initial radionuclide bolus as it traverses the cerebral vasculature. During this time little of the radionuclide crosses the blood-brain barrier, and intravascular content of the tracer is depicted. It is possible to distinguish a large aneurysm from an AVM by the early venous drainage of the latter. An AVM larger than 2 cm is easily demonstrated by this method. Maynard³ found brain imaging studies to be positive in 22 of 26 patients with lesions larger than 2 cm. There were no negative studies.

HYDROCEPHALUS

Radioisotope scanning in hydrocephalus, as described by Di Chiro et al.,^{1,2} now plays an important role in the evaluation of "normal-pressure" hydrocephalus and in certain instances of childhood hydrocephalus. As is well known, Adams et al.¹⁴ in 1965 described an occult symptomatic normal-pressure hydrocephalus characterized by dementia, urinary incontinence, gait disturbance

Fig. 8 Arteriovenous malformation. This illustration shows a typical early filling of a large arteriovenous malformation in the left anterior fossa. Shunting of blood through the malformation succeeds in filling the superior sagittal sinus earlier than usual. The left middle cerebral artery arborization appears to be somewhat underperfused compared to the right, indicating a vascular steal. Static scintiphotographs demonstrate a focal labeling abnormality low in the left frontal area. This is adjacent to the midline but apparently does not extend across it. The abnormality is less well seen from the right lateral view than from the left due to the difference in the amount of tissue intervening between the scintillation camera and the abnormal localization of radionuclide.

with long tract signs, and cerebellar dysfunction. On pneumoencephalography the ventricles were dilated, and air failed to pass completely or not freely through the basilar cisterns and over the convexity of subarachnoid spaces. Pneumoencephalography was often followed by rather drastic deterioration in the patient's condition.

Several causes for normal-pressure hydrocephalus have evolved, including arachnoidal thickening secondary to trauma, subarachnoid hemorrhage, meningitis, surgical intervention, tumor, elongated basilar artery, and idiopathic causes. The neurosurgeon immediately became interested in this problem as one of the few varieties of dementia to gain symptomatic relief through surgery. However, difficulty was encountered in distinguishing cases which would respond to shunting from those which would not, and a physiologic test of CSF dynamics was needed. Measurement of CSF pressure in itself proved to be of limited value and was often inaccurate as an expression of CSF dynamics. Radionuclide cisternography and the "flush" test¹⁵ both proved valuable. Radionuclide cisternography utilizes physiologic solutions, does not cause hydrodynamic changes, affords good distribution of the isotope in the subarachnoid space in a characteristic pattern secondary to CSF flow regardless of posture (Fig. 7), and causes insignificant morbidity.

The normal flow pattern has been well worked out; an abnormal flow pattern¹⁶ exists when there is ventricular reflux at 24 hr or longer, a lack of radioactivity over the surface of the convexities, or a delay of 72 hr or longer in passage of the tracer from the base to the convexity. Ventricular reflux may indicate alternative routes by which the ependyma absorbs the CSF. Correlation of air studies with radionuclide cisternography indicates that if the pneumoencephalogram is normal the cisternogram is usually normal, and if the pneumoencephalogram shows a definite block, the cisternogram will show reflux. Therefore it is with the equivocal air study that a positive cisternogram and flush test become important in predicting the response to operation. Heinz, Davis, and Karp¹⁶ cite a series of 130 patients, 17 of whom had positive cisternograms. Operation was done in 12; nine showed improvement.

With atrophy, i.e., with hydrocephalus ex vacuo, no reflux is present. Dementia may be profound in this disease, but no other stigmata of occult hydrocephalus are present. This may be a difficult and important distinction because with atrophy air does not always fill the peripheral convexity sulci.¹⁷ Patients with atrophy never respond well to shunting. Arteriography may be helpful in showing tortuous arteries in the case of atrophy or an elongated basilar artery as described by Breig et al.¹⁸ It is believed that ectasia of the basilar artery in the latter condition causes compression and deformation of the third ventricle, often associated with essential hypertension. Pulsation of the artery and a water-hammer effect may impair flow through the foramen of Monro, resulting in hydrocephalus.

With infantile and childhood hydrocephalus, isotope cisternography with RISA is safe, and it provides a picture of extraventricular CSF pathways adequate for identification of major cisterns.¹⁹ A normal study in communicating hydrocephalus indicates that the process is compensated; however, passage into the ventricles indicates progressive hydrocephalus. Studies of this type have shown that the basilar cisterns and hemispheric subarachnoid spaces decrease in volume with increased pressure,²⁰ and they give us an insight into why internal shunting is ineffective in most types of childhood hydrocephalus.

Brain imaging may show the elevated torcular and abnormally high lateral sinuses diagnostic of the Dandy-Walker deformity.²¹

Radionuclide imaging may be useful in the evaluation of surgical and spontaneous CSF shunts. Many times, methods, such as palpation, fluid withdrawal, pressure measurements, and numerous dyes, as well as radiologic tests, are equivocal,²² and they offer no direct visualization of shunts and no information about patency of the proximal and distal ends of the apparatus. Direct introduction of radiopharmaceuticals into the tubing, pumping mechanism, ventricular system, or lumbar subarachnoid space yields considerable information (Fig. 9). For example, for a functioning ventriculoatrial shunt with communicating hydrocephalus, RISA introduced into the lumbar CSF takes the path of least resistance via the ventricular system and out the shunt. Films taken

at 4, 6, 24, and 48 hr delineate patency and rate of CSF outflow. For a nonfunctioning shunt, radioactivity would remain in the basilar cisterns.²³

CEREBROVASCULAR DISEASE

We have not actively used radionuclide imaging techniques in the diagnosis of cerebrovascular disease; however, it is important to be cognizant of the changes in radionuclide images that are caused by cerebral infarction. Approximately 40% of cerebral infarctions will have positive scans²⁴ (Fig. 10). The scan does not become positive immediately, and the number of positive scans peaks between 3 and 4 weeks and then gradually declines. Fifty percent of those which will be positive are so during the first 28 days. Some are positive as early as 3 days after insult, and most become normal by 6 months even if the patient has not recovered clinically. Usually, for 6 months improvement in the imaging study correlates well with the clinical findings. Positivity is characterized by irregular uptake and may be caused by breakdown of the blood-brain barrier, edema, or increased vascularity. Should a scan be positive initially, it may fail to distinguish between a tumor and the infarction. Flow studies may show a radioisotope image of "luxury perfusion" due to dilation of vessels in anoxic areas and a resulting prolongation of transit times.

We have not yet utilized intra-arterial radionuclide cerebral angiography as described by Rosenthal, Chan, and Stratford.²⁵

SUMMARY

Radionuclide imaging techniques have a valuable place in the armamentarium of the neurosurgeon. Although they in no way replace neuroradiologic procedures, they provide a major contribution to the collection of information about difficult neurosurgical problems.

EDITORS' NOTE

An excellent editorial on "Brain Scanning— Is It Becoming Unnecessarily Complicated?" by A. Gottschalk appeared in Amer. J. Roentgenol., Radium Ther. Nucl. Med., 111: 851-852 (1971). Brain scanning is at a stage where selective medical judgment is important, and each study should be planned and monitored by the physician. This, the author hopes, will lead us to abandon the concept of a routine brain scan and try instead to tailor each study to the individual problem. It is no longer efficacious for the nuclear medicine specialist to try to do "everything" on each brain examination. Thus clinical information before the scanning procedure can help considerably to save valuable time and improve our diagnostic accuracy in the study of brain lesions.

1 1/4 hr after injection

5 1/2 hr after injection

24 hr after injection

Anterior head

Left lateral

Anterior abdomen

Left lateral

Fig. 9 Functioning lumbar-peritoneal shunt. After introduction of ^{131}I -RISA into the lumbar cerebrospinal fluid, this patient showed rather rapid labeling of the basilar cisterns, a large cisterna magna, interpeduncular cisterns, and the lateral ventricles, which are obvious both on the anterior and the lateral views at 1 1/4 and 5 1/2 hr. At these times some radioactivity is seen low in the left abdomen in an anterior view of the abdomen. Thus radioactivity has both ascended into the lateral ventricular system, an area that would normally be swept free of any radioactive tracer due to formation of fluid by the choroid plexus, and descended to leave the spinal canal via the lumbar-peritoneal shunt; so tracer is seen in the left lateral abdomen. At 24 hr after injection, there is only a trace of radioactivity within the head, and none of this appears to be at normal sites of cerebrospinal fluid absorption. The lumbar area appears to be devoid of any radioactivity within the spinal canal, although there is evidence of increased body background due to systemic absorption of the tracer.

Fig. 10 Cerebrovascular thrombosis. One month after onset of symptoms, a thrombosis of the left middle cerebral artery is demonstrated as an absence of filling of the arborization of this vessel in the 8- to 12-sec scintiphotograph, followed by late filling of the left hemisphere and even some focal-labeling increase in the 16- to 20-sec photograph. This focal labeling during the venous phase of the flow study suggests prolongation of transit time through vasculature in the region of the thrombosis. Static scintiphotos show a focal abnormality extending from the posterior temporal lobe superiorly into the parietal and occipital regions. This is irregular in distribution, as best seen in the left lateral view. Brain damage due to vascular lesions tends to appear in radionuclide images as irregular distribution of abnormal capillary permeability rather than a single discrete lesion, which is more common with neoplasms. The area of brain damage is seen to extend to within approximately 1 in. of the midline but appears to be predominantly near the cortical surface. It is typical of a cerebral thrombosis to show capillary permeability in static scintiphotos only after an interval of hours to days after onset. The capillary permeability usually appears maximum at 2 to 4 weeks and slowly subsides with healing until there is no further residual abnormality in static scintiphotos after several months. The asymmetry in the vascular patterns persists in the flow study.

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DISCUSSION: BRAIN

Viamonte: I would like to tell you of our experience in Miami with a very large elderly population. The usual reported morbidity is about 2 or 3%, but we have had about 8%. We looked into this in some detail and found that the older the patient, the higher the morbidity, and the longer the duration of the procedure, the higher the morbidity. For patients who were in the department more than 1 hr, the morbidity was about twice that seen in patients there less than 30 min.

In dealing with ischemic disease, where one must consider the neck vessels, one must always do a combination of arteriograms of the neck vessels plus cerebral angiography. To decrease the morbidity of selective brachiocephalic arteriography, we have developed a technique in the last 6 months which consists of injecting a very large bolus of contrast material (60 to 70 ml total) in a period of 2 sec by using electrocardiogram triggering of the injection and a large No. 8 catheter. One can put a bolus in the root of the aorta at 30 to 35 cm³ per second. It is remarkable the anatomic detail one sees of the neck arteries. The assessment of the neck arteries is the primary reason for the study, and it is unnecessary with this technique to do selective studies. One can do the screening procedure much more quickly and with equal results. Selective injection of the carotid and vertebral arteries is the technique of choice.

Dr. Zingesser, probably because of shortage of time, did not talk about enhancement techniques. The resolution of cerebral angiography now allows us to visualize arteriolar vessels that are about 0.1 mm in diameter. Other enhancement techniques have been briefly shown, particularly by Dr. Wilson, including image subtraction by the single or double subtraction technique. For the assessment of pathology at the base of the brain, where there are overlapping bony structures in the lateral cerebral arteriogram, one can virtually eliminate the image of the bone by subtraction photography and thus see the vessels in greater detail. We may eventually see application to the brain of what is now being applied to the liver and to other organs, i.e., the use of pharmacangiographic techniques. The inhalation of carbon dioxide preceding the angiographic examination has been proposed. It is possible, although so far as I

know no one has done it, to use some compounds like epinephrine in very small amounts to enhance the demonstration of tumor vascularity. I shall show you later when dealing with liver disease that an area that appears vascular may reveal abnormal vessels if the injection of the contrast material is preceded by the injection of a small amount of epinephrine. This type of response was shown first in the kidney.

I would like to comment on Dr. Oldendorf's statement that radiography is to anatomy what isotopes are to physiology and to indicate that in the last 15 years radiology has become a very dynamic discipline and that through it morpho-physiologic information is readily available. We do not base our interpretation just on morphologic findings. It is still mainly a morphologic discipline, but, for example, when looking at pulmonary angiograms, we can often predict the levels of pulmonary arterial pressure, and this information of altered vascular physiology is an important part of our diagnostic possibilities. I am sure that he agrees that the images in diagnostic radiology have a great deal of similarity to the interesting little dots that are the basis of the poor anatomic resolution of most presently used scintiscans. This symposium is about both disciplines and the value of cooperation between those using isotopic and radiographic techniques. The two are complementary, and in many situations isotope studies should follow the conventional radiographic techniques before more extensive and difficult catheter techniques are employed.

I would like to refer to the experience of my colleagues in Florida, Dr. Fisher, Dr. Miale, Dr. Smoak, and Dr. Sheldon (Dr. Miale will talk later in this course). They did some work on radionuclide angiography in vascular disease. In 143 patients with strokes and 120 with transient cerebral ischemic attacks, they have found that the combination of static brain scanning and radionuclide angiography when using radiosodium pertechnetate and the scintillation camera yielded the following results: The static brain scan was reported positive in approximately 42% of patients with strokes. Radionuclide angiography combined with static imaging showed an 80% positive result in strokes and 33% in transient ischemic attacks. So this increase in the positive findings of the isotope studies should be kept in mind when studying cerebral vascular disease. One technique that has not been mentioned today is thermography. It can be done in a very simple, inexpensive way. At our institution it costs about \$25. It has absolutely no morbidity. The unit costs about \$27,000. This technique is quite useful for assessing occlusive vascular disease. Preoperatively the thermogram may reveal unequal distribution of heat patterns in the forehead, in the angle of the eye, which will indicate impairment of perfusion. Thermography has been quite helpful as a screening test and, combined with other techniques, such as hemodensitometry, is another simple method in the armamentarium of the radiologist for assessing vascular problems of the brain. I believe we can get more out of each of these tests when we have adequate information about the patient, the results of conventional X-ray examinations, and correlate the results of all the examinations. This correlation

gives the highest yield for diagnosis, not only for the brain but also for any organ as well. Recently we have some bizarre scans of the head in patients with Paget's disease of the bone, and it just takes a simple look at a conventional skull X ray to realize that the process is not in the scalp or the brain but in the bone. Unfortunately many radiologists doing special procedures pay primary attention to this examination without making a careful assessment of the conventional radiologic examinations that have been done earlier. Often we find abnormalities in these conventional studies that will later be corroborated by the more elaborate techniques. This is applicable not only to the brain but also to the liver, pancreas, etc. By studying the several types of examinations performed, we will have a greater diagnostic success, and the course this week should be a good example of this by showing the limitations and contributions of these various approaches.

Zingesser: In response to the comment of Dr. Viamonte, I would like to mention that pharmacological agents have been tried in conjunction with carotid angiography. I think you will find references to some of these attempts by David Rockoff and others in *Investigative Radiology* [D. Rockoff et al., Altered Opacification of the External Carotid Circulation by Changes of End Expiratory Carbon Dioxide Tension, *Invest. Radiol.*, 1: 123-128 (1966); C. A. Athanasoulis et al., Bradykinin in Cerebral Angiography, *Invest. Radiol.*, 4: 323-326 (1969); Reviews of Selected Publications, *Invest. Radiol.*, 4: 113 (1969)].

Because the intracranial carotid circulation is autoregulated, pharmacological vasoconstrictors may work mainly through an effect on the external carotid circulation. For example, Rockoff took advantage of the fact that low CO₂ tension causes increased flow through the external carotid (and decreased flow through the internal carotid) to enhance the angiographic demonstration of a meningioma.

Changing the CO₂ tension is the most potent way to affect the intracranial circulation [R. A. Grange et al., Influence of Carbon Dioxide Tension on the Angiographic Appearance of Intracranial Tumors, *Acta Radiol., Diagn.*, 9: 292-299 (1969)]. Some of the English neuroradiologists, notably George du Boulay and Desmond Hawkins, have used this approach in their angiography, but the technique has not caught on in this country because carotid angiography is not usually done under general anesthesia here.

Beierwaltes: How long does the scan image remain positive as the result of postoperative reaction from brain surgery, and what is the cause of the positive image?

Wilson: We know that healing goes on in the scalp and the bone for a considerable period of time. We also know that in the brain itself there are persistent changes in vessels and edema even after a nontraumatic removal of a meningioma. After a period of 2 or 3 months, any further change will be very slow, and, when we see something deep to the operative defect after that period, we make the assumption that this is residual or recurrent tumor. We do not just

throw up our hands and say that scans are no good for 3 to 6 months after operation; serial scans are most informative.

Quinn: The crescent-shaped area of uptake seen postoperatively has a two-compartment disappearance. The scalp portion is essentially gone by 6 weeks. The skull component can clear within a year but has persisted as long as 56 years in one of our patients who was subjected to neurosurgery during the battle of the Ardennes in 1914. His was a craniectomy procedure.

Andrews: Dr. Wilson, do you have any recommended routine for postoperative scanning, or does it vary with the individual case?

Wilson: We are now doing a prospective study of patients randomized with various types of treatment and are attempting to detect asymptomatic recurrence. We have under observation a patient who is 18 months postoperative and we knew 3 months ago that he was beginning to develop a recurrence. We have been scanning him at intervals of about 3 months because we did not really expect a recurrence for 1 or 2 years. However, in a patient with a highly malignant glioma, in whom recurrence might be expected to occur within 3 to 6 months, in order to be closely in touch with the situation it would require scans at least every 4 to 6 weeks, and this is what we have done recently in patients with this type of lesion.

Quinn: We routinely obtain postoperative scans on brain-tumor patients as a baseline follow-up study. Granted, the anterior and posterior views are almost worthless because of the scalp trauma, but the laterals do not show very much uptake in the craniotomy or scalp defect, and we have been able to secure vital information, as has Dr. Wilson, with regard to recurrence or persistence of tumor.

Beierwaltes: What is the etiology of brain edema around a brain tumor and/or infarct? When and how do you expect it and recognize it?

Wilson: Any brain abscess or malignant tumor will be associated with a certain amount of brain edema; benign tumors have less edema as a rule. The cause of the edema is obscure. Why should a small metastatic tumor of the lung, 2 cm in diameter, be associated with such massive edema that we resort to radiation therapy in an effort to relieve it? There must be some type of biochemical message and certainly some impairment of the blood-brain barrier. One of the questions is why it should respond so specifically to corticosteroid medications. I am afraid I do not know. We know that in a tumor such as glioblastoma the capillary endothelium is affected; after all, this is the blood-brain barrier. In the normal brain there are tight junctures between the capillary endothelial cells; whereas in the tumor, such as glioblastoma, these are loose junctions. This is the major reason that glioblastomas show up so well in scans, and of course the same thing is true for metastatic tumors.

Oldendorf: I have one comment about the edema that surrounds lesions. If you make a lesion of almost any kind in an experimental animal, regardless of what histological abnormality is produced there will be a local defect in the

blood-brain barrier. If you put a dye or any tracer into the blood, it will appear very rapidly in the center of that lesion. If you watch its distribution over the next several hours, you will see that, once the material has gotten into the extracellular space of the brain, it will diffuse freely in the extracellular space into the normal regions of the surrounding brain. Once anything gets into the extracellular fluid of the brain, it freely distributes in all directions and is not limited to the areas of a lesion. It is the point of entry that is produced by the lesion. The injury in the blood-brain barrier is not necessarily specific for tumor. We can see the same diffusion of a dye or radioisotope in an infarct, but we do not get the huge amount of edema that surrounds a glioblastoma. In the latter situation the tumor probably dumps some neurotoxic substance into the extracellular spaces of the brain, a substance that spreads by simple diffusion through the tissue.

Loken: I would like to make three comments to emphasize certain aspects of radionuclide imaging of the brain: (1) We must be very cognizant of the normal anatomy in the interpretation of brain scintiphotograms. The very fine atlas published by DeLand and Wagner is very helpful in this regard (F. H. DeLand and H. N. Wagner, *Atlas of Nuclear Medicine*, Vol. I, Brain, W. B. Saunders Company, Philadelphia, 1969). (2) Delayed brain scintiphotos at 4 to 6 hr after injection of the radioactive material are often helpful in identifying relatively small avascular lesions of the brain. We have recently found subdural hematomas (unilateral and bilateral) on delayed scans that were not apparent even in retrospect of the "initial flow" (very early distribution of the radioactive material in the brain) or on the scintiphotos made at 1 hr. Delayed views are now routine in our institution for all patients whose studies are interpreted as normal through the 1-hr views. (3) Oblique views have been found to be very valuable for the detection of midline lesions which might otherwise underlie normal structures, notably those near the sagittal sinus and confluence of the sinuses.

Powell: Using ^{99m}Tc -oxide we find that late views taken 3 to 8 hr after administration of the material are essential in 30 or 40% of the brain studies done at our hospital. These late views show regions of increased brain vascular permeability at a time when the intravascular content of the tracer is very low. On the other hand, at the 1-hr interval the radioactivity in the blood of the scalp and skull often obscures intracranial abnormalities. In our experience late views are most useful for evaluating metastatic cancer in the brain, subdural hematomas, cerebral hemorrhages, and postoperative changes. If the surgical abnormality is studied 3 weeks or more after operation and is observed serially for several hours after administration of the tracer, it tends to become less evident as compared with the 1-hr scintiphoto study or scan, whereas an intracranial abnormality of capillary permeability tends to become more evident compared to its surroundings. Acute traumatic lesions and skull metastases often show as focal abnormalities in the late views. The extracranial locations of these

abnormalities can best be identified by careful comparison of radioisotopic images and skull X rays by using several different views of each.

Wellman: We should discard the terms "AP projection" and "PA projection" for scintillation imaging since these terms from diagnostic radiography do not apply and, in fact, are erroneous.

Each patient who has a brain scan should have a physical examination of the head region at the time of scanning. Such abnormalities as hematomas of the scalp can then be identified, and the change in the scan image will be properly interpreted.

More important, I wanted to comment on and invite discussion about Dr. Zingesser's values for percent positives in brain scans. One must be specific about indicating which radiopharmaceutical was used. Many of the quoted figures about percent positives are based on the use of chlormerodrin. It was not clear which radiopharmaceutical his values were based on. I believe that most people in the audience would estimate a value for positives higher than 80% when using recent techniques and pertechnetate. I would also raise the question about whether the percentage that was quoted for angiography was based on only tumors for which appropriate examinations were done; for example, one may miss tumors of the posterior circulation if it is not included in the routine examination.

Zingesser: I do not think that technetium has increased our accuracy very much. I believe that it is about the same as it was with chlormerodrin.¹⁻⁴ Using optimal equipment and technique may help.^{2,5,6}

Regarding Dr. Wellman's comments about doing a physical examination of the head before scanning and about doing the appropriate arteriographic examination, the patients who have scans in our institution are examined not once but several times, and the history, physical examination, scan, electroencephalogram, lumbar puncture, etc., serve as a guide for selecting the "correct" procedure. Dr. Wellman may have been misled by my comments on the case that I showed of the patient with a subgaleal collection and negative

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angiographic and pneumoencephalographic studies. This was the first case we had (in 1963) of a positive scan caused by scalp injury. Nobody had written about the fact that subgaleal collections could produce positive scans.

I might add that there was surprisingly little to feel on the examination of the scalp of that patient as the trauma was 4 weeks earlier.

Berg: Do you have any information about the rapidity of development of positive scans, originally negative, in stroke patients? Does scan density or the rapidity of appearance or clearing provide any information on prognosis?

Quinn: Mike Usher wrote a paper on serial scans in stroke that correlated prognosis with the scans, including intensity changes and time sequence [M. S. Usher and J. L. Quinn III, Serial Brain Scanning with Technetium 99m Per technetate in Cerebral Infarction, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 105: 728-733 (1969)]. The conclusion was that, although the scans are very good diagnostically, they offer very little from the standpoint of prognosis.

Oldendorf: As Dr. Wilson mentioned, the blood-brain barrier, according to modern thinking, is the endothelium of the capillaries of the brain. Indeed the blood-brain barrier persists for several hours after death. Many years ago Broman rapidly removed the human brain after death, injected it with Trypan blue and found that within the first hour or two at least one does not see staining of the normal brain. Yet we know that the blood-brain barrier can be immediately damaged by various pathologic processes. The clinically observed delay in the appearance of abnormal scans after infarction probably means that the damage to the blood-brain barrier is a secondary external influence on the brain capillaries as a result of necrosis in the surrounding brain. It is probably not a direct effect of ischemia on the endothelium. I do not know of any studies that would establish how rapidly this damage to the endothelium occurs, how long it persists, and the prognosis. We do know that the size of the lesion is not very closely related to the clinical signs. We have many lesions which involve less than 1 cm³ of tissue but which would, if critically placed, produce a permanent hemiplegia. Yet other patients will have a sizable infarction of the cerebrum and have virtually no symptoms whatever. I do not know of any strong correlation between the prognosis and the rapidity of appearance or the intensity of the appearance. It would seem logical that the earlier it appears and the more dense it is, the more severely necrotic the area of brain tissue is and therefore the less likely it is to ever recover its function.

Haynie: My comment is on false-positive brain scans arising from the abnormal accumulations of radioactivity in lesions in the scalp and skull. In my practice in a cancer hospital, we are quite frequently faced with a problem of patients with scalp and skull metastases. The purpose of the brain scan is usually to detect intracranial lesions, but, with the agents presently used, extracranial lesions are also frequently positive on scan. When an abnormal area of isotope uptake in the scalp or skull is interpreted as a positive brain scan, this can cause confusion for the physician reading the report. For this reason my interpretation

of such a scan would be as follows: (1) negative brain scan, and (2) abnormal uptake in lesion in the scalp or skull. In this way I try to differentiate those lesions which are outside the brain, those which are in the brain, and those which are indeterminate.

Gorten: Various figures for percent abnormal brain scans have been presented this morning. These are influenced not only by the quality of the scanning technique, as has been called to our attention, but also by the means of deciding finally on the answer to the patient's diagnostic problem and by what is called interpreter attitude. It would be very helpful if some of the speakers could accompany their figures for percent correct abnormal scans with respective percents false abnormal, false normal, and correct normal interpretations. In that way I think we would have a better chance to evaluate the total effectiveness of the procedure.

Oldendorf: The false negative should be, I think, about 10%. False positives are rather rare. If you are familiar with all the technical factors that may result in false positives, you can eliminate many of them. Much depends on when the study is made in relation to the course of the patient's disease.

Quinn: It is impossible to give a general answer to Dr. Gorten's question because the timing of the procedure is so important. You may recall the instance of a patient reported in the *Journal of Neurosurgery* about a year ago who had a normal brain scan and then had a convulsion. The scan was repeated without another injection of radioactive material, and an abnormality about 3 cm in diameter was found. This represented the 15 or 20 μCi of the radioindicator that was contained in the acute intercerebral hematoma that occurred. In stroke patients we report that about 25% have abnormal scans during the first week. This is an extremely rough figure depending on the time the scan is made after injection of the radioactive material. Our colleagues in Sweden for some years have said that they find 60 to 70% positive scans during the first week after the stroke. I believe this is because they are scanning at the somewhat longer intervals of 4 to 6 hr after injection. In a prospective study using delayed scanning, at 4 hr we found a higher incidence of positives than on the scans done at 1 hr. This was also true for recent scalp injuries. When you scan right after injection, you will have a lower percentage of positives, and, if you are in a situation where the blood-brain barrier can change very dramatically, you will have a higher incidence of false negatives with these early scans. I can point to our figures in which we have shown that around 90% of 750 brain tumors have been shown to have positive scans. This figure, however, cannot be used for any general situation since it depends on the conditions and interpretations made in your own laboratories.

Edwards: What percent of brain scans done in a nuclear medicine facility would be expected to be positive? Such a value might be an index of whether the procedure is being overused or underused as a screening method. My question is simply that I would like to know how many scans were done so that

we could have some assessment of what percentage should be positives in the average nuclear medicine facility and some index of how often the study is done with negative results.

Quinn: We have a very active neurology-neurosurgery service at North-western; so our figures cannot be easily transferred to other institutions with differing thrusts of medical care. Many of our neurosurgery cases are admitted with a diagnosis of brain tumor having been made in another medical center. The last time I reviewed it, in 1970, we had 14% positive brain scans. Of the 86% reported negative, I do not know how many were truly in patients without significant brain disease. I think at least we know about most of the brain tumors that have been missed, but there may be other brain diseases which we have overlooked and which were not later called to our attention. I think 14 or 15% of positives in a nuclear medical facility may indicate that the brain scan is being overused a little bit for screening purposes, but I am not sure. It depends entirely on the needs and judgments of the physicians making the decisions at each local institution.

Wellman: I am not sure that the problem of assessing false positives and false negatives is as hopeless as it seems. Dr. Lusted, in Boston, has published reports on how to do this with diagnostic radiography [L. B. Lusted, *Decision-Making Studies in Patient Management*, *New Engl. J. Med.*, 284: 416-424 (1971)]. Dr. Saenger, in Cincinnati, is presently applying these procedures to scans, and I think he has some very interesting results with regard to ways that we can get at legitimate valid figures for numbers of positives and negatives in relation to the actual disease state.

Eckhardt: Dr. Quinn, would you amplify on your comment in the *Year Book of Nuclear Medicine* about minification techniques applied in the interpretation of scans? Are they clearly helpful in the reliability and consistency of interpretations by observers? I would also like to know your opinions about the best camera recording device, whether the Polaroid, 35-mm, or 70-mm film has any particular advantages in improving the correctness of interpretation.

Quinn: My personal feeling is that the 35-mm film is better than the Polaroid because it gives us a great deal more recording latitude. We try minification in a very simple way by standing 30 ft away from our brain scans when we interpret them. Minification is something that we radiologists use a lot and are familiar with.

Haynie: My question is directed toward Dr. Quinn. I agree with him that we need better radionuclides for cisternography, but I would like to know what the chances are of obtaining ^{111}In - or ^{123}I -labeled compounds to carry out the procedure in the manner that has been advocated.

Quinn: At present these radionuclides are available only on a limited basis; however, there is one manufacturer now preparing to market ^{111}In as DPTA, and the Brookhaven National Laboratory is preparing to produce large quantities

of ^{123}I . Although these two nuclides are not going to be used widely for some time, I believe that they are the best investigated to date.

Oldendorf: I would like to make a further comment on one of my statements made earlier. The comment was that radioisotopes are to physiology what radiography is to anatomy. The information we are likely to get from radiography is primarily structural, and we may draw indirect inferences about physiology. However, nuclear medicine, because of the availability of a large number of specific molecules that can be subjected to dynamic study of their distribution and behavior, offers many, many more parameters of tissue function that can be assessed than are now being commonly evaluated. The potential for physiologic assessment is there and offers the opportunity of going far beyond any radiologic techniques. I am referring to the very wide choices of specific chemical compounds available, including various size macromolecules. The future potential for development of highly specific ways of assessing physiologic functions is very good.

Moderator:
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BONE and JOINT

RADIOLOGIC APPROACH TO DIAGNOSIS OF BONE DISEASE

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ABSTRACT

The radiologic approach to bone lesions is discussed. Osteoporosis may be distinguished by morphologic changes in bone rather than by density changes.

Bone tumors cause destruction of bone, but their aggressiveness may be established by the morphologic changes in the periphery.

Increased density of lesions occurs with calcification and may be due to either reactive changes in the normal bone or ossification by tumor. The differentiation is discussed.

The radiologic appearances of bone disease are subject to some important misconceptions.

Bone density is easily evaluated qualitatively but not quantitatively. If the amount of mineral or bone mass is evaluated in routine X rays, densitometric readings may be 50 to 100% from the true value. This is due to variable kilovolt and different energy levels in the beam and to variations in darkroom technic, in film, and in the electric current reaching transformers and the X-ray tube. Equipment can be standardized so that densitometric readings may be within 10%, but this is extremely time-consuming and expensive.

Evaluation of the morphologic bone changes associated with osteoporosis is more accurate than assessment of the density.

In the normal spine the trabeculations in the vertebral body are oriented vertically with buttressing strands running perpendicular. With osteoporosis the buttressing transverse strands are resorbed, and the vertical trabeculations decrease in number. The remaining trabeculations become more prominent. The roentgenogram reveals exaggerated density of the cortical plates because of the contrast with the normal.

In acute osteoporosis, as seen in Sudeck's atrophy, spongy bone is resorbed more rapidly than the compact cortical bone because of its easier mobilization. In the early phases the spongy bone ends show marked deossification whereas

the cortical bone seems to be intact. Later the cortical bone also resorbs and the contrast is not as apparent (Fig. 1).

With Cushing's disease there is marked osteoporosis, but there are other factors that aid in establishing the diagnosis. For instance, fat is accumulated in the upper portion of the body and evidenced clinically by obvious abnormal fat distribution, purple skin striae, and a moon face. This appearance occurs with other corticosteroid syndromes whether resulting from oral administration or from internal derangements. The spine may be brilliantly outlined by a dense cortical margin; the vertebra collapses. Vertical trabeculations of the vertebral bodies are prominent and the horizontal buttressing lacking. The inner surface of the vertebral body cortical outline is irregular in active osteoporosis, which helps to differentiate it from postmenopausal or stabilized osteoporosis (Fig. 2).

The metacarpals may also show evidence of osteoporosis but not so much by change in the radiodensity as by resorption of their cortical margins. This has been defined by Meema¹ and, if the cortices of the metacarpals are examined with a magnification lens after examination with a small focal spot tube or with industrial film, vertical striations may be demonstrated which are not apparent in routine films. Even though the cortex may maintain its thickness, the vertical striations of deossification may cause 50% or more bone resorption which is not apparent on cursory examination. These changes are most striking in hyperthyroidism and hyperparathyroidism but may also be present in other forms of osteoporosis (Figs. 3 and 4).

Osteomalacia is another cause of bone deossification; however, the bone density may be normal. The early X-ray evidence of osteomalacia may be symmetrical fracture lines (Fig. 5), usually in the necks of the femur or mid-shafts of the tibia and femur but sometimes in the pelvis and other bones. In the United States osteomalacia is usually found in widows who have stopped cooking and eating regularly and who have developed nutritional osteomalacia.

Rapidly absorbed bone may be apparent if normal bone surrounds it. This occurs commonly in the earliest phase of Paget's disease. In the skull it is known as osteoporosis circumscripta (Fig. 6), and in the long bones it appears as a triangular area of decreased density (Fig. 7). It must be emphasized that the bone is dynamic; in addition to being resorbed, bone is being built up that has not yet caught up with the normal bone. This recalcification is abnormal in Paget's disease and eventually yields bone denser than normal. If the resorptive process continues, the cortex may be very thin, and therefore its density decreases.

Lesions within the marrow cavity will not become apparent until the cortex erodes. The entire medullary cavity may be filled with tumor, but until the cortex is eroded the density remains the same. Fifty percent of the bone may be destroyed before it becomes evident roentgenographically.

Destructive lesions of bone are dramatic, and it is important to establish the aggressiveness of a lesion. Lesions may be nonaggressive or stable and then develop various degrees of aggressiveness. If we can categorize the aggressiveness,

Fig. 1 Acute osteoporosis, Sudeck's atrophy. Left: There is resorption of spongy bone as contrasted to the intact cortical bone which is more difficult to mobilize 3 weeks after an injury. Right: Three weeks later there has been resorption of cortical bone and there is less contrast in density between the spongy and cortical bone.

Fig. 2 Cushing's disease. There is collapse of a dorsal vertebra. The cortical margin appears denser than normal and brilliantly outlines the body. The inner surface of the cortical outline is irregular, indicating active osteoporosis.

Fig. 3 Normal metacarpal. The cortex is solidly dense and the inner margin smooth. An oblique radiolucent line represents a nutrient foramen.

Fig. 4 Hyperthyroidism. The cortices are of normal thickness, but the solid dense appearance has been lost due to vertical striations. Approximately one-half to three-quarters of the cortical bone is lost but the cortex maintains its normal width. [From H. E. Meema and D. L. Schatz, Simple Radiologic Demonstration of Cortical Bone Loss in Thyrotoxicosis, *Radiology*, 97: 11 (1970).]

Fig. 5 Osteomalacia. Incomplete fracture line in the neck of the femur (arrow) may be the only distinctive sign of osteomalacia.

we can often establish the diagnosis statistically or at least give a differential diagnosis which will include the disease process. Aggressiveness can be evaluated by the margins of bone destruction. The least aggressive lesion is outlined by a sclerotic margin, which usually indicates a benign bone tumor, a healed infection, or a developmental anomaly. A nonosteogenic fibroma is an excellent example of a nonaggressive lesion which disappears when the bone matures. The sclerotic margin is the sign of nonaggression (Fig. 8).

A more aggressive but still nonmalignant lesion is a unicameral bone cyst, which shows a destructive area with a sharp margin that is not sclerotic (Fig. 9). The transition between the abnormal bone and the normal bone is small. It is more aggressive than a nonosteogenic fibroma but less so than malignancy.

A more aggressive lesion has an irregularly ill-defined periphery. It is difficult to tell where the abnormal bone ends and the normal begins. There is a wide transitional zone that indicates activity. It may be an aggressive benign tumor or a slowly growing malignant lesion (Fig. 10).

The most aggressive lesion has an ill-defined periphery and its transition zone is very wide. It is impossible to tell where abnormal bone ends and normal bone

Fig. 6 Osteoporosis circumscripta. There is an osteolytic area in the posterior parietal and occipital areas. The margin is smooth and well defined.

Fig. 7 Paget's disease. An area of decreased density extends from the femoral condyles to the shaft. The most proximal portions show a triangular area of decreased density, whereas there is recalcification in the distal portions. There is a soft-tissue mass in the posterior portion near the knee joint due to malignancy.

Fig. 8 Nonosteogenic fibroma. An example of a nonaggressive lesion with a sharp sclerotic margin. The transition between the abnormal bone and normal bone is small

Fig. 9 Unicameral bone cyst. This is more aggressive than that shown in the previous figure, although the margin is sharply defined without a sclerotic border. A pathologic fracture is present.

Fig. 10 Aneurysmal bone cyst. This lesion is more aggressive than that shown in the two preceding figures. The margins are ill defined, and the lesion has broken out into the soft tissues. The aggressiveness does not indicate malignancy.

Fig. 11 Osteogenic sarcoma. This is a very aggressive lesion. The transition zone is ill defined and very wide, and it is impossible to tell where abnormal bone ends and normal bone begins. These lesions are usually malignant but can be due to an infection.

Fig. 12 Ewing's sarcoma. There is a destructive area with a rather well-defined margin. However, within the osteolytic area are small rounded radiolucencies indicating aggressiveness. Compare this with Fig. 13.

Fig. 13 Eosinophilic granuloma. This lesion is somewhat similar to that shown in Fig. 12 but does not contain the small radiolucencies within the osteolytic area. This would indicate less aggressiveness than the previous figure.

Fig. 14 Osteosarcoma of the rib. Extending from the anterior portion of the third rib is a homogeneous density which indicates osteoid formation.

Fig. 15 Chondrosarcoma. A large exophytic tumor with multiple punctate calcifications indicating its cartilaginous nature.

begins (Fig. 11). These lesions are not invariably malignant; infections may also cause this appearance. Another appearance indicating aggressiveness is that of multiple small osteolytic lesions in bone. If this is associated with a soft tissue mass, we can establish pronounced aggressiveness and indicate a malignant tumor (Figs. 12 and 13).

Increase in density in lesions denotes calcification, which may be due to formation of new bone or to ossification by tumor (frequently referred to as tumor new bone). If it can be established that there is ossification by tumor, then one of two types of tumors may be considered, osteoid-forming or chondroid-forming, which may be benign or malignant (Figs. 14 and 15). If they are aggressive and show homogeneous dense osteoid formation, then the diagnosis of osteosarcoma may be established. A popcorn or snowflake calcification indicates cartilage and, if aggressive, a chondrosarcoma may be considered. If there is calcification within the bone that does not extend into a soft-tissue mass, we may suggest that the calcification or increased density is due to reactive new bone and may occur in tumors that do not form a matrix, such as Ewing's sarcoma or reticulum-cell sarcoma.

SUMMARY

The roentgenographic evaluation of bone lesions is difficult to make by density change alone. The morphologic characteristics must be considered. Osteoporosis has been discussed, and the morphologic changes that occur in the spongy portion of the vertebrae, the long bones, and the cortices are presented. Aggressiveness in bone tumors and infections are indicated by peripheral margins of varying definition. Increased density in bone may occur with calcification due to either tumor or new bone formation or reactive bone formation.

REFERENCE

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RADIOISOTOPE SCANNING OF ROENTGENOGRAPHICALLY OCCULT DISORDERS OF BONE

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ABSTRACT

Bone scanning is capable of detecting reactive osteoid before roentgenographic changes (radiodensities), and clinically this has occurred in about 20 to 30% of patients with osseous metastases. A correlative study has shown that the scan reflects the rate of new bone formation whereas the roentgenogram depicts cumulative concentration; the two studies are therefore complementary in evaluating local bone metabolism. Normal scans are found in less than 7% of cancer patients with roentgenographic changes in bone (always radiolucencies), usually in patients with anaplastic tumors (e.g., reticulum-cell sarcoma) or slow-growing metastases (e.g., thyroid carcinoma). In some instances abnormal scans are attributable to causes other than reactive bone formation; these processes include malignant bone (e.g., osteogenic sarcoma), increased bone blood flow (e.g., myelofibrosis), and heterotopic calcification (uremia with hypercalcemia). A wide variety of bone-seeking agents are currently under investigation, emphasizing the wide interest in the technique as well as our lack of a truly satisfactory scanning agent at this time.

The past few years have witnessed a tremendous interest in radionuclide scanning as a diagnostic tool for the detection of roentgenographically occult disorders of bone. For example, in the past 3 years alone no less than 14 new radiopharmaceuticals have been investigated as possible scanning agents, and most of these have been studied clinically.¹⁻¹² That so many have been tested indicates that the ideal agent has yet to be found; it also points up the wide interest in the procedure. This is because bone scans often reveal the presence of significant disease when conventional roentgenograms are normal. Before dealing with the correlation of these two methods of examining bone, let us consider the ability of roentgenograms to detect space-taking osseous lesions.

ROENTGEN STUDIES

Several studies done in the 1940s showed that conventional roentgenograms and tomograms cannot detect holes smaller than 1.0 to 1.5 cm drilled into trabecular bone, which is equivalent to the loss of 30 to 50% of the calcium content of a vertebra.¹³⁻¹⁶ More recently Edelstyn and associates,¹⁷ who made irregular spherical holes in the spongiosa of vertebrae (to closely simulate metastases), found that 50 to 75% of the calcium content must be lost before the lesion can be identified radiographically. Since the vertebral column is the most common site for bone metastases,¹⁸ it is clear that classical roentgen methods will not detect most space-taking lesions until they are well advanced (in the series by Bachman and Sproul,¹⁵ 52% were missed; and in the series by Galasko,¹⁹ 50% were missed). Incidentally, this is not true of metastases to cortical bone.^{17,20}

It has been apparent since the work of Desgrez²¹ and Dudley²² with ^{72}Ga almost 20 years ago that bone-seeking agents could detect painful metastases before roentgenographic changes. Several years ago my colleagues and I made a careful study²³ of the histopathology, ^{85}Sr concentration, bone scan, and roentgenogram in 34 patients with malignant disease who underwent bone biopsy or were examined at autopsy to better understand the relation between these measurements. The following material summarizes the methods and the conclusions we reached from this study.

BONE-BIOPSY STUDIES

Patients suspected of harboring bone metastases from primary cancers or having primary bone tumors were injected with ^{85}Sr nitrate or chloride (usually 100 μCi). Scans and roentgenograms of painful areas were made usually 2 days later. Total bone weight was estimated to be 10% of body weight (B.W.) ("standard man" data).²⁴ The maximum possible ^{85}Sr concentration, assuming uniform distribution, was, therefore, dose injected (microcuries) divided by 10% B.W. (grams). From our own data and those of others,²⁵ we were aware that the injected ^{85}Sr was not uniformly distributed between different bones in the same person and that the estimate of bone weight might be in error as a result of obesity, bed rest, weight loss, etc. Nevertheless, this method appeared to provide a reasonable estimate of strontium distribution in the body.

Biopsy or autopsy specimens from scanned areas were blotted dry on filter paper, weighed, counted in a well scintillation counter, and then sent to the pathology laboratory for routine processing. The ^{85}Sr concentration was expressed as microcuries per gram of wet weight, and this figure was divided by the maximum possible concentration, the calculation given above. The ratio of the two was called the "percent of maximum uptake." An experienced pathologist later reviewed all the biopsies (without knowledge of the ^{85}Sr

findings) and graded them from 0 to 4+ with regard to width of osteoid seams, presence of calcified trabeculae, number of osteoblasts, and decalcification time required for sectioning. The last item is an estimate of the total calcium content, whereas the other features are measures of the activity of newly formed reactive bone. From these data we drew our conclusions.

RESULTS

Sections taken from bones that were histologically normal served as controls. The ^{85}Sr concentration in these bones, as a percent of maximum uptake, ranged from 10.7 to 36.3% for trabecular bone and 27.4 to 49.0% for cortical bone. The data from diseased specimens were plotted as a function of the maturity of reactive bone present and are given in Table 1 and Fig. 1. When these data were correlated with the scans and roentgenograms, an interesting association was apparent; the bone scan reflected the rate of the calcification process in the reactive bone. It was also apparent that this time sequence could be divided into three distinct phases:

Phase I (Fig. 2)

In its earliest stage, tumor incites the formation of osteoid tissue, identified as pink-staining seams on H & E sections, by proliferating osteoblasts. It is known that virtually all tumors do this to some extent.²⁶ The ^{85}Sr concentration in these specimens was about two to three times normal, and this increase could be detected on the bone scans. The roentgenograms, however, were either normal or showed radiolucencies only, but never radiodensities. The reason for this discrepancy is that the twofold-to-threefold increase in ^{85}Sr (and, by analogy, calcium) content is too small to be visualized by X-ray examination. In these early lesions, therefore, the scan has its greatest diagnostic value.

Phase II (Fig. 3)

As more reactive bone is formed, the ^{85}Sr concentration increases up to 15 times normal, and the scan, therefore, becomes progressively denser. Osteoblasts are plentiful. Enough calcium is now present for the lesion to be identified as a radiodensity on a roentgenogram.

Phase III (Fig. 2)

Finally, reaction is complete, osteoblasts disappear, and the pink-staining osteoid seams are now well calcified. The ^{85}Sr concentration is then no different from surrounding normal bone, and thus the scan appears normal. However, because of the considerable calcium content of this bone, it is seen as a

TABLE 1
CORRELATION OF ^{85}Sr CONCENTRATION, ^{85}Sr SCAN,
ROENTGENOGRAM, AND HISTOPATHOLOGIC FINDINGS IN
HUMAN BONE BIOPSY AND AUTOPSY SPECIMENS*

Type of study	Normal bone	Histopathology		
		Reactive bone		
		Phase I	Phase II	Phase III
^{85}Sr concentration†				
Cortical bone	49.0, 27.4 42.8 31.8			
			195	38.1
Trabecular bone	36.3 32.9-15.6 27.2 17.5 10.7	107 87	543 145 96	57.5 37.2
Malignant bone			365 122	
Scan findings‡	0	+ to ++	++ to ++++	0 to +
Radiodensity §	0	0	++	++++

*Based on data from N. D. Charkes, I. Young, and D. M. Sklaroff, *The Pathologic Basis of the Strontium Bone Scan*, *J. Amer. Med. Ass.*, 206: 2483 (1968).

†In nanocuries per gram of wet weight.

‡(0) normal, (+) minimal increase, (++) moderate increase, (++++ marked increase.

§ Radiolucencies may occur in any phase.

radiodensity on a roentgenogram. This, then, is the "healed" stage of reactive bone formation.

It is important to note that the bone scan reflects only reactive bone formation and not the presence of tumor cells themselves. Other disorders that cause reactive bone to form, such as fracture, infection, and aseptic necrosis, can therefore give rise to an abnormal bone scan.

Uncommonly, the bone scan is normal in the presence of advancing metastatic disease. Roentgenograms in these patients show radiolucencies only, never radiodensities. Bone biopsies revealed, as expected, normal ^{85}Sr concentration (owing to the presence of destroyed normal trabeculae) and no reactive bone formation. Fortunately, from a diagnostic standpoint, this situation occurs in fewer than 7% of lesions in large reported series. In our own experience²⁷ this figure is 3%. So-called false-negative scans are seen in some patients with rapidly advancing lesions, such as reticulum-cell sarcoma, where presumably reactive

Fig. 1 Strontium-85 concentration in bone-biopsy and autopsy samples (solid line) and estimated total calcium content (dotted line) vs. maturity of reactive bone (abscissa). ○, trabecular bone, Δ, cortical bone. See text for details. [From N. D. Charkes, I. Young, and D. M. Sklaroff, *The Pathologic Basis of the Strontium Bone Scan*, *J. Amer. Med. Ass.*, 206: 2487 (1968).]

bone is either not formed or is rapidly destroyed, and in some patients with very slow-growing, indolent tumors (exemplified by thyroid carcinoma) in which bone reaction is minimal or absent or takes place at a rate too slow to be detected by scanning. All these lesions are typified by radiolucencies, and radiodensities are absent.

Others^{2,8} have confirmed this interpretation of the scan and roentgen changes as manifestations of reactive bone formation. It seems clear from these studies that simultaneous bone scan and roentgenogram allow an accurate interpretation of the activity of newly formed reactive bone.

CLINICAL RESULTS

In most large series of patients with metastatic cancer studied by both techniques, the frequency of bone lesions visualized by scanning but not by roentgenography ranges between 14 and 34% (Table 2). In many, but not all, cases these lesions are painful, and the scan aids the radiotherapist in setting portals.⁵⁰ An abnormal scan calls for a review of previous roentgenograms; in one third of the cases in which roentgenograms were interpreted as normal, careful inspection of the scan-positive area in retrospect revealed abnormalities.^{2,9}

Strontium-85 scans were abnormal in 16% of 64 patients with stage II breast cancer (axillary node metastases),³⁰ and ¹⁸F scans were abnormal in 24% of 50

Fig. 2(a) Roentgenogram of hemisected lumbar vertebrae from a 56-year-old man who died from carcinoma of the pancreas. Note that the upper and lower thirds of L4 are dense (solid arrows) whereas the midportion is normal (open arrow).

(b) Strontium-85 scintigram of the specimen superimposed on the roentgenogram. Note that in L4 the greatest amount of uptake is in the midportion.

(c) Photomicrograph of midportion of L4 [area of open arrow in (a)] shows immature osteoid laid down by osteoblasts (arrows), in reaction to proliferating tumor (T). This is a Phase I lesion. (H & E stain; magnification, 430x (reduced 30%).

(d) Photomicrograph of lower third of L4 [area of solid arrow in (a)] shows mature reactive bone (M), and absence of immature osteoid and osteoblasts. This is a Phase III lesion. (H & E stain; magnification, 250x (reduced 30%). (N. D. Charkes, I. Young, and D. M. Sklaroff, unpublished data.)

(c)

(d)

(b)

(a)

(c)

Fig. 3(a) Gross photograph of hemisected thoracic spine of 62-year-old woman with history of endometrial carcinoma. Collapsed T8 is indicated by arrows.

(b) Roentgenogram of hemisected thoracic spine. Superimposed scan of specimen shows marked ^{85}Sr uptake in outer half of collapsed T8 (solid arrow) corresponding to radiodensity (open arrow).

(c) Photomicrograph of radiodense, "hot" area of T8 reveals osteoblasts (arrows) laying down immature osteoid (I) that is moderately calcified in the deeper portions (M). (H & E stain; magnification, 430x (reduced 30%). No tumor cells were seen, and interpretation is osteoporotic infraction with callus formation. This is a Phase II lesion (N. D. Charkes, I. Young, and D. M. Sklaroff, unpublished data.)

TABLE 2
CLINICAL EFFECTIVENESS OF BONE SCANNING

Disorder	Percent abnormal scans	No. of patients	Roentgen examination	Remarks	References
Primary and metastatic cancer	14 to 34		Normal	Large series	19,27,29,32, 33, 34-42
	13 to 41	34 to 143	Normal or equivocal	^{85}Sr , $^{87\text{m}}\text{Sr}$, ^{18}F	27,35,41, 43,44
Breast cancer	16	64	Normal	Stage II, ^{85}Sr	30
	24	50	Normal	"Early," ^{18}F	19
	72	50	Normal	"Advanced," ^{18}F	19
Prostatic cancer	19	93	Normal	Consecutive cases, ^{85}Sr	45
	21	34	Normal	All stages, ^{85}Sr , ^{18}F	46
	34 to 73	34 to 93	Normal and abnormal	All stages	45-47
Lung cancer	50	53	Normal and abnormal	^{85}Sr	48
Lymphomas	57	28	Normal	^{85}Sr	32
	84	19	Most normal	^{85}Sr	49
Hodgkin's disease	12	51	Normal	^{85}Sr	31
	28	51	Normal and abnormal	^{85}Sr	31
Osteomyelitis	81	11	Most normal	Stages I and III	50
	50	8	Normal	^{85}Sr	32
	72	18	Normal and abnormal	^{85}Sr	32

patients with "early" mammary carcinoma; all these patients had normal roentgenograms. These results suggest that a significant number of women are undergoing needless radical surgery for incurable disease. Several groups, including our own, are now using $^{87\text{m}}\text{Sr}$ scans to evaluate patients with breast masses suspected of being cancer. To date, fewer than 20% of our patients have abnormal scans (this group includes some stage I patients) (Table 3).

Other malignant disorders in which bone scans have shown significant changes despite normal roentgenograms are listed in Table 2. Scanning has been included in the staging of Hodgkin's disease by one group.³¹

Bone scanning has also proved useful in the diagnosis of osteomyelitis when roentgenograms are normal.^{32,51} Ahlbäck, Bauer, and Bohne⁵² have studied osteonecrosis by digital scanning (scintimetry) and have reported abnormal ^{85}Sr uptakes before roentgen changes; the location of the abnormal uptake, particularly in the medial femoral condyle, aids in differentiating the disorder from osteoarthritis (Fig. 4).

TABLE 3
CORRELATION OF PREOPERATIVE ^{87m}Sr BONE SCAN
WITH HISTOLOGIC FINDINGS IN AXILLARY LYMPH
NODES IN 24 WOMEN WITH BREAST CANCER *

Lymph node metastases	No. of patients	^{87m}Sr bone scan		
		Abnormal	Equivocal	Normal
Negative	6	1	0	5
Positive	17	3	3	11
Not submitted	1	0	0	1
Total	24†	4	3	17

*Supported by a grant from the Fraternal Order of Eagles.

†All patients were free of bone pain, and X-ray examination revealed no metastases. Abnormal scans resulting from degenerative joint disease are classified here as "normal."

OTHER MECHANISMS

Not all instances of abnormal deposition of bone-seeking radionuclides are due to reactive bone formation (Table 4). For example, some bone-forming malignant tumors (osteogenic sarcoma and chondrosarcoma) take up the tracer in a manner identical to normal bone,⁵³⁻⁵⁵ and the roentgen correlation is the same. It is interesting to note that at the periphery of these tumors one finds phase I reactive bone; the edge of the tumor is phase II malignant bone, and the midportion is phase III and often necrotic.^{23,56} When these tumors metastasize to lung or soft tissue, deposition of a bone-seeking tracer may be identified by scanning before roentgen changes.^{56,57} Samuels,⁵⁸ however, found uptake in only 6 of 12 patients with pulmonary metastases, the smallest measuring 0.5 cm, and Schall et al.⁵⁵ noted absence of uptake in several patients with both small and large lesions identified on chest roentgenograms. The amount of uptake in extraosseous metastases of osteosarcomas appears to depend both on the degree with which malignant bone is formed and on the absence of necrosis.⁵⁵

Radiostrotrium deposition has been noted in a number of instances in association with dystrophic calcification without osteoid formation, sometimes before roentgen changes. These disorders reported have included uremia with hypercalcemia,⁵⁹ urolithiasis,⁶⁰ and myositis ossificans.⁶⁰ Strontium phosphate complexes transiently sequestered in the liver have also been identified by scanning.⁶¹

Fig. 4(a) Roentgenogram of legs of 69-year-old man with osteonecrosis of right medial femoral condyle. Note typical radiodensity (arrow). Left knee joint appears normal. Intermittent severe pain was present in right knee for 6 months, necessitating use of crutches, and subsequently he developed dull ache in outer aspect of left knee.

(b) Strontium-85 scan of legs shows marked uptake over right medial femoral condyle (solid arrow). Note also increased uptake over left lateral femoral condyle (open arrow), most likely due to osteoarthritic changes secondary to increased weight bearing rather than to osteonecrosis.^{5,2} (Patient was referred by Mary Moore, M.D., and J. Lachman, M.D., and scans were published with permission.)

Recently, it has been suggested that some patients with myelofibrosis show increased strontium or fluoride uptake as a result of augmented skeletal blood flow.^{62,63} This could represent one means by which the lesions of Paget's disease are visualized.

Finally, we must consider the possibility in some patients with multiple myeloma that the increased strontium uptake in the skull associated with multiple lytic lesions may represent increased bone surface area²⁷ since sclerosis of these lesions is exceedingly rare.

TABLE 4
PATHOPHYSIOLOGICAL MECHANISMS IN BONE SCANNING

Mechanism	Example	Radionuclides
Reactive bone formation	Metastasis	Bone seekers (e.g., ^{85}Sr , ^{18}F)
Malignant new bone	Osteogenic sarcoma	
Increased bone blood flow	Myelofibrosis; Paget's disease	
Increased bone surface	? Myeloma	
Dystrophic calcification	Uremia with hypercalcemia (lungs, kidneys)	
Tumor blood flow	Metastasis	$^{99m}\text{TcO}_4$, ^{131}I HSA, ^{87m}Sr
Tumor uptake	Metastasis	^{197}Hg -chlormerodrin, ^{67}Ga
Reticuloendothelial system deficit	Metastasis	^{99m}TcS colloid, ^{198}Au

Other methods of visualizing bone lesions are given in Table 4. These have received little clinical attention, although blood flow through soft-tissue lesions has proved to be a source of considerable confusion when using ^{87m}Sr if the tumor abuts upon bone (Fig. 5).⁶⁴ In these cases the soft-tissue lesion is usually well seen on the roentgenogram, and a radionuclide with a higher bone-to-blood concentration than ^{87m}Sr is preferable for scans to detect bony involvement.

In an effort to improve the bone-to-background counting rate ratio with ^{87m}Sr , we have studied the effect of parathyroid extract and thyroid hormone on the skeletal uptake of radiostrontium in rats (Malamud, Charkes, and Reidenberg, unpublished data). We found that parathyroid extract significantly augmented ^{85}Sr uptake ($p < 0.01$), resulting in a 49% increase in contrast (Table 5). We are currently investigating the effect of this hormone on skeletal uptake of ^{87m}Sr in man, and preliminary results suggest an acute osteoblastic action similar to that seen in the rat.

(a)

(b)

(c)

Fig. 5 This 45-year-old woman developed upper midback pain 9 years following radical mastectomy for breast cancer.

(a) Roentgenogram shows retrocardiac density (arrows). Its medial border was not seen, and the possibility of bone involvement was raised.

(b) Strontium-37m scan of chest revealing concentration in region of retrocardiac mass (open arrows) and slight increase in uptake over midthoracic spine (solid arrows), suggesting bone involvement.

(c) Strontium-85 scan, 2 days postdose, is normal; thus the apparent bone uptake on ^{87m}Sr scan was due to blood in the mass overlying the spine. At operation a large retrocardiac metastasis was found, involving the sensory root of T8 but not impinging upon bone.

TABLE 5

EFFECT OF PARATHYROID EXTRACT (PTE) AND/OR THYROID HORMONE (TH) ON SKELETAL UPTAKE OF ^{85}Sr IN IMMATURE RATS*†

Treatment	No. of rats	Percent ^{85}Sr bone uptake‡	p§	Bone-to-nonbone concentration¶	Change in contrast
None	5	46.0 $\pm$ 4.0**		4.84 (C_N)	1.0 (C_N/C_N)
PTE	6	56.0 $\pm$ 2.3	<0.01	7.22 (C_P)	1.49 (C_P/C_N)
TH	5	54.1 $\pm$ 2.6	<0.05	6.69 (C_T)	1.37 (C_T/C_N)
PTE and TH	4	52.6 $\pm$ 2.5	<0.10		

*L. S. Malamud, N. D. Charkes, and M. Reidenberg, unpublished data.

†Treatment given 24 hr before and at time of ^{85}Sr dose.

‡Rats sacrificed 2 hr after intraperitoneal dose.

§Compared with no-treatment group.

¶Assuming skeleton 15% of body weight; C_N , none; C_P , parathyroid extract; C_T , thyroid hormone.

**1 SD.

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JOINT SCANNING

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ABSTRACT

Research in the technique of joint scanning after an intravenous injection of ^{131}I -labeled human serum albumin and ^{131}I -labeled iodipamide documented that this technique could be used to detect synovitis in many types of arthritis. Routine clinical use of these radiopharmaceuticals was precluded by the moderately high radiation dose and the long scanning time. The use of short-half-life tracers, such as $^{99\text{m}}\text{Tc}$ -pertechnetate, with a stationary imaging device now makes joint scanning a practical clinical procedure.

Localization of the radiopharmaceuticals used for visualizing the synovitis is nonspecific, but the pattern of joint involvement may aid in the differential diagnosis of arthritis. Joint scanning is of particular value in the patient with joint pain when other laboratory and clinical studies are borderline and/or normal. A demonstration of only normal localization in the synovial membrane is further confirmation of the lack of synovitis, and it suggests that the pain is nonarthritic in origin. Conversely, a positive scan has a high degree of correlation with eventual confirmation, weeks or months later, of arthritic synovitis.

The synovial membrane scan is 30% more accurate in the detection of synovitis than is the routine roentgenogram. In addition, the scan exceeds clinical evaluation, particularly of the knee joint, and is an objective method for documenting progression or response of the disease. Several authors have demonstrated the usefulness of joint scanning, an indication that evaluation of the synovial membrane of peripheral joints by scanning should be a routine procedure in most nuclear medicine laboratories.

Radiopharmaceuticals were first used to evaluate the synovial membrane in the early 1950's and consisted in measuring the clearance of intra-articularly injected radiopharmaceuticals.¹⁻³ The technique of joint scanning after the intravenous injection of ^{131}I -labeled Human Serum Albumin (^{131}I -HSA) or ^{131}I -iodipamide was initiated by Weiss and Maxfield et al.⁴⁻⁹ The ability of these radiopharmaceuticals, when administered intravenously, to demonstrate synovitis in the joints of the extremities is shown in Fig. 1. The evaluation of the

knees and hands with a 3-in. rectilinear scanner required approximately 4 hr. This long scanning time and the relatively high radiation dose precluded the use of this tracer as a routine clinical procedure. The high background in the trunk precluded evaluation of the sacroiliac or vertebral column areas.

The joint scan, which in effect is the visualization of the synovial membrane, in addition to documenting synovitis in patients with known active disease, can frequently detect the synovitis before roentgenographic changes become apparent (Fig. 2). Although the scan may show minimal involvement of a joint at first, serial scans can document progression of the disease. Though the localization of the tracer is nonspecific, the pattern of synovitis may aid in the diagnosis of disease and can indicate the site for biopsy (Fig. 3).*

Technetium-99m-pertechnetate ($^{99m}\text{TcO}_4$) for synovial membrane scanning provided a readily available, short-half-life tracer.⁹⁻¹⁶ With $^{99m}\text{TcO}_4$ and a stationary imaging device, such as an Anger camera,[†] the time required for synovial membrane scanning of all peripheral joints of the extremities is 1 hr or less. This reasonable time with low radiation dose makes synovial membrane scanning of all peripheral joints a technically practical clinical procedure.

TECHNIQUE

Radiopharmaceuticals

Table 1 shows the dose schedule and the radiation dose for radiopharmaceuticals used in synovial membrane scanning. We will discuss the scanning technique using $^{99m}\text{TcO}_4$, the most popular of these radiopharmaceuticals. Techniques for other radiopharmaceuticals can be found in the references or the summary article by Maxfield et al.¹⁷

$^{99m}\text{TcO}_4$

The thyroid gland is blocked with 200 mg of potassium perchlorate given orally 1 hr before the $^{99m}\text{TcO}_4$ is injected intravenously. Usually the scans are begun 5 to 30 min after injection. Figure 4 demonstrates the positions used for synovial membrane scanning with an Anger camera and $^{99m}\text{TcO}_4$. A normal study [Fig. 5(a)] and a positive scan of a patient with rheumatoid arthritis [Fig. 5(b)] show the ability of this scan technique to document the presence or absence of synovitis. It is important that no other joint be superimposed in the field of view of the detector during the examination. Using the positions illustrated in Fig. 4 will eliminate this problem. Although patients without much disability can be scanned comfortably while in a sitting position, a stretcher is of particular value for those with arthritic pain. Minimal motion by the patient is

*Figures 3, 4, 7(a) and (b), 8(d) and (e), 9(a), 10, and 11(b) and (d) are from W. S. Maxfield, T. E. Weiss, and S. E. Shuler, *Seminars Nucl. Med.*, 2: 50-70 (1972).

†Nuclear-Chicago Corporation, Pho/Gamma Mk. III.

(b)

(d)

(a)

(c)

Fig. 1 Patient with confirmed active rheumatoid arthritis. Clinically there was involvement of both wrists, the metacarpophalangeal joints of both hands, and proximal interphalangeal joints of the second and third digits bilaterally. Both knees were clinically involved. Photographs of the hands (a) and knees (b) are shown. Roentgenograms confirmed the clinical findings in the hands (c) and knees (d). The presence of the synovitis detected clinically and on the roentgenograms is also demonstrated by the ^{131}I -HSA scans of the hands (e) and knees (f).

Fig. 2 Patient with rheumatoid arthritis, confirmed by laboratory tests, involving the knees. The hands clinically were within normal limits as suggested by physical examination and the photographs of the hands (a). Roentgenograms of the hands (b) were interpreted as within normal limits. The ^{131}I IHSA scan demonstrated a positive localization in the left wrist with a minimal localization in the right wrist (c). At that time the patient complained of pain in the left wrist. A follow-up evaluation scan 4 months later demonstrates positive localization in both wrists and now also involvement of the metacarpophalangeal joints and proximal interphalangeal joints of both hands (d). Radiographically, the hands were unchanged from the pattern shown in Part b. There was now pain and tenderness in both wrists by history and physical examination.

(c)

(d)

Fig. 3 Comparison of roentgenograms and ^{131}I -HSA scans of patient admitted with probable diagnosis of gonococcal arthritis on the basis of pain in one ankle. Roentgenograms of the knees (a) and right hand (c) were interpreted as normal. The scan, however, demonstrated positive localization in both knees (b) and in the palm of the right hand (d). Biopsy of the knee and hand gave a diagnosis of polyarteritis. After a year of corticosteroid therapy, the roentgenograms of the knees (e) were interpreted as showing osteoporosis, possibly secondary to progression of the patient's arthritic condition, although an effect of the corticosteroid therapy could not be excluded. Scans of the knees (f) and hand (g) at that time showed no evidence of abnormal localization correlating with the patient's lack of pain in the knees and hand. The normal scans were further evidence of the absence of synovitis, which confirms the patient's response to the therapy of her disease.

TABLE 1
RADIOPHARMACEUTICALS FOR SYNOVIAL MEMBRANE SCANNING*

Tracer	Intravenous dose of tracer	Maximum dose to whole body, mR	Maximum dose to blood, mR	Maximum dose to critical organ, mR
^{131}I HSA	25 $\mu\text{Ci}/10\text{ lb}$	300	5400	Blood
^{131}I -Iodipamide	40 $\mu\text{Ci}/10\text{ lb}$	30	450	Blood
^{99m}Tc -albumin	1 to 3 mCi	15	141	Blood
^{99m}Tc -pertechnetate	5 to 15 mCi	180	210	Stomach, 3000 Colon, 1700
^{99m}Tc -DTPA	5 to 10 mCi	160	160	Bladder, 555
^{113m}In , pH 3.5	8 to 10 mCi	75	75	Blood

*From W. S. Maxfield, T. E. Weiss, and S. E. Shuler, *Seminars Nucl. Med.*, **2**: 59 (1972).

required to achieve the desired positions. For the $^{99m}\text{TcO}_4$ tracer, it is particularly important to study one area and then immediately the correspondent area on the contralateral side. If the pattern of localization is to be compared from patient to patient, a standard routine of progression from one joint area to the next must be used for both normal controls and patients with arthritic disease. As $^{99m}\text{TcO}_4$ concentration within the vascular system falls, the localization in normal synovial tissue increases, reaching the maximum at 30 to 90 min after intravenous injection. The pattern, therefore, of a given joint will vary depending on the time of the scan after intravenous injection.^{9,12,15}

The 4000-hole low-energy collimator of the Anger camera is used for this technique. The spectrometer setting is usually a 15% window with the range set for ^{99m}Tc . The scan of one joint is obtained for a preset number of counts, usually 70,000 counts for the hands and knees and 50,000 for the elbows and ankles. The contralateral joint in the same view is then counted for the same amount of time. The shoulders are counted for a preset 1-min count since the majority of the counting rate for this projection may come from activity within the lungs rather than within the region of the synovial membrane of the shoulder.

Perfusion studies of a single joint can be obtained by serial scintiphotos with the Polaroid camera and either 35-mm images from the second oscilloscope or movies from a persistence oscilloscope. The use of a direct-storage tape unit or computer-controlled readout accessory would provide a more accurate presentation method for evaluating the degree of localization in the synovial membrane of a given joint than does the usual evaluation of the scintiphotos. The ability to quantitate the counting rate of the synovial membrane area from one study to another would be of particular value in measuring progression or response to

Fig. 4 Positions used for synovial membrane scanning with an Anger camera.

Fig. 5 (a) Normal $^{99m}\text{TcO}_4$ synovial membrane scan.

Fig. 5(Continued) (b) Positive $^{99m}\text{TcO}_4$ scan of a patient with active rheumatoid arthritis.

therapy through serial scans. The evaluation of the synovial membrane areas of the trunk, such as sacroiliac joints and vertebral column, has not been practical in the past because of high body background. Tomographic scanning units may make it practical to study these areas.

INTERPRETATION

General

Positive localization has been reported in synovitis associated with rheumatoid arthritis, gout, infectious arthritis, tendonitis, bursitis, osteoarthritis, polyarteritis, lupus erythematosus, psoriasis, and Reiter's disease. The localization of the radiopharmaceuticals in areas of active synovitis is nonspecific and gives no information on the etiology of the inflammation. All radiopharmaceuticals used for synovial membrane scanning seem to give a similar pattern of localization with the exception of ^{113m}In . Comparison of ^{113m}In and $^{99m}\text{TcO}_4$ scans in rheumatoid arthritis by Martinez et al.¹¹ demonstrated that some joints were hot with both indium and technetium but other joints showed a positive localization with technetium whereas with indium they showed less localization or a normal pattern.

The mechanism of localization of the radiopharmaceuticals used for synovial membrane scanning has not been defined unequivocally, but it appears to be a change in the permeability of the synovial membrane and an increase in vascularity. If the localization were due to increased vascularity alone, the degree of localization in the inflamed area should parallel the concentration of the radiopharmaceutical in the blood. Several experiments have indicated that the concentration in the synovial membrane increases during the time that the vascular activity is falling. The point of maximum concentration in the normal synovial membrane for $^{99m}\text{TcO}_4$ appears to be 30 to 90 min, whereas the maximum concentration for the tagged albumin is 3 to 6 hr. For synovitis the localization is more rapid, but it still occurs while the level of tracer in the vascular space is falling. Though the localization of the radiopharmaceuticals is nonspecific, indicating only active synovitis, the pattern of localization can aid in differentiating various types of arthritis.

Interpretation of the normal pattern with the tagged albumin and ^{131}I -iodipamide presents no problem since the degree of localization in the normal synovial membrane with these materials is not sufficiently great to permit it to be outlined with current scan techniques [Figs. 2(c) and 3(f and g)].

Technetium- 99m -pertechnetate has the disadvantage of minimal localization in the normal synovial membrane in most cases, as shown in Fig. 5(a). The degree of localization varies with time after intravenous injection, as shown by Maxfield^{9,17} and McCarty et al.^{15,16} Rapid-sequence scintiphotos have shown that the initial perfusion of the synovial membrane is less than that of adjacent

soft tissue.^{12,17} The localization of the $^{99m}\text{TcO}_4$ seems to vary depending on the activity level of the person studied. Though there is not conclusive evidence, my impression is that a sedentary person will show a minimal localization in the synovial membrane areas whereas an active one may have more, suggesting an almost abnormal scan. A change, therefore, in activity or occupation could produce some change in the $^{99m}\text{TcO}_4$ synovial membrane scan. The changing pattern of localization in the vascular and synovial membrane areas, however, seems to produce the most difficulty for the neophyte in interpreting scans of synovial membranes. It must be reemphasized that it is extremely important to cover the joint areas in a routine order and to go from one joint to the same view of the contralateral joint if the degree of localization with $^{99m}\text{TcO}_4$ is to be compared in different studies. The standard sequence will minimize the changes with time after the injection of the $^{99m}\text{TcO}_4$. Though this changing localization is a disadvantage of $^{99m}\text{TcO}_4$, the ready availability of this tracer and the lack of administration of a foreign protein outweigh this minor problem. The guideline we use to diagnose abnormal localization is that the visualization of the synovial membrane area should not be greater than the activity in the adjacent major vascular bundles. The localization in the synovial membrane may slightly exceed that in adjacent soft tissue. Epiphyseal centers in children are frequently visualized. These should not be misinterpreted as areas of abnormal localization in the synovial membrane.

The comparison of photographs, roentgenograms, and synovial membrane scans with ^{131}I HSA in Fig. 1 demonstrates that the synovial membrane scan can show the areas of arthritic involvement revealed by the roentgenograms. Even though the roentgenogram may not appear significantly abnormal, the synovial membrane scan can detect synovitis. Note the left fourth metacarpophalangeal (MCP) joint and the left knee. Thickening of the synovial membrane of the left knee was observed on physical examination and is shown in the photograph, but tenderness in the left fourth MCP joint was not noted. Once the area was identified on the scan, reexamination elicited tenderness and a history of pain in that joint.

The photograph taken as part of the evaluation of the hands of a patient with early rheumatoid arthritis is shown in Fig. 2(a). The roentgenograms of the hands were interpreted as being within normal limits [Fig. 2(b)], but the scan showed marked localization in the left wrist with a small area of positive localization in the right wrist and suggested involvement of the MCP and proximal interphalangeal (PIP) joints, as noted in Fig. 2(c). A subsequent follow-up scan 4 months later demonstrated marked progression of the synovitis in both hands, documenting the accuracy of the diagnosis of early synovitis in the right wrist [Fig. 2(d)].

As noted, the localization of the tracers is nonspecific, but the pattern of localization may aid in the differential diagnosis. The patient in Fig. 3 complained only of pain in the ankle, but, after the synovial membrane scan

showed positive localization in both knees and the right hand, questioning revealed tenderness and pain in these areas. The positive scan was used as a guide in the biopsy of the knee and the hand. The biopsies confirmed a diagnosis of polyarteritis, whereas the admitting diagnosis had been infectious arthritis of the left ankle only. Figures 5 and 6 show that the ^{99m}Tc scans obtained with an Anger camera have the same degree of accuracy in detecting areas of synovitis as do the rectilinear ^{131}I HSA scans.

Rheumatoid Arthritis

One of the problems with the roentgenographic evaluation of arthritic conditions is that when deformity secondary to the arthritis develops, it is frequently difficult to determine the degree of synovitis present. Figure 7 shows the roentgenograms and scan of a patient with advanced rheumatoid arthritis. Note particularly the thumbs, which are markedly deformed. Yet the scan shows minimal localization in these areas, indicating that the synovitis in these regions is not active. When the synovitis burns out or has been controlled by therapy, the scan will return to an essentially normal pattern. This lack of synovitis is also demonstrated by the second MCP joint of the left hand.

Gout

Gout can simulate the pattern of synovitis found in rheumatoid arthritis, as noted in Fig. 8(d); however, gout and rheumatoid arthritis can usually be separated by laboratory studies. The follow-up scan on this patient after 3 months of antigout therapy showed a decrease in the degree of the synovitis, though some was still identifiable [Fig. 8(e)]. When the synovitis is totally controlled, the synovial membrane scan will return to a normal pattern.

Osteoarthritis and Keinböck's Disease

Osteoarthritis and other types of localized arthritic disease, such as Keinböck's disease, may produce a positive localization on the synovial membrane scan. Not all areas of osteoarthritis will appear positive in the scans; however, when synovitis is associated with the disease, a positive localization can be identified. It is usually a localized area of synovitis that correlates with areas of osteoarthritis identified on the roentgenogram. Figure 9(a) shows a positive localization at the base of the right thumb of a patient with osteoarthritis; other synovial membrane areas depict a normal pattern. Also included in Fig. 9 is a positive localization in the wrist of a patient with Keinböck's syndrome showing positive findings on both the roentgenograms and the scan of the right wrist.

Reiter's Disease

Reiter's disease and early rheumatoid arthritis are difficult to differentiate on the basis of roentgenographic and laboratory studies. The synovial membrane

scan can aid by showing a pattern of synovitis for Reiter's disease that is usually different from that typical of rheumatoid arthritis. The synovitis of Reiter's disease usually affects the tendon areas to a greater degree than the synovial membrane regions. Intense localization in the Achilles tendon and in the tendinous attachments in the region of the knee are frequently found in Reiter's disease, as demonstrated in Fig. 10(a). Occasionally, increased localization in the heels or soles of the feet will be identified. Though localization in the Achilles tendon can occur with rheumatoid arthritis, the localization in the tendon areas is usually minor in comparison to involvement of a more characteristic synovial membrane region, such as the metacarpals, metatarsals, and knees, as shown for rheumatoid arthritis in Fig. 10(c) and (d).

DISCUSSION

As previously noted, the localization of the radiopharmaceuticals currently used for synovial membrane scanning is nonspecific; however, the pattern of localization may aid in making a differential diagnosis. For instance, the ability to assist in the differentiation of Reiter's disease from early rheumatoid arthritis was pointed out.

The synovial membrane scan is of particular value in the patient with joint symptoms when the roentgenographic findings are within normal limits and other tests are borderline normal. If the synovial membrane scan is normal, then it provides further evidence that the joint complaint is not due to synovitis and, therefore, is more likely to be of nonarthritic origin. Conversely, a positive synovial membrane scan has a high degree of correlation with eventual confirmation of arthritic disease weeks to months later. Figures 2 and 3 show the ability of the synovial membrane scan to detect synovitis, later confirmed by biopsy or other studies. Figure 11 demonstrates the roentgenograms and scans of two patients with joint complaints. In one patient the scan showed a normal pattern with follow-up showing no evidence of arthritic disease. In the other patient the scan showed a positive localization in the area of pain in the right hand and also demonstrated abnormal localization in both elbows, which eventually became symptomatic. Figure 12 is another demonstration of a patient with joint symptoms whose roentgenograms were within normal limits and whose scan was positive. In addition, Figs. 3, 8, and 12 show that the synovial membrane scan can be used to follow the course of the patient's disease, demonstrating improvement in the synovitis with time. Figure 2 documents a case of progression of the patient's disease. The scan is of particular value in showing improvement because once roentgenographic abnormality is evidenced, regression is frequently difficult to demonstrate by that method.

Our experience and that of others indicates that the synovial membrane scan is 30% more accurate in the detection of synovitis than is the roentgenogram. The incidence of false positive scans has been 2 to 5%. Sholkoff^{1,8} has used

(a)

(b)

(c)

Fig. 6 Correlation of abnormality shown by roentgenograms and on $^{99m}\text{TcO}_4$ synovial membrane scan obtained with an Anger camera in this patient with rheumatoid arthritis is excellent. Soft tissues and bony changes were identified in the first metacarpophalangeal joint of the left hand (a) and are demonstrated in the left hand on the synovial membrane scan (c). The soft-tissue density and the thickening of the synovial membrane of the right knee were identified on the roentgenograms of the knees (b) and correlate well with the greater degree of localization shown on the synovial membrane scan for the synovial membrane of the right knee.

(a)

(b)

Fig. 7 Patient with advanced rheumatoid arthritis as demonstrated by the roentgenograms of the hands (a). Note particularly the deformity of the thumbs and the proximal interphalangeal joint of the right fourth digit and the metacarpophalangeal joints. Roentgenogram of the knees shows erosion of the lateral margin of the left tibia in the proximal area. The right knee, roentgenographically, appeared essentially normal (b). The

(c)

(d)

$^{99m}\text{TcO}_4$ synovial membrane scans of the hands, elbows, and shoulders (c) show localization in the areas of most of the radiographic deformity in the hands, but there is minimal localization in the thumbs and the PIP joint of the fourth digit. The metacarpophalangeal (MCP) joint of the left second digit also shows essentially no localization, but there is marked localization in the MCP joints of the right hand. This case is a demonstration that when the synovitis burns out, the joints can revert to a normal pattern, though radiographic abnormality is still identified. The positive localization of $^{99m}\text{TcO}_4$ in the left knee correlates with the roentgenographic changes in the left knee. The ankles were radiographically interpreted to be within normal limits, but they show a positive localization greater on the right than on the left on the synovial membrane scan (d).

experimental animals to evaluate the sensitivity of the synovial membrane scan. In this study the synovitis from infectious arthritis was detected by the scan before it became clinically evident, confirming the ability of the synovial membrane scan to detect synovitis at an early stage.

The radiation dosimetry for diagnostic radiographic procedures and nuclear medicine studies is difficult to compare. The diagnostic X-ray exposure is brief and to one area of the body. The nuclear medicine exposure is to the whole body during the period of initial vascular distribution and then concentrated in the critical organ to produce the maximum dose to that organ system. The nuclear medicine exposure occurs over hours or days, whereas diagnostic X rays are given in seconds or minutes. The biologic effectiveness of radiation at these fractionations of low dose over short times has not been determined. The radiation dose for $^{99m}\text{TcO}_4$ is given in Table 1. Table 2 provides the average radiation dose for several common roentgenologic procedures.^{19,20} The radiation dose for a series of roentgenograms on the hands, knees, ankles, elbows, shoulders, vertebral column, and pelvis would seem to equal or possibly exceed the radiation dose from the $^{99m}\text{TcO}_4$ scan procedure.

(Text continues on page 150.)

(a)

Fig. 8 Patient with acute gout confirmed by laboratory studies. Roentgenograms of the hands (a) and knees (b) show changes that were interpreted as synovitis. The feet (c) show unequivocal abnormality in the metatarsophalangeal (MTP) joint of the first digit bilaterally. The $^{99m}\text{TcO}_4$ synovial membrane scan in the acute phase (d) shows positive localization in the areas noted on the X rays. The increased localization in the antecubital fossa on each

(b)

(c)

side is due to partial infiltration at time of injection. Note that although roentgenographically the MTP joint of the first digit of each foot appears to be equally involved, the synovial membrane shows a much greater degree of localization in the left MTP joint. The pattern shown in the hands, knees, and ankle could be rheumatoid arthritis, indicating the nonspecificity of the localization. Repeat scan after 3 months of therapy when the patient was clinically asymptomatic shows that a minimal degree of synovitis persists; thus the degree of localization is less than on the previous study (c).

(Figure 8 continues on the next page.)

(d)

Fig. 8 (Continued)

(e)

(a)

Fig. 9 Patient with osteoarthritis at the base of the right thumb. Roentgenogram shows positive findings in this area. Synovial membrane scan shows a positive localization at the base of the right thumb but a normal pattern in other joint areas (a). Patient with Kienbock's syndrome showing roentgenographic abnormality in the semilunar bone (b). Positive localization in the region of abnormality is identified in the synovial membrane scan (c). Other joint areas were within normal limits.

Fig. 10 A $^{99m}\text{TcO}_4$ scan of a patient with typical Reiter's disease. Note localization in the tendon areas of the knee and Achilles tendon of the ankles (a). Localization in the hands (b) could be that of rheumatoid arthritis. Localization in the elbows and shoulders is abnormal. Though the localization of the tracer is not nonspecific, rheumatoid arthritis (c) and (d) usually shows a greater degree of localization in the synovial membrane of the major joints,

(c)

(d)

such as the knee and tarsal areas of the ankles. There is a faint localization in the Achilles tendon of both ankles, more marked on the left than on the right, indicating that rheumatoid arthritis may also involve tendons. Localization in the hands involves wrists, metacarpophalangeal, and proximal interphalangeal joints, and is indistinguishable from the pattern of localization as shown in Reiter's disease or gout.

Fig. 11 Roentgenograms of the knees of a patient who complained of pain in both knees. Roentgenograms were within normal limits (a). Synovial membrane scan (b) shows no evidence of abnormality, further substantiating a nonarthritic origin for the joint complaint.

(b)

(Fig. 11 continues on the next page.)

(c)

Fig. 11 (Continued) Roentgenograms of the hands of a patient who complained of pain in the right third MCP joint were interpreted as normal (c). Synovial membrane scan (d) shows positive localization in the right third MCP joint as well as in both elbows. One month later rheumatoid arthritis was confirmed by laboratory studies. On the 1-month follow-up, the elbows were now unequivocally involved.

One of the problems of synovial membrane scanning up to now has been the inability to visualize the synovial membrane areas of the sacroiliac joints and the vertebral column. Possibly with the development of tomographic scanning techniques, these areas may be delineated. Another advantage of modern instrumentation that will improve the accuracy of synovial membrane scanning is the ability to quantitate the degree of localization in regions of interest. This should improve initial diagnosis and also provide a more accurate means of evaluating progression, or response to therapy.

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(d)

Fig. 12 Roentgenogram of the knees of a patient with ulcerative colitis who complained that each time the ulcerative colitis was active there was pain in the left knee. Roentgenograms (a) and clinical examination indicated no evidence of abnormality. A $^{99m}\text{TcO}_4$ synovial membrane scan (b) showed positive localization in the left knee with other joint areas except for the first toes, which showed a completely normal pattern. Follow-up scan 1 month later when ulcerative colitis was under control shows only faintly positive localization in the left knee with the right knee again being within normal limits (c).

(b)

TABLE 2
LOCAL RADIATION DOSE FROM VARIOUS DIAGNOSTIC RADIOLOGIC
PROCEDURES*

Procedure	Skin	Midplane	Testes	Ovary
Dose, mR per Film				
Lumbar spine	480 to 17,000	600 to 1500	0 to 36	20 to 1500
Dorsal spine	400 to 10,000	550 to 1000	0.3 to 13	0.1 to 60
Pelvis, AP	350 to 4700	50 to 600	26 to 2600	50 to 700
Intravenous pyelogram	500 to 1750	50 to 600	15 to 1200	15 to 300
Pelvimetry	1500 to 120,000	200 to 3300		200 to 4000
Fluoroscopy with Image Amplification, mR per Examination				
Stomach and upper GI	15,000 to 205,000	3000 to 100,000		1000 to 65,000
Barium enema	5000 to 130,000	1000 to 30,000	10 to 100	10 to 34,000

*Summarized from Refs. 19 and 20.

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CLINICAL VALUE OF BONE SCANNING WITH FLUORINE-18

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ABSTRACT

Fluorine-18 bone scans of 89 patients were reviewed. Fifty-two of the patients had a diagnosis of breast cancer; these were divided into three categories for the purpose of determining the value of bone scanning in patients with breast cancer. The data suggest a strong correlation between the presence of musculoskeletal symptoms and abnormalities on the bone scan. In the absence of symptoms in a clinically operable patient with breast cancer, the yield of abnormal bone scans is low.

Radionuclide bone scanning has attained wide acclaim in the early detection of osseous metastasis. What we seek is a critical means of determining those patients most likely to benefit from radical local therapies, as well as those patients most likely to benefit from early systemic therapy for generalized neoplasia. This paper makes no pretensions of a critical evaluation of the literature of bone scanning, early detection of malignancy, or the choice of bone scanning as a superior diagnostic aid but rather presents my experience with a limited number of cancer patients undergoing bone scanning for a variety of reasons.

MATERIALS AND METHODS

The bone scans were performed using 4 to 10 mCi of ^{18}F administered intravenously to patients who had had nothing by mouth since breakfast. Injections were given around noon, and the scans were started approximately 2 hr later. The patients were instructed to void before beginning the scan, which was started in the pelvis and proceeded cephalad.

A dual 5-in. Raytheon scanner with high-energy collimators (HC 150/12, 151-hole, 6-in. focal depth, with a resolution of 1.2 cm) was used. The recordings were obtained with 30% suppression and with an information density of 300 to 400 counts/cm². At the end of the procedure, the patient was instructed to force the intake of fluids to promote excretion from the bladder. The approximate dose for 4 mCi of ¹⁸F has been estimated at approximately 0.2 rad to the whole body, 0.5 rad to bone, and 8 rads to the bladder.

This study consists of 89 patients on whom ¹⁸F bone scans were performed within the past 10 months at Chicago Wesley Memorial Hospital. Sixty-eight of these patients were women and 21 were men. The dominant diagnosis was breast cancer, present in 52 of the 89 patients. The remaining 37 included 7 patients with prostate cancer, 4 with cancer of the colon, 15 with a variety of miscellaneous cancers, 1 with an unknown primary, and 10 with the diagnosis of "rule out carcinoma." Those 52 patients with the diagnosis of breast cancer form the basis for this study. Of those 52 patients, 51 were women and 1 was a man; 1 had a synchronous diagnosis of carcinoma of the cervix. The incidence of positive bone scans for the entire series was 38/89 (43%) and for the breast cancer group was 23/52 (44%). Of the entire group of patients, 50/89 (56%) were known to the Department of Therapeutic Radiology, whereas 39/52 (75%) of the breast cancer group were patients known to that department. Of the entire group of 89, none of the breast cancer patients and only 2 of the others had bone scans requested by the Department of Therapeutic Radiology (these two patients had genitourinary malignancies). It should be obvious that there is no "loading" of patients by the Department of Therapeutic Radiology.

Numerous parameters can be used to judge the value of bone scanning. In this study the procedure is viewed as a screening procedure, a confirmatory procedure, or a discovery procedure. The screening procedure was used for patients who were clinically operable (Columbia Stage A) and had neither laboratory nor radiographic evidence of osseous metastasis; the confirmatory procedure was used for patients with a known diagnosis of breast cancer, with clinical, laboratory, or radiographic evidence to suggest osseous metastasis; and the discovery procedure was used for patients with clinical symptoms, but no laboratory or radiographic evidence of osseous metastasis from a known breast cancer were submitted to bone scanning.

RESULTS

Of the 52 patients with breast cancer, 23 (44%) had positive bone scans (Table 1). When scanning was performed as a screening procedure on patients with clinically operable breast cancer, 25 of 27 had negative bone scans (Fig. 1). Of the 2 with positive bone scans, 1 patient, on reevaluation of the radiographic bone survey, had positive findings. This patient had a diffuse marrow involvement proven by biopsy. In the 18 patients on whom bone scanning was

TABLE 1
BONE SCANS IN PATIENTS WITH PRIMARY BREAST CANCER *

Patients with no musculoskeletal complaints†	
Positive	2 (1 patient had false-negative X ray)
Negative	25
Patients with musculoskeletal symptoms but no laboratory or radiographic evidence of metastases	
Positive	6
Negative	3
Patients with strong laboratory or radiographic evidence of osseous metastases	
Positive	15
Negative	0

*Does not include the male patient with breast cancer.

†Columbia Stage A, clinically operable patients.

Fig. 1 Normal ^{18}F bone scan of abdomen and pelvis. Note renal excretion.

used as a confirmatory procedure, 15 had positive bone scans with areas of abnormalities usually greater than recognized on radiographic examination [Figs. 2(a) and (b)]. Three of the 18 patients had musculoskeletal pain with negative X rays and confirmatory negative scans. There was a category of patients with no laboratory or radiographic evidence of osseous metastasis but with musculoskeletal symptoms who had positive bone scans. It is indeed clear that the ^{18}F bone scan was the significant factor in planning the treatment of these 6 patients.

Finally, one can look at the entire group of 52 patients in relation to the presence or absence of significant musculoskeletal symptoms. There is a very strong correlation between presence or absence of such symptoms in the findings on bone scans. Of the 23 positive scans, 20 (80%) patients had symptoms that suggested metastasis, and in only 3 (11%) patients were the symptoms absent when the bone scan showed abnormal changes. Of the 29 patients on whom the bone scan was interpreted as negative, 24 (89%) had no symptoms suggesting metastases; 5 (20%) had symptoms. This demonstrates the obvious importance of selection of patients in maximizing the yield of abnormalities from bone scanning. More importantly, however, it emphasizes our need to define the population under study when we report the value of any laboratory test.

DISCUSSION

Bone scanning of patients with breast cancer obviously is an effort to separate patients into curable and incurable categories. In the present state of cancer management, this is indeed a valuable determination before a decision is made on therapy. Clinicians have become accustomed to laparotomy staging procedures for patients with Hodgkin's disease, and recently such surgical staging has been extended to prostatic cancer and cancer of the bladder. In each instance it is felt that the search for the incurable patient is a valuable procedure that permits appropriate local treatment as well as the early initiation of systemic therapy. The well-studied, curable patient whose disease is correctly staged then benefits from the appropriate local measure with fewer uncertainties concerning the need of adjunctive therapy.

Sklaroff and Charkes¹ reported finding 10 (16%) of 64 patients with abnormal bone scans in the absence of significant pain. All these patients had histologically proven lymph node metastases at the time of mastectomy. Gastesi and associates,² using ^{18}F , reported early detection of osseous metastases in 11 (27%) of 40 patients with various malignancies. All 11 of these patients who had so-called early detection by bone scanning did, in fact, have symptoms referable to the lesions demonstrated on the scan.

It is apparent that the results of fishing for trout in a stocked pond will be significantly different from fishing for trout in a polluted river. In describing the results of bone scanning, one must define the situation to which it is applied. The results of this review would indicate that in patients without symptoms or

Fig. 2 Abnormal ^{18}F bone scan of chest (a) and abdomen and pelvis (b) of patient with metastatic breast cancer. Note abnormal uptake in ribs in (a) and left femoral head in (b).

laboratory or radiographic evidence of metastases the procedure has a very small yield, but in those patients who are symptomatic but without radiographic or laboratory abnormalities, it is likely to show a considerable number of positive findings. As a confirmatory procedure bone scanning would appear to give excellent results, and indeed it appears that the information gained from the ^{18}F bone scan exceeds that obtained from the radiograph even though both may be abnormal. It is not difficult to foresee the time when the ^{18}F bone scan may be preferred to the radiographic "metastatic series" in those patients being evaluated for radical surgery.

SUMMARY

The results of 89 consecutive ^{18}F bone scans were reviewed. A clinical analysis was made of the 52 patients with the diagnosis of breast cancer. Of the 52 patients, 23 (44%) had positive bone scans. The clinical setting that led to bone scanning could be recognized, and three categories were defined. The first category included 27 patients who received bone scans for screening purposes before definitive therapy of the breast cancer. In none of these patients were osseous metastases known or suspected before scanning. Two of the 27 patients had positive bone scans. The next category consisted of 18 patients on whom the bone scan confirmed the available clinical and laboratory data. The final group of six patients were those with pain but no laboratory or radiographic evidence of osseous metastases, and all six patients had a positive bone scan which led to appropriate treatment of the metastases. The presence or absence of significant musculoskeletal symptoms correlates very strongly with the presence or absence of abnormalities on the bone scan.

Fluorine-18 bone scanning yields valuable information to the clinician, who must manage not only the curable but also the incurable cancer patient.

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APPLICATIONS OF RADIONUCLIDES IN THE EVALUATION OF BONE DISORDERS

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ABSTRACT

The gross, microscopic, and ultramicroscopic anatomy of bone correlated with its physiology and biochemistry are outlined. With this background one can consider further detailed investigations of various aspects of bone. This may vary from the method of action of cyclic AMP to variations in its circulation. Sophisticated study of this structure, its turnover rate in health and disease, can be done most readily by the use of radionuclides—some presently used, other compounds under development. Bone scanning is valuable in clinical medicine, particularly in the management of the cancer patient and in early diagnosis of metastatic disease. As in other laboratory procedures, proper preparation and thorough examination of the patient are important for an accurate interpretation of the bone scan. The interpreter must always remain alert to the numerous pitfalls that make evaluation of these scans difficult.

GENERAL CONSIDERATIONS OF BONE STRUCTURE AND FORMATION

Knowledge of bone anatomy, physiology and growth, both normal and pathological, is needed to interpret radioisotopic studies of bone. Consideration of cartilage is also basic. Undifferentiated primitive precursor bone cells normally differentiate into osteoblasts, osteocytes, and osteoclasts. However, theoretically, undifferentiated cells can, with malignant intervention, become invasive through blood and lymph, whereas differentiated bone cells are more likely to remain trapped in the developed bone.

Figures 1 to 7 concern bone development and structure.*

*Figures 1 to 6 are from I. Stein, R. O. Stein, and M. L. Beller, in *Living Bone in Health and Disease*, pp. 6, 7, 10-13, J. B. Lippincott Company, Philadelphia, 1955.

Fig. 1 Development of diaphysis of a long bone showing perichondral splint: (1) cartilage anlage, (2) cartilage-cell hypertrophy with secretion of alkaline phosphatase by mature chondrocytes, (3) initial transformation of perichondrium into osteoblastic tissue at periphery of diaphysis, (4) calcification of cartilage cells accompanied by their necrosis, and (5) final stage of osteoblastic and capillary invasion of the centrally placed dead and dying chondrocytes originates from the peripheral perichondral splint.

Fig. 2 Epiphyseal plate (after A. W. L. Ham). The zones of cartilage cell at the epiphyseal line are shown in the course of their participation in the process of endochondral bone formation.

Consideration of development provides a general background for internal study of these processes through the use of radionuclides.

The ultrastructure of bone has been studied by the use of the electron microscope and the scanning electron microscope. Microradiography and X-ray diffraction have also been used as study tools.

Some information about bone components, e.g., collagen and minerals, is inferred from studies of other parts of the body. Some recent studies specifically of bone suggest that enzymatic degradation of protein polysaccharide chains may produce calcium release close to collagen nucleation sites.¹ In the upper tibial epiphyseal plate of normal mice, there are vesicles within the cartilage matrix.² Matrix vessels were found in juxtaposition to needlelike structures identified as hydroxyapatite and/or fluorapatite crystalline structures.³ Minerals may be made within tiny vesicles within the bone matrix where hydroxyapatite crystals are formed or the hydroxyapatite material may be extruded as part of a

Fig. 3 Epiphyseal plate and metaphysis of a long bone. Composite cross section and longitudinal section (after A. W. L. Ham). The zones of resting, proliferating, and calcified cartilage are shown. Capillary loops and osteoblasts invade the dying cartilage to form metaphyseal bone trabeculae. The central trabecular capillaries become surrounded by concentric bony lamellae and thus haversian systems are formed.

histochemical process during which substances such as alkaline phosphatase are active. Study of the transport of tagged amino acids can produce data on the development of bone. This has been studied in fetal rat calvaria with the use of tritiated thymidine.⁴

SPECIFIC PHYSIOLOGICAL FACTORS RELATED TO LIVING BONE

Normal progressive physiological development of bone structure is the result of a concert of harmonious activity of numerous factors, a few of which are:

1. Messenger RNA for protein synthesis (a process that breaks down if RNA blocking occurs).

Fig. 4 Three-dimensional diagrams showing a composite cross section and a longitudinal section of the shaft of a long bone. The relationship of the haversian and the Volkmann canals to the periosteum is depicted. In addition, the development of a haversian system by the conversion of a trough on the periosteal surface of the bone into a longitudinal tunnel surrounded by concentric lamellae is shown on states 1 to 6.

Fig. 5 Cross section of the haversian systems. Schematic drawing of dried undecalcified bone. The lacunae are shown as black areas with radiating lines representing the canaliculi.

Fig. 6 Intramembranous bone formation in the fetal skull. Direct osteoid formation is brought about by osteoblasts in the proliferating stage. Simultaneous modeling of the bone trabeculae occurs in the presence of osteoblasts.

Fig. 7 Modeling at the end of a long bone. The interplay of bone deposition and reabsorption is shown. [From A. W. L. Ham, *Some Histophysiological Problems Peculiar to Calcified Tissues*, *J. Bone Joint Surg.*, 34A: 711 (1952).]

2. Transport of protein, vitamin, and mineral into the intestinal tract, then into the bloodstream via the intestinal wall to the skeleton. In this process vitamin D has an important role.

- a. The vitamin D molecule or a derivative thereof may act as a carrier mediating the transfer of calcium across the intestinal membrane.⁵
- b. Vitamin D influences calcium transport by affecting primarily the active mechanisms rather than by simple diffusion.⁶
- c. Vitamin D specifically increases the permeability of the intestine to calcium by a process not dependent on an "intracellular system that uses oxidative energy for ion transport."⁷

Vitamin D is essential for the proper utilization of calcium in bone development.

Wasserman^{8,9} found that vitamin D appears to induce the formation of a protein in intestinal mucosa of rachitic chicks. The protein forms a tight complex with calcium. Vitamin D-dependent calcium-binding protein (Ca-BP) was found in the intestinal mucosa of rat, monkey, cow, and dog. The Ca-BP content decreases with age. The appearance of Ca-BP in a rachitic chick given a single dose of vitamin D₃ correlates with increased absorption of radiocalcium. Another approach would be the actual labeling of the vitamin D-induced protein.

"Dietary strontium inhibits both the synthesis of 1,25-dihydroxycholecalciferol and intestinal calcium absorption in vitamin D₃-repleted chicks. 1,25-dihydroxycholecalciferol restores calcium absorption to normal, while 25-hydroxycholecalciferol is without effect in the strontium-fed chick. It is suggested that strontium induces rickets by blocking the biosynthesis of 1,25-dihydroxycholecalciferol, the metabolically active form of vitamin D in the intestine." (Authors' abstract¹⁰).

Calcium absorption may be reduced by excess fat, which is eliminated through the gut as a saponified form of calcium. The measurement of fat excreted is therefore helpful in evaluation of relative calcium absorption, but the value must be inferred.

Poor kidney function may, by inadequate clearance of phosphorus, produce increased parathyroid hormone secretion and an osteoclastic effect on bone.

Normally there is an exchange of substances directly from the bloodstream to bone and vice versa. Mineral and protein elements are carried into the bone areas from the medullary circulation via the nutrient artery, from the epiphyseal ends of the bone and a membranous vascular area about these ends, and also from the periosteum into the bone itself. Elements also diffuse into bone through lymphatic material containing calcium and phosphorus; protein compound with calcium nucleates from the lymph into collagen spaces.³

Bone, as all other tissues formed by direct metaplasia from primitive tissue cells, must by osteoblast activity replace osteocytes that are dying and being removed by osteoclasts and enzymatic action. This is a process of remodeling that goes on throughout life. This is not universal throughout bone, however. In addition, it appears that some osteocytes may remain entombed deep within bone substance.

CLASSIFICATION OF BONE DISORDERS

One must be able to classify bone disorders to properly utilize radioisotopes to study bone. An outline of bone disorders follows:

1. Defect in transport of essential components: proteins, minerals, vitamins, and hormones.

- a. Inadequate intake, e.g., rickets, osteomalacia, and scurvy.

- b. Inadequate absorption, e.g., rickets and osteomalacia.

2. Circulatory disorders, which may lead to bone necrosis.
 - a. Direct rupture of arterial pathways as in fracture.
 - b. Thrombosis of major vessels to or within bone.
 - c. Compression on circulatory tree, a mechanism that possibly may explain Legg-Perthes disease (a current hypothesis).
 - d. Blocking of lymphatic channels.

The circulation is basically the media of transport of all needed components for bone formation and for the nutrients to maintain it. The circulation is supplied by direct entrance of the nutrient arteries within the central shaft of the long-bone areas, by periosteal structures in turn supplied by many small vessels from surrounding tissue, and by the epiphyseal area from capsular structures surrounding this area. Fracture of the neck of the femur is sometimes associated with aseptic necrosis of the femoral head (an end point of circulation). As for the study of circulation, materials that remain in circulation may be used, although there are some limitations to these agents, e.g., red blood cells labeled with diisopropyl fluorophosphate (DFP)-P-32, a pure beta emitter that does not lend itself to external monitoring studies. Clearance of a radioactive material, e.g., sodium, can also be a measure of circulation to a degree. This is not so accurate as the actual measurement of circulation in an area or deposition from circulation because bone tends to clear large amounts of fluid easily and quickly. In pathological conditions the bone may be more rapidly formed or more rapidly absorbed or there may be mixtures of both. Increased vascularity will be evident when there is increased absorption or formation of bone.

3. Disorders related to bacterial or viral disease.
 - a. Pyogenic.
 - b. Granulomatous.
4. Disorders related to tumor formation.
 - a. Primary, from a true component of bone.
 - b. Metastatic, invasion and destruction of bone by tumor originating elsewhere.
 - c. Invasion of bone: Gaucher's disease, reticuloendotheliosis, and ochronosis.
5. Disorders related to metabolic disturbances.
 - a. Hyperparathyroidism and hypoparathyroidism.
 - b. Hyperpituitarism and hypopituitarism.
 - c. Enzymes.
 - d. Kidney disorders: renal rickets, secondary hyperthyroidism.
 - e. General catabolic excess, as in osteoporosis.
 - f. Gout.

Diagnosis of bone disorders may be helped by a technique that can measure important enzymes, hormones, and other substances. Some hormones that may be tagged and measured by radioimmunoassay are parathyroid hormone, calcitonin, insulin, thyroid-stimulating hormone (TSH), and cyclic adenosine

monophosphate (AMP).¹¹ Hormonal agents may produce perivascular infiltration as well as bone disintegration, especially when corticosteroids are injected either over a considerable period of time or an excessive number of times into a joint. The prime responses of bone are osteolytic or osteoblastic. If mineral metabolizes so too does that portion of organic structure.

As an example, Paget's disease of bone is a condition, even now not fully understood, that is related to a very rapid turnover of bone. For this reason one is not surprised to find that an antimetabolite such as mithramycin has a slowing effect on the disease process. Indeed, in an active case of our own, a similar beneficial effect was obtained with methotrexate. However, these agents are a pile driver to kill a fly, and their hepatotoxicity and nephrotoxicity do not justify the end.

6. Genetically determined disorders.

In disorders of genetic etiology (e.g., Paget's disease and achondroplasia), tagged substances can be useful in tracing metabolic pathways and in finding abnormal accumulations of enzymes.

Any metastatic process to bone produces bone reaction and as a result produces increased incorporation of radionuclides. Of course, the more specific the radionuclide bone-seeker, the more concentrated the isotope.

Any infectious process, pyogenic, for instance, will also produce a similar reaction, either proliferative or destructive or both. If the structures surrounding the bone and affecting the circulation to the bone are involved, this too will be reflected in bone. In this instance the late effect will be disintegration and collapse of the area involved. Such an example is aseptic necrosis of the femoral head after subcapital fracture of the femur.

Studies of ^{45}Ca and ^{47}Ca turnover unquestionably are helpful and meaningful, and computer-determined compartment studies for various mineral elements are also challenging. We still do not know the significance of the mineral alone. There are large numbers of enzymes, hormones, and chemicals of all types that affect the collagen as well as the bone. Measurement, even when accurate, of the bone lattice is of value but not necessarily a finite study. Indeed, we are to a degree like the blind men who examined various parts of an elephant and came up with accurate descriptions, yet startlingly great differences dependent on the area examined, i.e., the tusk, ear, or leg, were found.

RADIONUCLIDES IN THE STUDY OF BONE AND JOINT DISORDERS

Radionuclides are known to enter into old or new bone and into bone that is undergoing destruction with reactive changes about it. For this reason such nuclides are truly helpful in determining changes such as those from metastatic tumors. Here, however, we must realize that other physiological and aging changes may result in uptake, thereby simulating changes due to tumor metastasis. For this reason we present the other side of the coin. This is not to

deprecate the well-established value of radioisotopic study of tumors which is confirmed by other presentations of this symposium. Our emphasis is on the fact that this very helpful tool must be fully understood and in that way may be all the more useful.

The provocative work of Dr. Maxwell and associates now provides a method for the study of early changes in synovium about a joint which later manifests itself by changes in the joint as well. Such a tool is helpful not only in delineating arthritic changes but also appears to be of value in following the effects of various forms of treatment and in anticipating remissions of the disease. This is helpful in rheumatoid arthritis and in other forms such as osteoarthritis as well.

Dr. Jack Edeiken's extremely well illustrated presentation to this symposium has clearly defined location, bone absorption, bone destruction, regular or irregular outline of lesion, and other proliferative reaction or lack of reaction. Any one of these findings alone suggested various abnormal physiological or pathological processes. Combinations further delineated changes that may be specifically diagnostic. Examples given were changes related to Paget's disease, osteomyelitis, osteogenic sarcoma, chondrosarcoma, unicameral cysts, osteoclastomas as in hyperparathyroidism or von Recklinghausen's disease, and enchondroma, to state a few. In Dr. Edeiken's article and particularly in the textbook published by Edeiken and Hodes,¹² these lesions are beautifully illustrated and described.

Certainly the diagnosis of a bone disease clinically must always be uppermost in a physician's mind. However, just as the radiogram is a most useful tool, it is also limited, especially in its standard form, and must be supplemented by tomograms (body-section studies), spot radiography with varying intensities at various angles, occasional studies in stereo, and finally searched further by the use of various radionuclides, which infer further changes by their specificity for blood, soft tissue, or bone.

An example of real aid in diagnosis of bone and joint lesions is demonstrated in Dr. Maxfield's paper (this volume). Drs. Maxfield, Weiss, and Shuler indicate that localization of radiopharmaceuticals is nonspecific but that the pattern of deposition is helpful when laboratory and clinical studies are borderline or normal. It would not indicate the etiology of the underlying synovitis, but it does relate to circulation and permeability as well as exudation of the synovium in association with hyperemia of the synovium. A negative synovial membrane scan indicates a nonarthritic origin, except where synovitis may be present for mechanical reasons, as well as in a tumor such as synovioma or in villonodular synovitis. A positive scan may forecast later arthritic changes. Scans are more effective than roentgenograms inasmuch as soft-tissue changes are not readily seen on roentgenograms. However, thermography may be helpful here too.

Synovitis is often a rapid response not only to the usual disease factors but also to trauma. Provocative, however, is the use of radionuclides to measure resolution of synovial reaction either spontaneously or as a result of general or

local treatment, including corticosteroid injections. Scans can show early changes with evidence of progression. The material used must remain in the circulation because if it leaks quickly there is the problem of clearance, and exudate is a part of synovial reaction.

If the intravenously injected material reaches a maximum concentration in 30 to 90 min, is that a defect in circulation, or diffusion, or exudation? Circulation time per se is measured in seconds. Overlapping tissues make problems for the study of pelvic joints and the spine. The mechanism may be an increased transport to the synovial area, then increased permeability or hyperemia and exudation into the subsynovial space.

Would a radionuclide such as sodium help in measuring permeability and clearance vs. circulation? Synovial membrane mass or size varies also and is not always proportionate to joint size, especially when it is inflamed.

In regard to Reiter's syndrome and study of the Achilles tendon, one must remember the limited synovial sheath for that tendon as related to others.

The diagnosis of synovitis unquestionably is helped by use of radiopharmaceuticals, but also needed is clinical study that includes color of the part, heat, the sensation of the tissue to touch (whether it be brawny, soft, or any variations from the normal), as well as nontraumatic method, rather than direct aspiration, to determine increase of joint fluid. The sedimentation rate should be used for evaluating tissue destruction and rheumatoid factor studies. Direct-version arthrography and even biopsy are also indicated. We emphasize again that there is no ideal isotope yet, but even those in current use are more diagnostic of significant disease than conventional roentgenograms may be in many instances. Large amounts of bone mass must be gone for conventional roentgenograms to be of diagnostic aid.

Work as indicated above clearly shows formation of hydroxyapatite and fluorapatite in the vesicle areas of matrix adjacent to cartilage cells; there also appears to be evidence of mineral such as the above occurring in vesicles in bone matrix.² Obviously calcium and strontium uptake will be found in such areas. Whenever the uptake is increased, the inferred activity is also greater. A radionuclide will appear in greater concentration in an area of greater bone activity due to physiological, inflammatory, or primary bone processes or due to tumor metastasis.

Radioisotopes that are very specific in regard to uptake provide invaluable diagnostic information; some such nuclides are still undiscovered. In this context the papers presented at this symposium by Dr. Charkes (on the use of ^{85}Sr) and Dr. Brand (on ^{18}F) are germane. Calasko,¹³ Dr. Brand, and others have noted a positive scan in clinically operative breast carcinoma. In some instances such a scan before surgery would indicate the value of simple tumor excision for that unfortunate person rather than a futile disfiguring radical breast excision. Furthermore, when 25 of 27 patients reported by Dr. Brand had negative bone scans, these would be the cases in which a radical approach may be considered.

Bone scanning is a highly useful aid in the early diagnosis of metastatic disease of bone. However, the interpretation of bone scans is not easy and there are many pitfalls. The concentration of strontium and fluorine isotopes in bone is not limited to those situations which involve the development of metastatic lesions. Any process that increases calcium exchange in bone results in the deposition in bone of the isotopes used.

Figure 8 shows anterior and posterior views of a normal individual scanned with a dual-probe rectilinear scanner 3 days after 200 μ Ci of ^{85}Sr . Normally the sternum, costal margin, and knees on the anterior view and the sacroiliac joints and knees on the posterior view are prominent.

Normal ossification during skeletal maturation results in increased ^{85}Sr uptake. For most patients scanned this is not a problem, but it was in the 19-year-old shown in Fig. 9. The iliac crest epiphyses were not yet closed, and there was marked uptake of isotope in this region.

Figure 10 shows a patient with multiple metastases of the spine from a carcinoma of the lung. A collapsed T-5 seen on the bone film coincides with one scan lesion, but the other lesions are not yet seen in the bone films.

Figure 11 might have been mistaken for a scan of bone metastases in the lower lumbar area, but actually it shows degenerative disease noted in this area on the spine film. The abnormal scan in Fig. 12 is due to degenerative disease in the spine and to degenerative changes secondary to a fracture of the humerus in the left shoulder. The spine film shows extensive osteophyte formation.

Increased uptake in the dorsal spine and L-5 in Fig. 13 was due to the degenerative changes and spondylolisthesis seen in the bone films. Degenerative disease is common in the age group usually studied, and, in most cases, the bone films clearly show the lesions. However, if bone scans become abnormal with metastases before bone films show abnormalities, it is also possible that bone scans may show degenerative disease before the bone films.

Stresses on bone seem to increase the concentration of radiostrontium. This is seen in patients with scoliosis even without evident degenerative disease. In Fig. 14 the ^{85}Sr deposition appears greater on the concave side of the curvature as might be expected on the basis of greatest stress. Pelvic asymmetry in isotope patterns may also be due to differences of stress (Fig. 15). Stress must explain the tremendous uptake of radioactive strontium in the knee joints of most normal individuals.

Paget's disease also results in tremendous isotope uptake in the affected areas. This is well documented in the literature.¹⁴ Figure 16 is the bone scan of a patient with back pain and suspected prostatic carcinoma. The uptake in T-12 is due to a compression fracture and that in the left pelvis is Paget's disease. Compression fractures may be secondary to osteoporosis or metastases, and one cannot always distinguish between the two on the bone films. Figure 17 shows another instance of Paget's disease in the pelvic rim. Paget's disease in the sacrum and a fracture of the right pubis with callus formation explain the abnormalities

(Text continues on page 183.)

Fig. 8 Posterior and anterior total-body scans in a normal individual given 200 μCi of ^{85}Sr 3 days earlier.

Fig. 9 Area scan of lower back and pelvis (a) after ^{85}Sr injection and an X ray (b) of the same region in a patient whose iliac crest epiphyses [arrows in (a)] were not yet closed.

Fig. 10 Total-body scan (a) and X ray of vertebral spine (b) in a patient with bone metastases from a primary carcinoma of the lung.

Fig. 11 Strontium-85 bone scan (a) and X ray of lumbar--sacral region (b) in a patient with degenerative disease of the spine.

(a)

(b)

Fig. 12 Abnormalities in thoracic spine and left shoulder on bone scan (a) and increased bone density on X-ray film (b) in a patient with a fracture of the left humerus with associated degenerative disease.

Fig. 13 Total-body scan after ^{85}Sr injection (a) and lateral view of a lumbar spine X ray (b) seen in a patient with degenerative disease and spondylolisthesis.

Fig. 14

Fig. 15

Fig. 14 Torso and lower extremity scan after ^{85}Sr was given to a patient who had scoliosis but no degenerative disease.

Fig. 15 Strontium-85 total-body scan. Stresses on bone may explain pelvic asymmetry or the increased uptake in knee joints of normal individuals.

Fig. 16 Increased ^{85}Sr uptake in a compression fracture of T-12 and in the left pelvis due to Paget's disease.

Fig. 17 Paget's disease localized to the right pelvis evidenced by increased concentration of ^{85}Sr on scan (a) and by increased bone density on X ray (b).

in the scan shown in Fig. 18. Although Paget's disease may be identified on the bone films, the bone scans may become abnormal before the bone films.¹⁵

Calcium deposition in soft tissues also results in abnormal ^{85}Sr scans.^{16,17} Figure 19 shows isotope deposition in a uterine fibroid and Fig. 20 shows isotope in a metastatic tumor in the right lung. Osteogenic sarcoma metastases in soft tissues are sometimes seen on a ^{85}Sr scan.¹⁸ Figure 21 shows the original tumor and Fig. 22 shows the pulmonary metastases. Calcifications in scleroderma will also show up on scanning. Figure 23 is one example with calcification in the left shoulder. A right fourth rib fracture is also seen.

Surgical procedures involving bone will also result in abnormal scans. Figure 24 is the scan of a patient with carcinoma of the lung with recent lobectomy. What might have been interpreted as rib metastases was due to removal and regeneration of these ribs.

Accumulation of radionuclide in the organs of excretion is another source of bone-scan misinterpretation. For ^{85}Sr this pertains to the gut and requires laxatives and enemas for proper preparation. In Fig. 25 the ^{85}Sr has become bound to a barium plug and sits in the rectum. In Fig. 26 the radioactivity is seen in the descending colon and possibly in the transverse colon. The metastatic lesion in L-1 might have been misinterpreted as colon radioactivity but the bone film confirms the abnormality in L-1.

For ^{18}F the excretory path is the urinary tract,^{19,20} and it is difficult to avoid radioactivity in the bladder. Figure 27 shows a ^{18}F bone scan of a patient with carcinoma of the breast and multiple metastases of spine and left sacroiliac region. However, the bladder is also seen and the mass to the left of the spine in the upper lumbar area is a hydronephrotic kidney. Figure 28 shows a collapsed vertebra and degenerative disease below, but visualization of bladder and right kidney complicate the picture. Figure 29 is another example of kidney visualization with ^{18}F .

Many laboratories do only posterior views in bone scanning. This may result in missing lesions. Figure 30 shows a patient with breast carcinoma and multiple metastases. Metastases to the sternum would have been missed without the anterior view. Sternal metastases were the most remarkable finding in the bone scan of the patient shown in Fig. 31. Skull metastases, missed on the skull film, were clearly demonstrated on the ^{85}Sr scan of the skull of a 31-year-old patient with Hodgkin's disease (Fig. 32). Positive bone scans of Hodgkin's disease are well documented in the literature.^{20,21} Unusual sites for metastases from breast carcinoma are the calcaneus and metatarsals, but this was the case in the patient whose foot scan is shown in Fig. 33.

Bone has been presented from the point of view of its anatomy, gross and microscopic, as well as its physiology and biochemistry. The consideration is that review of these highlights will suggest to the inquiring mind a method of study of the physiology and biochemistry of bone with the aid of radiopharmaceuticals.

(Text continues on page 192.)

(a)

(b)

Fig. 18 Paget's disease localized to the sacrum and a fracture of the right pubis associated with callus formation. Scan (a) and X ray (b).

Fig. 19 Abnormal concentration of ^{85}Sr in a pelvic scan (a) of a patient with uterine fibroid and an X ray (b) of the same area showing the tumor's calcification.

Fig. 20 Metastatic tumor in the right lung visualized by a ^{85}Sr chest scan (a) and by a chest X ray (b).

Fig. 21 Primary osteogenic sarcoma detected in left tibia by ^{85}Sr scan (a) and by an X ray (b).

Fig. 22 Metastatic lesions to the chest from the primary lesion in Fig. 21 determined by scanning (a) and by X ray (b).

Fig. 23 Abnormal concentration of ^{85}Sr in the left shoulder and at site of a fractured fourth right rib in a patient with scleroderma (a). Chest X ray (b) does not visualize the abnormalities as well as the scan.

Fig. 24 Abnormal focus of ^{85}Sr activity in right chest on total-body scan (a) due to recent surgery involving removal and then regeneration of ribs. Chest film (b) shows remaining hyperaerated lung in same patient who underwent lobectomy for carcinoma of the lung.

(a)

(b)

(a)

(b)

Fig. 25 Scan (a) shows ^{85}Sr concentration in rectum where barium is well visualized on X ray (b).

Fig. 26 Demonstrates that bone scan (a) and X ray (b) are both needed here for correct interpretation. The increased activity over L-1 could have been interpreted as colon activity if the lumbar spine X ray did not delineate an abnormality more consistent with tumor.

Bone scanning is valuable in the early diagnosis of metastatic disease. However, because of the nonspecificity of strontium and fluorine isotope deposition in bone and the concentration of these isotopes in their excretory pathways, care must be taken in the interpretation of the bone scan. Abnormal ^{85}Sr deposition is shown in degenerative disease, bone stress, Paget's disease, fractures, and soft-tissue calcifications (benign and malignant). The importance of proper preparation of the patient to remove ^{85}Sr from the bowel and ^{18}F from the urinary tract before scanning is stressed. Multiple views and inclusion of all bones will reduce the percentage of missed lesions. The availability of newer radionuclides, which makes possible the scanning of patients who do not have a diagnosis of cancer, should lead to many new applications of bone scanning and reveal the frequency of abnormal bone scans that are due to nonmalignant disease.

(Text continues on page 201.)

Fig. 27 Fluorine-18 bone scan (a) indicates multiple metastases of spine and left sacroiliac area in a patient with carcinoma of the breast. Hydronephrosis of the left kidney is better visualized on X ray (b) than on scan.

(a)

Fig. 28 Fluorine-18 bone scan (a) also visualized right kidney and urinary bladder. Lateral (b) and anterior (c) lumbar spine films reveal a collapsed L-3 vertebra with degeneration of L-4 and L-5.

(b)

(c)

Fig. 29 Total-body scan illustrates concentration of ^{18}F in both kidneys.

Fig. 30 Posterior (left) and an anterior scan (right) after administration of ^{18}F points out the need for more than one view if metastases are to be detected.

Fig. 31 Sternal metastases evident on anterior scan (right) but not obvious on posterior scan (left).

(a)

(b)

Fig. 32 Skull lesion demonstrated on scan for ^{85}Sr activity (a) but not visualized on skull X ray (b).

Fig. 33 Scans of feet (a) compared to X ray findings of same (b) in a patient who had metastases from breast carcinoma.

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DISCUSSION: BONE AND JOINT

Shuler: We have found peripheral joint imaging to be of distinct value in pediatric practice. Our experience now includes over 500 adults and about 70 children. Our interest has been primarily in the patterns of localization of technetium as pertechnetate in children with arthritic complaints. However, to obtain a base line for these studies, we need to look at the normal child first, and the illustrations show that there are some differences in localization in normal children as compared with adults. These changes relate to the age and maturity of the particular patient. Most females over 16 or males 17 or 18 demonstrate a pattern similar to that Dr. Maxfield has shown. Children below this age with open epiphyses have intense localization of technetium in the epiphyseal region. Figure 1 shows a 15-year-old boy with rheumatoid arthritis who has diffuse synovial membrane localization in many of his peripheral joints. This is contrasted with a child of similar age demonstrating normal epiphyseal localization in these areas.

Figure 2 shows a child with mono-articular rheumatoid arthritis of the knee. There is a pattern of diffuse localization similar to that seen in the adult, with obliteration of the distal epiphysis of the femur and the proximal tibial epiphysis. The normal knee is shown as a control and demonstrates the localization in these epiphyses of the knee region. We see this in all children if the joints are scanned when a brain scan or renal scan is done with technetium.

In a normal 4 year old, whose ankle scan is illustrated in Fig. 2, you can appreciate the distal tibial epiphysis; there is also a little localization in the posterior aspect of the calcaneus. The other ankle view in Fig. 2 is from a 3 year old with diffuse arthritis; the biopsy of the synovial membrane was compatible with rheumatoid arthritis, and you see that the disease has almost obliterated the normal localization that you would see in the epiphyseal region.

We have been interested in what happens to this peripheral joint picture in children that are receiving corticosteroids. Figure 3 shows a normal 3 year old. Again you see the epiphyseal localization at the knee and at the ankle; the other part of the picture shows the pattern after the child received corticosteroids for 2 weeks. There is absolutely no localization in the epiphyses. We have now

Fig. 1 Scan of 15-year-old boy with rheumatoid arthritis compared with scan of normal 15 year old.

Fig. 2 Comparison of scans of normal children with those of children with arthritis.

studied 9 children in a similar fashion and find that within 2 weeks the localization just disappears. On discontinuation of the corticosteroids, it will return in months to come. Of course, as pediatricians we are concerned with children's growth during the period they are on corticosteroids, and I believe that this finding may be important; it is the kind of information we must explore to obtain further understanding of why they fail to grow adequately.

Figure 4 shows a child's knees; the left side is normal; on the right side there is increased activity in the distal femoral epiphysis and, in fact, up and down the femur. The child has osteomyelitis in this region, and the scan was taken a week before the X ray became positive. We have now seen four children with acute staphylococcus osteomyelitis in the region of the knee where we were able to see this uptake before radiographic changes developed.

Thus the few diseases that we have studied in children must be interpreted on the basis of an appreciation of the normal patterns of isotope localization for the age. We do see localization in the epiphyses of all the peripheral joints such as the knee and the wrist, and in our early experience we became quite alarmed by this, erroneously thinking that all the children we studied with joint complaints had generalized rheumatoid arthritis. Now we are able to appreciate

Fig. 3 Scan of normal 3 year old before (left) and after (right) receiving corticosteroids for 2 weeks.

Fig. 4 Scan of child's knees showing increased activity on right side where osteomyelitis is present.

it as a normal finding. Joint imaging will add some dimension to the information obtained by history, physical examination, routine laboratory findings, and radiographic studies. There are two articles to be published in the next few months concerning this work [C. N. Aprill, S. E. Shuler, and T. E. Weiss, Peripheral Joint Imaging: Variations in Normal Children, *J. Nucl. Med.*, 13(6): 367-372 (June 1972); S. E. Shuler, C. N. Aprill, and T. E. Weiss, Peripheral Joint Imaging: Method of Evaluation of Pediatric Bone or Joint Disease, *Amer. J. Dis. Child.* (in press)].

Beierwaltes: Dr. Maxfield, is there an increase in uptake of pertechnetate in the synovial membranes of patients who have undergone unusual exercise?

Maxfield: We do find that with the joint scanning there is variation in the degree of localization of pertechnetate based on the activity of the patient. Very active people, laborers, for example, tend to have higher localization in the synovial membranes. The technetium-tagged albumin seems to give us a better differentiation between normal and abnormal uptake than we obtain with the pertechnetate.

Adelstein: What is the incidence of false-positive bone scans in patients suspected of metastatic disease who have normal skeletal radiograms (i.e., no evidence of malignancy or other disease known to produce scintigraphic abnormalities)? In particular, do we have figures for prostatic carcinoma? I am particularly concerned about patients who may be treated for metastatic prostate carcinoma by orchiectomy or hormones entirely on the basis of an abnormal scan finding.

Charkes: This is a very intriguing question. I believe it is fair to say that it depends on where the abnormality is on the scan. As Dr. Shapiro showed, if the abnormality is in a vertebra, it is obviously not specific for metastatic disease because in the older age group we find patients with degenerative joint disease who have a similar type of scan. Here one must equivocate. Degenerative joint disease usually produces only a mild increase in count rate and not a very hot-appearing area [J. C. DeFiore, L. Lindberg, and N. S. Ranawat, ⁸⁵Strontium Scintimetry of the Spine, *J. Bone Joint Surg.*, 52A: 21-38 (1970)]. If possible, we should perform a biopsy of the lesion. This is not too easy with the vertebral body, but, if management depends on accurate diagnosis, then a biopsy is the answer. On the other hand, if the lesion is located in an area where other disease can be safely excluded and if multiple such areas are found, for example, the ilium, the proximal femur, and the ribs, then it is likely that one is dealing with metastatic disease. Basically it boils down to the fact that the technique itself is nonspecific. It simply indicates new bone formation. My paper, which preceded this discussion, includes a table that lists mechanisms for abnormal bone scans other than reactive bone formation. I recall one patient who had known lymphosarcoma. There was a selective uptake in certain bones, including ribs, in my report, and I commented on the fact that it looked atypical for lymphosarcoma. On autopsy it turned out that, in addition to his lympho-

sarcoma, he had metastatic epidermoid carcinoma to the areas that had been seen on the scan. This is an example of the type of case in which a clear diagnosis could only have been reached by a biopsy, and in these situations the advantage of the bone scan is to show the appropriate location for the biopsy.

Beierwaltes: Our radiotherapist, Dr. Lampe, practically never gives radiotherapy unless he has a histologic section to confirm the diagnosis. Fluorine-18 is great for picking up the lesions, but, before starting therapy, we should have a biopsy.

Shapiro: I think that Drs. Charkes and Beierwaltes have covered the subject well. We have had at least one unfortunate experience of having a patient treated for a metastatic lesion of the spine and finding later at operation that the disease was a disc problem rather than metastatic neoplasm.

Beierwaltes: We define disease as deviation from normality, and, when the deviation is slow and slight, we have to sharpen up our knowledge of the range of normality to interpret the abnormal. At our institution we have one scan conference a week in which we concentrate on what we believe are deviations from normality but which are not clearly diagnosable as disease on the basis of what is published in the literature. We try to pool our collective experience and decide what we will call normal and what we will call abnormal. It drives the residents mad because they want straightforward answers and here we are just groping.

Dworkin: I think we should get rid of the term false positive for a scan that shows an area of uptake when there is no malignancy present. It is a true positive not a false positive. It just does not indicate that metastases are present, and it is up to the interpreter to report the possible implications.

Brand: I would just like to comment briefly on Dr. Adelstein's question. It does not mean much to say that 40% of all patients with prostatic cancer have positive bone scans unless we define very specifically what we mean.

Dr. John Hammond at our institution is doing extraperitoneal iliac lymph-node biopsies in patients with clinically localized carcinoma of the prostate. At our institution 2 of 5 stage B and 16 of 18 stage C lesions have positive lymph nodes in the iliac fossa. I recently heard of a similar group of patients with biopsy-proven lymph-node metastases and only 1 of 15 had a positive bone scan.

At least 70% of the patients who come to an oncology department have metastasis of some sort to begin with, and so, by just giving overall figures for what the findings are for bone scanning in prostate carcinoma or breast carcinoma, you cloud the issue and the results become really meaningless.

Adelstein: I would like to go back to the earlier question. This is directed to Dr. Brand. It was reported by Dr. Charkes that 16% of patients with early carcinoma of the breast had positive bone scans. This was coupled with a similar observation in England where they found 24%. Of course, the results may vary depending on the degree of advancement of the disease and whether the bone

scan is obligatory as a routine part of the work-up. It would be particularly disturbing if a significant number of stage 1 carcinomas of the breast had positive bone scans and if they were true positives in the sense that they represented metastatic disease. If this proved to be true, there would be an enormous amount of bone scanning required to study all these patients, and it would take some planning of resources to scan every woman in the United States who has a potential diagnosis of carcinoma of the breast.

My impression is that Dr. Brand's study showed that those patients who are in stage 1 and are asymptomatic do not have a significantly high incidence of positive bone scans. Perhaps what I am asking is for a more precise definition of those patients in whom he thinks it would be worthwhile to do bone scans.

Brand: For breast cancer we distinguish between surgical stages and clinical stages. Dr. Charkes' cases were studied postoperatively and they were surgically stage 2. Clinically they might have been stage 1 or stage 2. Of the patients I reported, 23 of the 27 were clinically stage A. This is the Columbia clinical-stage classification. They were admitted to the hospital by a surgeon who is every bit as critical as Haagensen, and he would not operate on a woman with palpable adenopathy. If we translate Haagensen's data to the smaller group, we could assume that surgically 33% would turn out to be stage 2 and 67% would remain surgical stage 1. We do not know yet what the incidence of occult bone metastasis is in clinical stage A or surgical stage 1 cancer of the breast.

At any rate, if it is deemed desirable to screen the patients before they are operated on, then I think the ^{18}F bone scan is the best procedure to use.

Charkes: The group of women we studied several years ago all had histologically proven carcinoma of the breast. They were surgical stage 2. Not all were clinical stage 2. Brand's series had, I believe, 11% of patients who were asymptomatic but who had abnormal scans. That is a little lower than ours, but these groups are not identical because I am sure Brand included some who were surgical stage 1.

We have set up a prospective study to look into this question. We are scanning women with suspected breast cancer preoperatively with $^{87\text{m}}\text{Sr}$. So far 24 patients with breast lumps turned out to have cancer; one of these had only a simple mastectomy, so we do not know about her axillary nodes. Six patients with cancer had negative axillary nodes and 1 had a positive scan. Seventeen patients had metastases to axillary nodes, and from our previous series we would expect that 3 of the 17 should have had abnormal scans. Actually 3 of the 17 had such a scan; 3 others had equivocal scans (patients with osteoarthritis on X-ray examination are not included in this tabulation).

We are studying this group of breast cancer patients by clinical examination, roentgenography, and repeat scans, and we hope to be able to tell, in retrospect, whether or not the abnormal and doubtful scans represented bone metastases. There are similar series at other institutions to evaluate preoperative scanning such as Brand's.

My own impression is that the yield is going to be less than 20%. There was an article about 10 years ago on preoperative X-ray skeletal surveys for breast cancer [J. Gibbons, A. I. Holleb, and J. H. Farrow, An Evaluation of Routine Preoperative Skeletal Survey for the Patient with Operable Breast Cancer, *N. Y. State J. Med.*, 61: 4219-4220 (1961)]. Only 1 out of 85 patients had abnormal roentgenograms due to metastatic disease. The figure is going to be somewhat higher for scanning.

Maxfield: The X-ray bone survey has been well accepted as a preoperative measure for women who are to be operated on for suspected breast cancer. I think the bone scan is more accurate. Now that we have the short-half-life materials, it takes less time. If any type of preoperative screening is to be done, I believe that the procedure of choice is the bone scan and not the bone X ray. If you see a positive localization, then it is desirable to obtain an X ray of that area. The quantitation of degree of localization on the bone scan is also helpful. A high uptake, 100% or more higher than the comparable normal area, usually indicates fracture or metastatic disease rather than, for example, osteoarthritis.

Beierwaltes: Since we are talking specifically about active osteoblasts, I would like to ask Dr. Stein why we get heterotopic calcification in the lung, and, when we do, why is it that we occasionally find bone formation in these areas of previous calcification?

Stein: I should imagine that there must be extruded some calcific material or an area of hydroxyapatite. Osteoblasts get there and they are differentiated cells from a primitive precursor cell which may go one of three ways: osteoblast, osteoclast, or osteocyte.

Beierwaltes: Do you think you could ever get uptake in the lung with ^{18}F in a patient who had had pulmonary emboli of tissues from the site of a fracture?

Stein: I do not know; I have never thought of it.

Frelick: How useful is the bone scan or uptake in evaluation of the therapeutic responses to treatment of metastatic bone cancer? Can these results be quantitated?

Dworkin: We studied some patients treated with chemotherapy and failed to find any significant changes in the ^{18}F bone scans despite the fact that the patients reported improvement and showed signs of improvement in roentgenograms. It was a negative report [H. G. Kampffmeyer, H. Dworkin, E. A. Carr, Jr., and F. E. Bull, The Effect of Drug Therapy on the Uptake of Radioactive Fluorine by Osseous Metastases, *Clin. Pharmacol. Ther.*, 8: 647-657(1967)].

In one instance a patient with lymphosarcoma and a positive bone scan was treated with radiation therapy; he then improved symptomatically and the positive findings on the scan disappeared. Six months later his pain returned; the scan was positive in the new area. The X rays remained negative [H. J. Dworkin and E. V. Filmanowitz, Radiofluoride Photoscanning of Bone for Reticulum Cell Sarcoma, *J. Amer. Med. Ass.*, 198: 985-988 (1966)].

In general, we have very little information about the sequence of events after therapy, as they might be demonstrated by repeated bone scans.

Beierwaltes: In primary osteogenic sarcoma, Dr. David Woodbury at our institution showed uptake of ^{18}F in and between the osteoblasts of the malignant lesions. It would seem that a decrease in uptake after irradiation would indicate a favorable change. However, when we treat thyroid carcinoma metastatic to bone fairly effectively by means of radioiodine (although usually without cure), then we have trabecular bone growing through the regressing lesion and we expect to have increased uptake of ^{18}F . The question in that case would be, "Would increased uptake be good or bad?"

Charles: We have never studied such a patient in the way you suggest. When we do bone scans in patients who have previously had radiation therapy for metastatic lesions, we often notice a decreased uptake of radioactive strontium in the area of the radiation compared with adjacent normal areas. This is intriguing, and we are currently studying it quantitatively. Experimental work along these lines has been reported [E. G. Bell, M. F. Noe, W. C. Constable, and J. G. McAfee, *Local Radiation Damage to Bone Marrow Indicated by Radioisotope Imaging*, *J. Nucl. Med.*, **10**: 320-321 (1969) (abstract)].

Maxfield: We have used the ^{85}Sr bone scan to help select patients in whom we are going to use radioactive phosphorus for treatment of multiple bone metastases. The patients that show good uptake of radiostrontium in all known areas of metastatic disease have usually shown good palliation with the ^{32}P treatment. The patients whose lesions did not show uptake of the strontium have usually not done very well.

For a few patients receiving external radiation therapy to a single area for a known disease, I have studied bone scans before and again 4 to 12 months after the course of treatment. I found in several instances that the posttherapy scans showed the highest count rates in those areas which had received the full course of radiation therapy. This is in contrast to the reported animal work which indicates that irradiation of an epiphysis or of a fracture will decrease the radioisotope localization.

Beierwaltes: When Dr. Howard Dworkin was working in our department several years ago with ^{18}F , he found that the highest uptake in the dog was in the jawbone. This was because the dog is always chewing on something. When I saw Dr. Shapiro's example of the high uptake in the foot, I thought that I would like to inquire about the patient's occupation before making an interpretation. If he presses on a treadmill all the time, this might explain the pattern because he is constantly stressing that area.

Stein: I would like to bring up two things referring to arthritis. First, we must bear in mind whether we are dealing with a big bone or a little bone. Second, has there been a little displacement or slight bowing? Because very definitely there is always an increase in bone deformity reaction where there is stress and there is always a decrease in bone where there is strain, as in so-called Milkman's disease. We think on a clinical basis that a fracture is not really healed until we have had a full reconstitution of the medullary canal, as seen on careful radiologic examination.

Beierwaltes: I would like to ask how long there may be increased uptake in an area of previous fracture, and may it ever persist when there is no residual radiographic evidence of fracture?

Charles: Bessler¹ has reported continued uptake for 18 to 24 months following vertebral fracture, but DeFiore, Lindberg, and Ranawat² found normal values after 6 months.

In long bone fractures abnormal uptake persists as long as 7 years, even after the roentgenogram has returned to normal.³

Frelick: I would like to ask about the medicolegal implications of bone scans, for example, in patients who complain of prolonged pain after fracture of the lumbar spine and who may show no abnormalities or only a stable change in X ray yet the scan may show up sites of increased activity. Is this significant clinically or medicolegally?

Charles: In the state of Florida it turns out that the bone scan does have medicolegal implications. The group at the University of Miami has been using bone scanning for several years now in patients who have had auto accidents, who complain of back pain, and whose roentgenograms show a collapsed dorsal vertebra.⁴ The question arises concerning cause and effect. An abnormal bone scan suggests activity in the vertebral lesion, as opposed to a normal bone scan, which suggests that the collapse is of long standing.

Stein: The medicolegal implications of a positive scan would depend on several factors. One would be the age of the patient and whether other causes for a positive scan might be expected to be present. It does not seem to me that the reaction of healing of a fracture as indicated by the scan would be evidence of continuing difficulty. In the spine the question commonly is to differentiate posttraumatic lesions from possible degenerative changes. Some lawyers might do their best to make a great deal of the positive scan. One could counter by saying that long after an injury the evidences of the healing process may persist.

Wellman: I would like to elaborate on the availability of ¹⁸F. Dr. Vincent Sodd of our laboratories [Nuclear Medicine Laboratory (NML), Bureau of Radiological Health, Food and Drug Administration, U. S. Public Health Service] in Cincinnati has developed a rapid processing kit for use with reactor-produced ¹⁸F to remove tritium. In a current scientific display he has shown that most of the eastern half of the United States has accessibility to nuclear reactors for ¹⁸F. There are also many accessible reactors in the west too.

1. W. T. Bessler, Skeletal Scintigraphy as an Aid in Practical Roentgenographic Diagnosis, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, **102**: 899-907 (1968).

2. J. C. DeFiore, L. Lindberg, and N. S. Ranawat, ⁸⁵Strontium Scintimetry of the Spine, *J. Bone Joint Surg.*, **52A**: 21-38 (1970).

3. *Acta Orthop. Scand., Suppl.*, **52** (1961).

4. R. C. Flipse, A. J. Gilson, and M. F. Hall, Sequential Studies of Vertebral Trauma Employing Strontium-85, *J. Nucl. Med.*, **7**: 351 (1966) (abstract).

These reactors are usually within driving distances. The NMI. has also developed sample descriptions (useful in the investigation of new drugs) of the procedures to produce sterile, pyrogen-free ^{18}F and will make them available on request.

Dworkin: Fluorine-18 is available in many areas now and is being marketed by commercial firms.

Beierwaltes: For ^{18}F you generally need to have a reactor nearby. Now we are trying technetium polyphosphate, which a lot of people think is going to replace the ^{18}F almost completely. It was introduced by Subramanian, who is with McAfee's group, and I believe one of the commercial companies is now interested in shipping this around. We are making the compound ourselves, and I am sure a lot of other people will be very shortly.

For those who wish to get started with ^{18}F , our laboratory would be glad to provide methods. If you will write to Dr. Rodney Lee, he will be glad to send you the techniques.

Moderator:
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LIVER and PANCREAS

ANGIOGRAPHY OF THE LIVER

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ABSTRACT

Portal hypertension may develop from posthepatic, intrahepatic, and prehepatic venous obstruction. When portal hypertension is secondary to cirrhosis of the liver, prognosis and rational therapy require careful assessment of the status of the liver damage and hemodynamic alterations. Only with such information can an effective choice be made between nonoperative and operative therapy. If an operation is to be done, preoperative studies help also in selecting the best procedure.

Hepatic panangiography provides fundamental morphologic and hemodynamic information prior to treatment and will also permit assessment of the physiologic effects of the utilized surgical procedure.

Imaging techniques are complementary to liver panangiography.

Focal and diffuse liver lesions, which result in macroscopic alterations, may be recognized radiologically on plain films of the abdomen by changes in liver size, by calcifications, or by alterations in the liver vascular bed, which can be outlined on angiographic examinations.^{1,2}

The arterial inflow tract of the liver is studied by selective injection of the common hepatic artery (Figs. 1 to 4). For patients in whom technically superselective catheterization of the common hepatic artery cannot be accomplished readily, injection of the celiac trunk often suffices. When aberrant hepatic arteries arise from other vessels, these should be selectively injected. The most common anatomic variation is the origin of the right hepatic artery from the superior mesenteric artery. Depending on the liver size and caliber of vessels, approximately 40 ml of contrast media of 75 to 76% concentration is injected at the fastest delivery rate that does not cause recoil of the catheter tip during injection (usually 10 to 15 ml per second). To select optimum delivery rate, we observe fluoroscopically the behavior of the catheter tip during test injection of 1-sec duration.^{1,2}

Fig. 1 Selective common hepatic arteriograms in two different patients with liver cirrhosis. Note coiled intrahepatic arterial branches (arrows). CH, common hepatic arteries; GD, gastroduodenal artery; RGE, right gastroepiploic artery.

Fig. 2 Liver cirrhosis with spontaneous reversal of flow in the portal vein. Selective hepatic arteriogram shows marked hypertrophy of the arterial tree with severe distortion of intrahepatic arteries (arrows). HA, hepatic artery; GD, gastroduodenal artery.

Fig. 3 Same case as Fig. 2. Late phase of hepatic arteriogram. Observe spontaneous, retrograde flow of contrast medium into the portal vein (PV) with filling of coronary vein (CV). Opacification of the portal vein from the hepatic artery may be seen in advanced cirrhosis, intrahepatic arteriovenous fistula, Budd—Chiari syndrome, and in patients with hepatomas.

Fig. 4 Same case as Figs. 2 and 3. Wedged hepatic venogram showing a large gradient between the wedged and free hepatic-vein positions. Venographic study showed category IV (Ref. 7) of portal hypertension (spontaneous reversal of flow in the portal vein). PV, portal vein; HV, hepatic vein.

Various approaches are used to assess the venous inflow tract of the liver^{1,2} (Fig. 5). In emergency situations, such as massive gastrointestinal bleeding, direct splenic portography is the technique of choice. Relative contraindications are patients with ascites, jaundice, and hemorrhagic diathesis. Splenoportography is done by introducing a teflon sleeve during apnea, and the cannula is quickly removed before the patient resumes breathing. This is done in an attempt to minimize trauma to the spleen. Splenic pulp pressure should be obtained prior to the injection of contrast media. If the reverse is done, spurious elevated pressures may be obtained. A test injection will ensure correct position of the short catheter. For the test 10 ml may be injected at the delivery rate of about 5 to 8 ml per second and the passage of the opaque observed under television fluoroscopy; if the splenic vein or tributaries are opacified, then one may proceed to inject 60 to 80 ml. The total volume depends on the size of the splenic vein and the size of the liver: the larger the spleen, the greater the dilution of the contrast agent and the larger the volume of contrast medium necessary for obtaining adequate opacification.

(a)

(b)

Fig. 5 Patients with liver cirrhosis; good and bad candidates for portocaval shunt operation.

(a) Predominant hepatopetal circulation. Note small coronary vein (CV). PV, portal vein; CV, coronary vein; U, umbilical vein. SV, splenic vein. Predominant hepatopetal circulation places the patient under the category of a poor candidate for portocaval shunt.

(b) Excellent candidate for portocaval shunt from a hemodynamic standpoint. Note predominant hepatofugal circulation with filling of markedly enlarged coronary vein (Cor. V). Sp. V., splenic vein; I.M.V., inferior mesenteric vein; P.V., portal vein. Note incidental gallstones in the right upper quadrant.

(c)

(d)

(c) and (d) Same patient with hemodynamics favorable for the surgical construction of a portocaval shunt but with active, severe liver disease which caused the demise following portocaval shunt operation. (c) wedged hepatic venogram showing spontaneous reversal of flow in the portal vein [category IV (Ref. 7)]. (d) splenoportogram demonstrating predominant hepatofugal circulation. Coll., collaterals; I.M.V., inferior mesenteric vein; S.M.V., superior mesenteric vein; P.V., portal vein.

The technique of choice for portography is the indirect arterial approach.^{3,4} With the splenic artery selectively catheterized, a large volume of contrast medium is injected. The larger the spleen, the greater the volume necessary to obtain adequate contrast density of the portal venous tree and of the liver. The subtraction photographic technique may be necessary to establish the location and size of tributaries and collaterals in patients with portal hypertension and massive splenomegaly. The usual volumes are between 60 and 100 ml of contrast medium of 75 to 76% concentration injected at rates of 10 to 15 ml per second. The image is recorded with a rapid film changer. One must ensure recording of the venous phase. Our experience with umbilical portography is limited.⁵ We do not consider this approach routinely for the study of the portal vasculature.

The venous outflow tract of the liver, the hepatic veins, is studied after a catheter with an open tip and no side holes has been introduced percutaneously using either the brachial or the femoral route^{1,2,6,7} (Figs. 6 to 9). The brachial route is preferred if an antecubital vein can be entered percutaneously.

To wedge a catheter into a branch of an hepatic vein when the femoral route is used, it is often necessary to use a deflector assembly, such as the Muller (U. S. C. I. Co.). Wedged hepatic-vein pressure is obtained first, then viewed and recorded. The catheter is then moved into the free hepatic-vein position and subsequently into the inferior vena cava. Pressures in the right atrium and inferior vena cava (above and below the renal veins) should be obtained always. If a gradient is observed between the infrahepatic and suprahepatic portions of the inferior vena cava, inferior vena cavography in two planes should be obtained. With the catheter in at least two wedged positions, a maximum of 6 ml of contrast medium is injected at a delivery rate of no more than 2 ml per second.

A last injection should be carried out in the left renal vein (Figs. 10 to 13). The distance between this vessel and the splenic vein is an important surgical consideration when a splenorenal shunt is contemplated. Wide separation of the two vessels will make the surgical construction of a splenorenal shunt technically very difficult or impossible.

RESULTS

Liver cysts, abscesses, and some necrotic tumors (primary or secondary) are characterized by focal avascularity. When an avascular lesion is well demarcated and spherical, it favors the diagnosis of a cyst or of an abscess.⁸

Some vascular malformations, such as capillary telangiectasias, cavernous hemangiomas of the liver, some inflammatory liver lesions, and liver neoplasias (hepatomas, hemangioendotheliomas, cholangiocarcinomas, and metastatic liver tumors), may present variable degrees of hypervascularity. Portography will not differentiate inflammatory from neoplastic processes because in both displace-

ment and compression of veins may be observed.⁹ Contrariwise, portal-vein invasion and obstruction is of frequent occurrence in hepatomas and may cause prehepatic portal hypertension. Hepatic venography may reveal normal findings in presinusoidal portal-vein obstruction (Figs. 14 and 15). This is the best technique to differentiate anatomical from hemodynamic obstruction of the portal vein.¹⁰⁻¹²

In diffuse liver disease, particularly cirrhosis, variable degrees of arterial hypervascularity may be encountered (Figs. 1 and 2). It seems to be related to compensatory arterial hypertrophy due to decreased portal venous blood flow and to the fact that the hepatic artery is the nutritive vessel of the liver parenchyma and, when liver necrosis is followed by regeneration, regenerated nodules are primarily supplied by hepatic arterial branches. Some types of hepatic hypervascularity may mimic poorly vascularized hepatomas.

We have observed that positive phagocytic liver scans (increased uptake of the radioactive material) at the site where increased arterial vascularity is demonstrated by angiography indicate an area of regenerated liver parenchyma.^{1,13,14} On the other hand, decreased uptake at the site of increased vascularity suggests another type of process, such as a neoplasia, primary or secondary. The degree of liver opacification by portography and flow pattern (predominantly hepatopetal or hepatofugal), when compared with the rate of disappearance of the opaque injected at wedged hepatic venography, and the degree of arterial hypervascularity provide qualitative evaluation of total liver blood flow.¹¹ According to some surgeons the best candidates for portocaval shunt operations occur when circulation is predominantly hepatofugal, and there is marked arterial hypervascularity, reversal of the portal vein, and inactive liver disease.² The worst candidates for portocaval shunt operations are those in whom the portal circulation is predominantly hepatopetal, the portal vein is large and provides a large amount of blood to the liver, and wedged hepatic venography reveals a minimal degree of portal hypertension. Modified splenorenal shunt operation combined with devascularization of the left upper quadrant have been suggested for the treatment of portal hypertension in such individuals¹² (Fig. 16).

The prognosis of liver disease is based not only on the activity and severity of liver damage but also on the degree of disarrangement of liver vascular physiology and on the type of treatment. Liver angiography and liver imaging procedures are complementary tests which together provide the best anatomic, physiopathologic, diagnostic, prognostic, and therapeutic information.

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Fig. 6 Wedged hepatic venogram; normal findings. Note flow of contrast medium toward the heart. Pressures were normal.

Fig. 7 Wedged hepatic venogram of a patient with liver cirrhosis with stage II (Ref. 7) of portal hypertension. Note the filling of branches of the portal vein which emptied toward the periphery of the liver.

Fig. 8 Wedged hepatic venogram in a patient with liver cirrhosis, category III (Ref. 7) of portal hypertension. Note irregular parenchymogram with filling of branches of the portal vein. The stagnant portal blood flow was indicative of category III (Ref. 7) of portal hypertension.

Fig. 9 Wedged hepatic venogram of a patient with liver cirrhosis showing category IV (Ref. 7) of portal hypertension. Note tip of catheter outlined by circle. Irregular parenchymogram indicated altered liver lobular architecture. There was spontaneous reversal of flow in the portal vein (PV). This indicates a severe degree of portal hypertension.

Fig. 10 Indirect portography via splenic artery injection. Note incidental aneurysm of midportion of splenic artery. A second catheter was placed in the left renal vein.

Fig. 11 Same case as Fig. 10. Venous phase of splenic artery injection. Note filling of coronary vein (CV). Observe streaming of contrast medium in the portal vein (PV) which is due to unopacified blood from the superior mesenteric vein.

Fig. 12 Same case as Figs. 10 and 11. Indirect portography following injection of contrast medium into the superior mesenteric artery. Note filling of a patent portal vein (PV). SMV, superior mesenteric vein. Enhancement of portography by this technique can be made by preceding the injection of contrast medium with 30 to 50 mg of Priscoline or by arterial injection of Bradykinine.

Fig. 13 Same case as Figs. 10 to 12. Selective left-renal-vein (LRV) injection relates the position of this vessel to the position of the splenic vein demonstrated at the time of splenic arteriography (Fig. 11). A wide separation between the splenic vein and left renal vein is a technical contraindication for splenorenal shunt.

Fig. 14 Wedged hepatic venogram of a patient with presinusoidal portal hypertension (portal-vein thrombosis). The hepatogram and pressures were normal. However, note extensive filling of normal-appearing branches of the portal vein.

Fig. 15 Wedged hepatic venogram of a patient with portal-vein thrombosis. Splenoportography showed extensive collateral circulation and filling defect in main portal vein and in some of its intrahepatic branches.

Fig. 16 Wedged hepatic venogram of a patient with liver cirrhosis with predominant hepatopetal circulation and hyperkinetic circulatory syndrome.

Top left: shows splenic artery injection (SA, splenic artery). Note marked splenomegaly.

Top right shows venous phase of splenic artery injection. Note predominant hepatopetal circulation with large caliber of splenic and portal veins. SV, splenic vein; PV, portal vein; CV, coronary vein.

Bottom left is common hepatic arteriogram showing a large common hepatic artery and slight tortuosity of intrahepatic arterial branches. CH, common hepatic artery; GD, gastroduodenal artery. Small circle indicates position of catheter tip.

Bottom right shows the patient following distal splenorenal shunt. Selective splenic artery injection in the venous phase showed drainage of the splenic vein (SV) into the renal vein (RV) and from there into the inferior vena cava (IVC).

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LIVER SCINTIGRAMS IN THE DETECTION OF HEPATIC NEOPLASMS: COMPARISON WITH LIVER-FUNCTION TESTS AND ANGIOGRAPHY

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ABSTRACT

Liver scanning with radiocolloids labeled with ^{198}Au and $^{99\text{m}}\text{Tc}$ is compared with alkaline phosphatase (AP), bromsulphalein (BSP) retention, and angiography in the study of patients with known or suspected cancer. The true-positive rates in cancer are not dissimilar for all four tests: AP, 71%; BSP, 81%; two series of liver scans, 83% and 88% (focal defects, 78%); and angiograms, 91% (diagnosis cancer, 86%). The false-positive rates in patients with no pathological liver disease show significant differences: BSP, 61%; AP, 41%; two series of liver scans, 9% and 29% (focal defects, 4%); and angiograms, 25% (diagnosis cancer, 4%). The comparative diagnostic usefulness of these tests is discussed. Liver-function tests have advantages of simplicity, low cost, and reasonable sensitivity, but they are nonspecific and do not correlate well with the extent of neoplastic involvement of the liver. Liver scans have no morbidity, good sensitivity, and correlate well with extent of disease, but they are nonspecific and may miss small lesions. Angiograms are sensitive and are helpful in differential diagnosis and in preoperative evaluation of extent of disease and hepatic vasculature, but they are associated with some morbidity and may miss small avascular lesions. All the procedures have a role in the diagnostic evaluation of the cancer patient. Newer radiopharmaceuticals that concentrate in liver neoplasms may improve both sensitivity and specificity of liver scanning in cancer.

In 1962, at the symposium on Progress in Medical Radioisotope Scanning at the Oak Ridge Institute of Nuclear Studies, Christie and MacIntyre¹ reported many of the pitfalls in the then current liver-scanning technique. In the 10 years that have followed, the diagnostic value of scintillation scanning of the liver has been well established in the literature with series as large as 1000 cases reported.² With experience, knowledge of the wide ranges in configuration of the normal liver has been expanded so that normal variants are not so easily confused with

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pathological abnormalities. In addition, the scanning abnormalities that occur with diffuse parenchymal disease and with focal hepatic lesions have become better defined, and, as a result, the recognition of abnormality on liver scans has improved.

The angiographic diagnosis of malignant disease of the liver has also been shown to be a useful technique, particularly in demonstrating the extent of disease.³ With angiography the identification of tumor vessels and staining are two highly specific findings indicative of neoplasm. Vessel stretching and displacement indicate the presence of a mass but do not assist in differential diagnosis. The angiographic procedure is of course limited as a general screening method by its expense and the considerable time required for each examination as well as the definite though slight morbidity.

Numerous references are available documenting the relative diagnostic accuracy of liver scintigrams with liver-function tests⁴⁻⁸ and with angiography.⁹⁻¹³ This report summarizes the experience at the University of Texas M. D. Anderson Hospital and Tumor Institute in the detection of liver disease with scintigrams as compared to liver-function tests [alkaline phosphatase (AP) and bromsulphalein (BSP) determinations] and angiography.

METHODS

Patient Selection

Two populations of patients were analyzed. The first consisted of 284 patients on whom simultaneous (within 1 month) liver scintigrams and liver-function tests (AP and BSP) were obtained. The second group was 150 patients on whom nearly simultaneous liver scintigrams and hepatic angiograms were obtained.

Method of Establishing Diagnosis

All primary cancer diagnoses were proved pathologically, and the status of the liver for disease or normality was substantiated by liver biopsy, laparotomy, or postmortem examination within 3 months of the study.

Liver-Function-Test Technique

Alkaline phosphatase and BSP analyses were performed using standard methods. The AP values of 2.3 Bessey-Lowry (BL) units or less were considered normal. In BSP tests, 6% retention or less in 45 min was considered normal.

Technique of Liver Scintigraphy

In the first group of patients, scans were about equally divided between colloidal ¹⁹⁸Au (200 μ Ci) and ^{99m}Tc-sulfur colloid (3.0 mCi). In the second

group all scans were performed with ^{99m}Tc colloid. The instrumentation for ^{198}Au scans was a rectilinear scanner with a 3- by 2-in. crystal and a 19-hole focusing collimator. Technetium- ^{99m}Tc scans were performed with a gamma camera with a 10- by 0.5-in. crystal and a 4000-channel Tc collimator. Scintigrams were interpreted within 24 hr of the study and assigned to normal or abnormal categories. Abnormalities noted were generally those of diffuse, uneven uptake or focal areas of decreased radioactivity. In several patients the configuration of the liver was abnormal, though there was no abnormality in the distribution of radioactivity.

Hepatic Angiogram Technique

Angiograms were performed using the Seldinger technique. Thirty to 50 cm^3 of 76% meglumine diatrizoate was injected at 8 to 10 cm^3/sec . Films were obtained at a rate of two per second for 3 sec, one per second for 3 sec, and one every third second for an additional 15 sec in the anteroposterior projection. Frequently, oblique projections were obtained with additional injections. Patients in whom an accessory hepatic artery originated from the superior mesenteric artery also were examined via superior mesenteric artery catheterization. Angiograms were interpreted with reference to specific abnormalities described, e.g., tumor vessels and stain, displacement, and avascular defects on the hepatogram. In patients with abnormal findings, we used the angiogram as the basis for the most likely diagnosis.

RESULTS

Liver-Function Tests Vs. Scintigrams

Table 1 shows the results of simultaneous liver scans and function tests in 284 patients. Of these, 139 had metastatic carcinoma, 59 had diffuse benign

TABLE 1
RESULTS OF SIMULTANEOUS LIVER SCANS
AND FUNCTION TESTS IN 284 PATIENTS

Diagnosis	Number of cases	Liver scintigrams	AP	BSP
Percent true positive				
Liver cancer	146	83	71	81
Nonmalignant liver disease	59	70	77	96
Percent false positive				
No liver disease	79	9	41	61

disease, 7 had primary liver cancer, and 79 had no pathological evidence of liver disease. Liver scintigrams and AP determinations had about equal sensitivity in the detection of liver disease. Liver scintigrams were associated with a higher true-positive rate in liver cancer, and AP was more often abnormal in nonmalignant liver disease. Alkaline phosphatase determinations showed a much higher incidence of false positives compared to liver scintigrams in this series of cases. Thus liver scintigraphy appears to be more specific than AP determinations as an indicator of liver disease. Determinations with BSP had higher sensitivity than AP, detecting 81% of liver cancer and 96% of nonmalignant liver disease; however, BSP determinations had an even higher false-positive rate (61%) than did AP.

Liver Scintigrams Vs. Hepatic Angiograms

Table 2 compares the results of liver scintigrams with hepatic angiograms in 150 patients. Liver metastases were present in 73 patients (Fig. 1) and 19 had

TABLE 2
RESULTS OF SIMULTANEOUS LIVER SCANS AND
ANGIOGRAMS IN 150 PATIENTS

Diagnosis	Number of cases	Liver scintigrams	Angiograms
Percent true positive			
Liver cancer	92	88 (focal defects, 78)	91 (diagnosis cancer, 86)
Nonmalignant liver disease	34	59	70
Percent false positive			
No liver disease	24	29 (focal defects, 4)	25 (diagnosis cancer, 4)

primary hepatic neoplasms (Fig. 2) for a total of 92 patients with liver cancer. Benign liver disease was present in 34 patients, including 18 patients with cirrhotic or fatty liver; 0 patients with hepatitis, pericholangitis, or other inflammatory diseases, and 6 with benign tumors, including cysts and abscesses. The results were very close in terms of both true-positive rates in diseased patients and false-positive rates in nondiseased patients. The higher false-positive rate for liver scans in this group compared to the first group is probably a result of difference in patient selection between the two groups. In 1 of 24 normal cases, the scan revealed a focal defect. In the same series the angiogram of

another patient was suspicious for malignancy, giving a false-positive rate for cancer of 4% for both tests.

Combination of Liver-Function Tests and Scans in Screening for Metastatic Disease

When AP, BSP, and liver scans were performed simultaneously in 104 patients with metastatic carcinoma (group 1), only 6 were normal to all 3 tests (3%). It would thus appear that the combination is very efficient in screening for metastases. In some cases abnormal liver-function tests were associated with benign diffuse liver disease, and the scan suggested a benign condition (Fig. 3). In other cases liver-function tests were normal, and the scan suggested metastatic disease (Fig. 4).

Results in the Use of Angiograms for Differential Diagnosis

No attempt was made in this study to define histopathological diagnosis on the basis of AP, BSP, or liver scintigram results. The information provided by angiography was used, however, in establishing a most likely cause of an abnormality. Table 3 is a correlation of the final diagnosis with the diagnosis suggested as most likely on the basis of the angiogram. The angiographic diagnosis of liver cancer was reliable in 79 of 81 (98%) cases (Figs. 5 and 6).

Use of Tests in Assessment of Extent of Disease

The results of all three tests were analyzed to attempt a correlation with the test result and the extent of involvement in patients with cancer. Figure 7 shows the increase in mean values for AP and BSP compared to increasing abnormality on scan and correlated with degree of involvement graded none, 1+, 2+, and 3+. The correlation between the true involvement determined by postmortem and/or laparotomy and the results of the scan was good, with a correlation coefficient of 0.81. The correlation coefficients for AP and BSP were much less accurate, being 0.37 in each case.

TABLE 3
DIFFERENTIAL DIAGNOSIS
OF DISEASE

Final diagnosis	Angiogram diagnosis		
	Liver cancer	Nonneoplastic liver disease	Normal
Liver cancer	79	6	7
Nonneoplastic liver disease	1	14	6
Normal	1	5	18

Fig. 1 Metastatic cancer. A 59-year-old man presented with a large mass in the upper abdomen. Alkaline phosphatase was elevated, but BSP retention was normal. Liver scintigram (a) revealed a large focal decrease in radiocolloid uptake in right lower lobe. Hepatic angiogram (b) revealed multiple, large, metastatic lesions in the right lobe. At surgery a metastatic leiomyosarcoma, primary in the stomach, was found.

Fig. 2 Primary cancer. A 79-year-old man presented with an enlarged, hard liver. Alkaline phosphatase was elevated. Liver scintigram (a) revealed a focal decrease in radioactivity in the right lower lobe. Hepatic angiogram (b) revealed a hypervascularized tumor in the right lower lobe. A liver biopsy diagnosed a primary hepatocellular carcinoma.

Fig. 3 Postnecrotic cirrhosis. A 74-year-old woman presented with an enlarged liver. Alkaline phosphatase was normal, but BSP retention was elevated. Liver scintigram revealed enlargement of the left lobe without focal defects. Liver biopsy diagnosed postnecrotic cirrhosis.

Fig. 4 Metastatic cancer with normal liver-function test. An 18-year-old girl presented with a malignant melanoma of the scalp. The liver was not palpable, and AP was normal. Liver scintigram revealed an enlarged liver with focal decrease in radioactivity in the left hepatic lobe. Surgery confirmed metastatic cancer.

TABLE 4
FOLLOW-UP OF DISEASE (ALL CANCER PATIENTS
UNDERGOING MULTIPLE SCANS)

Number of scans	Number of patients	Progression	Regression	No change	Post- surgery
2	17	8	2	6	1
3	13	6	1	4	2
4	6	4	1	1	
5	1		1		
6	3	1	1		1
8	2	2			
Totals	42	21	6	11	4

Correlation was made between the involvement of lobes, as determined by scanning and angiography, where both studies were localizing. There was good correlation in 47 of 69 patients (68%). In 11 cases the angiogram showed bilateral involvement when the scan indicated a unilateral lesion, usually because of the small size of the lesions. In 11 cases the scan showed bilateral involvement when the arteriogram indicated unilateral disease, usually because of difficulty in evaluating the left hepatic lobe. In most cases the study that showed the greater extent of disease was correct (Fig. 8).

Use of Scintigrams in Following Clinical Course of Disease

Table 4 shows results obtained in 42 patients with liver cancer on whom multiple scans were obtained. As many as 8 scans were obtained sequentially. Twenty-one cases showed progression of the disease during the period of observation (Fig. 9); 6 showed regression of disease, and 11 showed no change. Four patients were scanned following surgical resection of a neoplasm (Fig. 10).

DISCUSSION

Radiopharmaceuticals Used in Liver Scanning

Some of the radiopharmaceuticals that historically have been employed for scanning the liver are ^{131}I -rose bengal, ^{198}Au colloid, ^{131}I -microaggregated albumin, ^{131}I -macroaggregated albumin, ^{99m}Tc colloid, ^{113m}In colloid, ^{75}Se -selenomethionine, and ^{67}Ga -citrate. Colloidal ^{198}Au was the standard agent for liver scanning before the advent of ^{99m}Tc -sulfur colloid. A study¹⁴ of a small group of 48 patients suggested that ^{99m}Tc colloid might have a 10% higher true-positive rate than ^{198}Au colloid. Analysis of a large series of

Fig. 5 Metastatic cancer diagnosed by angiogram. A 72-year-old woman presented with upper abdominal pain, jaundice, and an enlarged hard liver. Alkaline phosphatase was elevated. Liver scintigram (a) revealed hepatomegaly and uneven uptake but no focal defects. Hepatic angiogram (b) suggested a hypervascular malignant neoplasm of the gallbladder extending into the hilum of the liver. Autopsy revealed adenocarcinoma of the gallbladder with direct extension into liver.

Fig. 6 Metastatic cancer diagnosed by angiogram. A 38-year-old woman presented with a mass in the abdomen and elevated AP and BSP retention. Liver scintigram (a) revealed a Reidel's lobe, uneven uptake, and a focal decrease in radioactivity in the posterior of right upper lobe. Hepatic angiogram (b) revealed numerous hypervascular tumors in the liver and an extensive cancer in the pancreas. Autopsy confirmed islet-cell carcinoma of the pancreas metastatic to liver.

patients,¹⁵ however, indicated that the true-positive rate between the two agents was quite similar (^{198}Au , 82%, and ^{99m}Tc , 81%). Such differences can probably be explained on selection of patients alone.

Indium-113m colloid has also been used in liver scanning,¹⁶ but no large series of cases reporting true-positive rates in cancer have been reported using this agent. Results should be comparable to those obtained with ^{99m}Tc colloid.

Iodine-131-labeled rose bengal has been used for many years for liver scanning. At present, it has been replaced largely for routine studies by the radioactive colloids, which are much simpler to utilize since they localize rapidly in the liver, even in cases of hepatic dysfunction, and maintain a plateau of counting rate over a prolonged period. Rose bengal, on the other hand, is excreted rapidly by the liver; therefore the scanning time must be carefully controlled. Excretion of radioactivity into the bile ducts, gallbladder, and gastrointestinal tract makes interpretation difficult. Rose bengal has a place in patients with jaundice where determination of the degree of obstruction of the

Fig. 7 Degree of abnormality of AP (a), BSP (b), and liver scintigram (c) correlated with degree of involvement in 104 patients with proved metastatic disease graded 1+, 2+, and 3+ and also with a group of patients with no liver disease. Correlation coefficient (γ) for liver scintigrams was significantly higher than for either AP or BSP. [From S. G. Jhingran, L. Jordan, M. F. Jahns, and T. P. Haynie, Liver Scintigrams Compared with Alkaline Phosphatase and BSP Determinations in the Detection of Metastatic Carcinoma, *J. Nucl. Med.*, 12: 229 (1971).]

(a)

(b)

Fig. 8 A 69-year-old man presented with an enlarged hard liver and ascites. Alkaline phosphatase and BSP were elevated. Liver scintigram (a) revealed a focal decrease of radioactivity in the left lobe. Hepatic angiogram (b) revealed multiple hypervascular lesions of both lobes. Surgery revealed adenocarcinoma in liver, consistent with biliary-tract obstruction origin. The angiogram defined the extent of the disease better.

Fig. 9 Liver scintigrams showing progression of disease. A 47-year-old woman presented with a carcinoma of the colon. The liver was not palpable, but AP retention and BSP retention were elevated. Liver scintigram (a) initially revealed focal defects in right upper lobe only. Hepatic angiograms revealed hypervascular tumors in both lobes. Follow-up scintigram 2 months later (b) revealed enlargement of the defects in the right lobe and the appearance of several new lesions in the left lobe.

biliary tract can sometimes be made with rose-bengal liver scanning.¹⁷ In addition, there has been a case of hepatoma reported where the tumor concentrated rose bengal.¹⁸ Combined scanning with a radioactive colloid may be helpful in those cases for assessing etiology of defects on liver scans.

Another radiopharmaceutical¹⁹ reported to concentrate in primary hepatocellular carcinoma is ⁷⁵Se—selenomethionine. Eleven patients with hepatoma and cold areas showed increased uptake of selenomethionine on liver scans with colloids. An analysis of a group of patients with metastatic carcinoma and benign liver diseases showed that in only one other lesion was a similar uptake of selenomethionine observed, metastatic malignant melanoma.

Perhaps the most promising of the newer isotopes for scanning malignant neoplasms is ⁶⁷Ga (Ref. 20). Gallium-67 citrate has been reported to concentrate in a wide variety of neoplasms throughout the body and could constitute a most helpful adjunct for assessing the importance of cold areas seen on colloid liver scans. A recent report of ⁶⁷Ga—citrate in scanning of primary cancer of the liver has been published, documenting increased uptake of this isotope in 5 of 25 cases.²¹

A novel approach to liver scanning that has been reported is the injection of ¹³¹I-labeled macroaggregated albumin into the celiac axis, so-called celiac scintiangiography.²² We have utilized this technique primarily to evaluate perfusion via hepatic-artery catheters in use for infusion treatment of liver cancer. Although celiac scintiangiography may have a place in diagnosis, contrast angiography would seem to be more informative because of the greater detail available from roentgenographic techniques.

Comparison of Liver-Function Tests, Scintigrams, and Angiograms

Some of the advantages and disadvantages of liver-function tests for the detection of hepatic neoplasms are as follows:

Advantages

1. Useful as screening tests.
2. Indicator of functional abnormality.
3. True-positive rate in cancer comparable to liver scan.

Disadvantages

1. Most abnormalities nonspecific.
2. Does not correlate well with extent of disease.

The presence of an elevated AP or BSP retention has long been used as an indicator of metastatic liver disease in cancer patients. The present study, indicating a true-positive rate of 71% for AP and 81% for BSP, is in general agreement with previous reports.⁷ The comparison of liver scintigraphy with liver-function testing has been made often with somewhat different conclusions drawn. Some authors, finding a quite similar true-positive rate, conclude that the liver scan is not essential for the detection of metastatic disease.⁴ Others found

Fig. 10 Postsurgical scintigram and angiogram. A 13-year-old boy presented with a mass in the upper abdomen. Alkaline phosphatase retention and BSP retention were within normal limits. Liver scintigram (a) revealed a large focal defect in the hilum of the liver. Hepatic angiogram (b) revealed a large hypervascular tumor in the anterior segment of the right lobe

and the medial aspect of the left lobe. At surgery a large hepatoma was resected. Follow-up liver scan (c) 1 year later revealed enlargement of the lateral segment of the left lobe and a suspicious area in the hilum. Follow-up angiogram (d) revealed no evidence of recurrent tumor, and the child has remained well.

the scan more accurate and more specific than liver-function studies and therefore of more value in diagnostic evaluation.⁵⁻⁸

Some of the advantages and disadvantages of hepatic angiograms for the diagnosis of liver cancer are as follows:

Advantages

1. Detects small vascular lesions missed by scan.
2. Helps in differential diagnosis.
3. Helpful preoperatively for visualization of hepatic vasculature.

Disadvantages

1. Some morbidity.
2. Difficult to evaluate left lobe.
3. Small avascular lesions may be unrecognized.

Angiography has been used for a comparatively short time for the diagnosis of liver disease, and no large series have been published. In one report of 24 cases of liver cancer, a true-positive rate of 88% was obtained.¹² Almost all studies comparing scintillation scanning of the liver with hepatic angiography have concluded that the studies are complementary, with each examination helping to elucidate the other, and that a fuller picture of the pathologic process involved can be obtained by the use of both procedures rather than by either one alone.^{9,12,13} Advantages of angiography that have been cited include help for the differential diagnosis of disease, occasional detection of lesions less than 2 cm and not demonstrated on the scan, preoperative visualization of the hepatic vascular architecture, and help for determining the extent of disease.¹²

Some of the advantages and disadvantages of liver scintigrams for the study of liver cancer patients are as follows:

Advantages

1. No known morbidity.
2. Useful for following disease.
3. Indicator of anatomical abnormality.
4. True-positive rate in cancer comparable to angiogram.

Disadvantages

1. Limited resolution for small lesions.
2. Most abnormalities nonspecific.

The major limitations in scintillation scanning of the liver continue to be those of limited resolution. This occurs from intrinsic limitations in the imaging devices used as well as from degradation in resolution brought about by respiratory motion. Newer short-lived radiopharmaceuticals, such as ^{99m}Tc-sulfur colloid, and new imaging devices, such as the gamma camera, have for the most part overcome the disadvantages brought about by the length of time required to scan the liver area. Whether or not they have enhanced diagnostic accuracy is less well assured.

The importance of liver scanning for determining treatment policies for cancer involving the liver is now well established.^{2,3} Clinicians find liver scans quite useful not only for the detection of metastatic liver disease but also for the differentiation between intra- and extrahepatic abdominal masses, for directing needle aspiration biopsies of the liver, for the evaluation of patients who are candidates for cancer chemotherapy, for the assessment of the results, and for follow-up of liver regeneration following hepatic lobectomy.

Since many abdominal cancers may remain undetected until advanced, particularly primary carcinoma of the liver, early application of the liver-scanning procedure in patients with liver disease of unknown etiology or with findings suspicious of intra-abdominal malignancy has been encouraged.^{2,4} Liver scans have been recommended before major tumor surgery in every patient with known malignancy regardless of normal liver size or normal liver-function tests.^{2,5} However, because of the incidence of false-negative and false-positive liver scans, additional procedures, such as biopsy or angiography, are indicated as a next step to the scanning procedure for confirmation of the diagnosis.

Liver scanning is also helpful in studying patients undergoing partial hepatectomy,^{2,6} and for the assessment of liver damage from therapeutic external irradiation.^{2,7} It has been shown that the human liver can regenerate from a small 10 to 20% remnant to full function and normal mass. A regenerated left lobe of the liver may present as a rounded mass in the epigastrium, which would be difficult to distinguish by palpation from recurrent tumor. Differentiation is possible with the liver scan. Observations indicate that liver scanning with radiocolloid may be a more sensitive index of localized radiation hepatitis than that provided by either clinical or biochemical data. Although the normal liver generally has been considered to be resistant to irradiation when given in the usual therapeutic range, observations of patients undergoing radiation treatment to mediastinal and abdominal areas reveal significant reduction in uptake of isotope in the liver beneath therapy portals compared to pretreatment scans. Both colloid and rose-bengal scanning may be affected by radiation, although the colloid scan seems to be more affected. Many times such changes are not associated with gross liver dysfunction, probably because of the small fraction of the liver usually exposed to radiation. The effect does have clinical importance for the recognition of these defects as associated with therapy and not with recurrent or progressive disease.

The fact that many benign conditions cause focal defects on the liver scan, indistinguishable from those seen in cancer, means that caution must be exercised in the approach to patients with abnormal liver scans. Such benign conditions include hematoma formation on the surface of the liver, such as may follow needle biopsy of the liver.^{2,8} Filling defects may also be associated with dilatation of the bile ducts in cases of stones in the common bile duct, carcinoma of the head of the pancreas, and carcinoma of the stomach obstructing the bile duct. In such cases percutaneous transhepatic cholangiogram

should permit differentiation between tumor and dilated biliary ducts.²⁹ In addition, focal defects or cold areas associated with alcoholic liver disease have been observed.³⁰

Extrahepatic tumors in the upper abdomen will at times cause defects on liver scans suggestive of metastatic disease when, in fact, only external pressure is involved.³¹ The mechanisms involved may differ among cases and include pressure by the tumor, producing decreased cellular function in the adjacent hepatic parenchyma, compromise of the vasculature in a localized part of the liver due to pressure from tumor, and simple compression by a mass. The phenomena of liver distortion is probably more common in children, where abdominal masses are often quite large in proportion to total abdominal volume, thereby facilitating liver compression.

CONCLUSION

For the clinical evaluation of patients, many diagnostic techniques are required to cope with the wide variety of diseases that present for study. For the diagnosis of liver cancer, liver-function tests appear to have reasonably high sensitivity but are nonspecific and do not correlate well with the extent of the disease. Liver scanning is a useful diagnostic procedure with a fairly high degree of sensitivity and specificity and correlates fairly well with the extent of disease. Because of its simplicity the liver scan is of value in follow-up of disease. The need for more definitive diagnostic procedures short of laparotomy is present in many patients suspected of liver disease on the basis of liver-function tests and/or liver scintigrams. The angiogram appears to offer a valuable tool to answer that need with high sensitivity and specificity.

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PROBLEMS ENCOUNTERED IN DIAGNOSIS OF PANCREATIC AND HEPATIC CONDITIONS

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ABSTRACT

A brief review of the function of the liver and pancreas and clinical diagnostic tests for diseases of these organs is made. Our ability to diagnose liver disease far exceeds our diagnostic ability for the pancreas. Some immunological tests for specific etiologies are now utilized in diagnosing liver disease. Anatomical tests to outline the organ are still used in diagnosing diseases of the pancreas. Urgent clinical needs are indicated.

Today diagnosis of conditions of the liver may be said to be very satisfactory, whereas diagnosis of conditions of the pancreas is very poor; thus we will discuss these two organs separately. For each organ we will consider the more recently introduced diagnostic techniques found useful and present some of the particularly baffling problems that remain.

PANCREAS

Table 1 indicates the range of tests available for the diagnosis of diseases of the pancreas, although frequency of use varies.

New diagnostic tests, usually involving another serum enzyme, appear as frequently as six times yearly and attest to the unsatisfactory state of the detection of pancreatic disease. Often the older techniques prove better than the new.

The most widely used test pertaining to the pancreas is the serum amylase. It is well known that approximately 15% of patients with an inflamed pancreas or a blocked pancreatic duct will have a normal serum amylase. Furthermore, parotid disease, hepatic inflammatory disease, renal insufficiency, or intestinal destructive disease may produce elevations. Very few patients have a persistent

TABLE 1
TESTS AVAILABLE TO DIAGNOSE DISEASE OF THE PANCREAS

Common and Widely Available

1. Serum and urine amylase and lipase.¹
2. Radiographic techniques:
 - a. Plain abdominal X rays, flat and upright.
 - b. Barium meals and barium enemas.
 - c. Cholangiography.
3. Studies of recovered intestinal secretion after secretin and pancreozymin stimulation.
4. Studies of the stool for malabsorption:²
 - a. Fat, nitrogen, and meat fibers.

Less Common but Widely Available

1. Hypotonic duodenography or cine studies of the duodenum.
2. Angiography and portal venography.
3. Duodenal cytology.
4. Scans.

New and Unproved

1. Study of intestinal-pancreatic performance on an aspirated meal.
 2. Other serum enzymes.³
 3. Direct intubation of pancreatic duct.⁴
 4. Carcino-embryonic antigen.⁵
 5. Iso-enzymes of amylase.⁶
-

elevation due to a large amylase molecule (macroamylasemia) that seems harmless.

The separation of renal insufficiency, acute pancreatitis, and macroamylasemia has become feasible as a result of a careful study by Levitt, Rapoport, and Cooperband.¹ They evaluated the common problems of amylase elevation and found that the ratio of urine amylase to urine creatinine in a single random specimen collected at the time of diagnosis would usually solve the dilemma. When expressed as a ratio, the value for normals was $2.3 \pm 0.1\%$; for hospitalized controls, $2.1 \pm 0.3\%$; and for renal insufficiency, $2.1 \pm 0.2\%$. Pancreatitis of from 0 to 4 days duration gave values of $6.6 \pm 0.3\%$; from 5 to 8 days, $4.3 \pm 0.3\%$; and from 9 to 15 days, $3.4 \pm 0.4\%$ (not different from normal). Macroamylasemia was $0.34 \pm 0.13\%$, clearly differentiating it from the normal. By applying their observations to several of our clinical problems in recent months, we have enhanced the value of an old test.

There is little new in routine X-ray studies. The finding of pancreatic calcification establishes only that there has been inflammation in the past, not that it is active; thus it has about as much information as a Ghon tubercle. The sentinel loop is even less specific. The secretin-pancreozymin stimulation of the pancreas is useful in the hands of those who perform this test regularly, but, for those who perform it occasionally, it is essentially worthless. However, there are useful stimulants of the pancreas, and cytological examination of the aspirated

fluid is of the greatest value in diagnosing cancer of the pancreas. When skillfully performed and when two aspirations are routinely done, this test invariably yields a positive result in patients with pancreatic carcinoma; it yields no false positives. The difficulty of conducting duodenal intubation, however, has limited its use. We have found this technique useful for the patient with obscure severe intra-abdominal pain.

When pancreatic malabsorption becomes clinically significant, it is not subtle. Most patients eat a little extra and overcome the mild malabsorption; in contrast to most other malabsorptive conditions, there are few systemic components that accompany malabsorption due to lack of pancreatic enzymes. When such patients do have wasting, the malabsorption is a combination of many factors, including poor alkalization of the duodenum and bacterial overgrowth; thus the absorption studies based on fat content of the stool are somewhat confusing. However, the presence of creatinuria and meat fibers are usually helpful.

Hypotonic duodenography is a substantial advance in the radiographic diagnosis of conditions of the head of the pancreas or conditions diffusely altering the gland. In this technique peristalsis in the duodenum is eliminated by a large dose of intramuscular Pro-banthine. Barium is usually introduced into the duodenum by tube, and X rays of the relaxed mucosa reflect underlying extrusions or edema and adhesions. Tumors, inflammations, and masses of the head of the pancreas are often disclosed by this technique. Its greatest value is in clearly defining possible abnormalities of the duodenum or head of the pancreas suggested in routine upper gastrointestinal X-ray examinations.

Angiography has been valuable in indicating neoplasia or avascular masses in the pancreas and remains the greatest new diagnostic tool for this area. Because identification of the pancreas as the source of abnormal symptoms is often not possible, angiography may provide the first significant clue that this is the organ involved. Almost every major hospital has available angiographic services. Small benign and malignant tumors have been identified if they are typically vascular or have a typical venous phase; false positives remain somewhat of a problem. Pseudocysts of the pancreas are usually adequately demonstrated by this method because in such instances the wall is usually vascular. Invasive tumors from surrounding nodes, organs, or lymphomas are occasionally confusing on angiograms but well-defined by portal venography. The late venous phase after arteriography is usually not sufficient in its opacification of the portal vein to demonstrate filling defects or irregularities.

Scans of the pancreas have been the basis of a major presentation at this symposium, but for most of us they have limited value because of the great difficulty of interpretation, particularly when these scans are most needed. The marked irregularity of the gland and the proximity to the liver, which is similar in its uptake of labeled substances, have made clear definition of the pancreas difficult.

Pancreatic enzyme deficiencies can be accurately diagnosed by a chemical examination of the partial digest of an aspirated fat and protein meal. This technique, however, is laborious, time consuming, and expensive and will not be used widely. A variety of other serum enzymes have been studied, including elastase, leucine-amino peptidase, and trypsin, but none have been more valuable than the simpler, currently used tests.

The carcinoembryonic antigen is frequently secreted into the serum by carcinoma of the pancreas as well as by carcinomas from other sites in the GI tract.⁷ In some instances of positive tests, the tumor is too small to demonstrate, appearing only after advanced growth invasion has occurred.

In Japan the pancreatic duct has been cannulated via duodenoscopy, but success in America has been spotty. This area needs much investigation so that we may properly plan therapy of patients with pancreatic disease.

Tests still needed in the diagnosis of pancreatic disease are:

1. A sensitive measure of destructive inflammation of a portion of the pancreas. Presumably some specific intracellular material originating in the pancreatic acinar cells is released into the serum, and this will be detected. There is no test for the pancreas which gives the information that transaminase gives for the liver, aldolase, or creatine phosphokinase for muscle, etc., and this is sorely needed. The amylase is quite nonspecific and insensitive; probably elements of ductula obstruction are needed for it to be elevated.

2. An adequate means of showing patency of the pancreatic duct. A cholangiogram type of study would be most desirable; if this is not possible, then a method of directly intubating the duct, such as injection of contrast media via endoscopy, would be acceptable. Although early diagnosis of tumors will probably be possible by means of cytologic examination of material aspirated from the duodenum, for the patient with pancreatitis there is still a great need for a nonoperative means of determining the status of the pancreatic duct.

3. An adequate anatomic outline of the pancreas to evaluate swelling and masses. Although angiography, venography, and scans provide information along these lines, they fall short in most instances of giving accurate, consistent data. The indirect means of opacifying the adjacent structures is highly inadequate. Thus it is difficult to determine serially whether an abnormality is improving or getting worse, leaving the management of many pancreatic conditions a matter of guesswork and inadequate evaluation.

4. An external means to biopsy the pancreas safely. Progress in the diagnosis of intestinal, hepatic, and renal disease followed rapidly the development of biopsy techniques; however, at present even open biopsy is of limited value because of its high rate (10%) of morbidity.

5. An easily applied measure of pancreatic malabsorption. The major digestion of protein and elastic fibers by pancreatic enzymes surely must indicate that a substance exists that could be used to test this enzyme activity, but a simple procedure for this has not yet been developed.

6. A specific test or device to determine whether or not abdominal pain is of pancreatic origin. Although this test is not available for any other organ, it would certainly ease our diagnostic problems.

We conclude that the state of the art for diagnosing conditions of the pancreas is poor. Careful study of serum and urine amylase and routine plane and barium films of the abdomen are our first-line effort. Hypotonic duodenography, angiography, and duodenal cytology belong in each internist's armamentarium. Among the potential advances, further evaluation of the carcinoembryonic antigen as a specific indicator for gastrointestinal cancer (including pancreas) seems the most hopeful.

LIVER

Our methods of diagnosis of liver disorders are good, and we can diagnose with nonsurgical techniques (up to and including biopsy) almost all its cellular, biochemical, and anatomic abnormalities. Table 2 contains some of the newer diagnostic techniques.

TABLE 2

NEWER DIAGNOSTIC TECHNIQUES FOR LIVER DISEASE

-
1. X-ray techniques
 - a. Angiography.⁸
 - b. Umbilical vein venography.⁹
 - c. Transhepatic cholangiography.
 2. Imagery
 - a. Serial and multidirectional views.
 - b. Use of multiple scanning substances in some patients.
 - c. Serial studies with rose bengal.
 3. Biochemical
 - a. Genetically determine conditions.
 - b. Rates of formation and removal of proteins.
 4. Immunological
 - a. Hepatitis-associated antigen.¹⁰
 - b. Alpha fetoglobulin.¹¹
 - c. Antimitochondrial antibody.¹²
 - d. Carcino-embryonic antigen.
 - e. Specifics.¹³
 1. Epstein-Barr virus for mononucleosis.
 2. Entamoeba histolytica for amebiasis.
 3. Hydatid cysts for hydatid disease.
 5. Hemodynamic
 - a. Combined flow and pressure studies.
 6. Minilaparotomy¹⁴
-

Radiology, scanning, and immunology have brought the most substantial advances to liver disease in the last few years.

Angiography is just on the horizon of useful application to diseases of the liver. The differentiation of benign from malignant tumors is becoming increasingly possible, and with scanning we will soon be able to consider differences in reticuloendothelial (RE) cell content and vascular space. Before long it will be feasible to distinguish cirrhosis from neovascularity of tumors and certain inflammatory conditions of the liver. The natural history of such catastrophic diseases as aneurysm of the hepatic and splenic arteries can now be defined, whereas in the past we knew them only as severe bleeding.

Umbilical venography is useful in the study of collateral circulation in portal hypertension. The collaterals in the area of the spleen can be far better defined, enabling us to develop new operations that will replace the nearly obsolete portacaval shunt.

Infrequently we have a need for transhepatic cholangiography, a procedure wherein we inject a needle percutaneously into the liver until a bile duct is encountered, as determined by the aspiration of bile or by the injection of radiocontrast media under fluoroscopy. A positive diagnosis would aid us with a few patients who possibly have surgically relievable cholestasis. This procedure can diagnose a common bile duct obstruction correctable by surgery, and, usually, can delineate the exact level of obstruction. The morbidity is somewhat greater than liver biopsy, and, if obstruction is demonstrated, a prompt decompression is essential to prevent serious bile peritonitis. The procedure is diagnostic in about 98% of the cases of extrahepatic obstruction; a negative study is less valuable than a positive one. This procedure is sometimes done during a minilaparotomy, in which, under local anesthesia, transhepatic cholangiography is accomplished through the incision into the peritoneal cavity. Bleeding and bile leakage may be controlled with a stitch.

Newer isotopes permitting better-quality scans in less time with less total irradiation to the patient have been developed. Newer imaging devices permit multiple views in less time, but with these advantages resolution has not increased. Multidirectional views of the liver have undoubtedly enhanced diagnosis. The easy attainment of scans has permitted us to observe the evolution of tumor nodules and abscesses. Vascular tumors are often delineated by cold areas on colloid scans and hot areas on radioiodinated albumin scans. Through the use of rose bengal and serial scans, we can appraise liver uptake and reexcretion and learn something of liver-cell function and whether the bile duct is patent. At present scanning has made the outline of the liver well known to each clinician.

Biochemistry has not offered great diagnostic progress in liver disease. Approximately 25 genetic defects involving enzymes in the liver cells have been described. Most of these are diagnosed by the absence of an enzyme in the liver biopsy but many by the appearance of an abnormal product in the blood or urine. These are not commonly thought of as liver diseases. The rates of

formation and of degradation of many proteins made by the liver have been determined. Though of little diagnostic value, this has enhanced greatly the understanding and treatment of certain conditions associated with liver disease; thus the synthesis and breakdown rates of albumin, coagulation proteins, transaminase, and alkaline phosphatase are known. When their level in the blood is low, we can now distinguish between diminished production and increased removal from circulation. This has led to treatment of activated coagulation (consumption coagulopathy) in liver disease.

The hepatitis-associated antigen (Australia antigen) as an indicator of long-incubation hepatitis (the old serum hepatitis) is well known. The widespread application of this test in diagnosis and prevention of transfusion-transmitted disease has probably already saved more lives than any other liver test of the last decade. In addition, it has revolutionized thinking about transmission of hepatitis. At present a patient with a positive test for hepatitis-associated antigen is more likely to be chronically or fatally ill than to be a hazard to his community through shared needles or blood donations.

Alpha fetoglobulin, uniquely found in hepatoma and embryonal cell carcinoma and present in about 60% of patients with either of these tumors, is of great diagnostic value. Nonspecific antimitochondrial antibody exists in about 90% of patients with active biliary cirrhosis in the destructive phase. Its presence is reason to suspect this disease; the common diseases considered in the differential diagnosis are not associated with a positive test.

When this test is positive and there are also typical findings on liver biopsy, it is now possible to make the diagnosis of biliary cirrhosis without surgical exploration. A variety of specific tests are now available for some of the common problem diagnoses of liver.

Our ideas of portal hypertension have changed drastically. To measure pressure and flow, we frequently catheterize simultaneously the hepatic and umbilical veins and the mesenteric artery. Used in conjunction with excellent radiograms of these vascular systems, such measures have indicated many previously unsuspected types of portal hypertension. With these better descriptions the entire question of treatment by surgical or medical means is under reevaluation. The portacaval shunt in its present form will probably disappear in about 5 years and be replaced by newer and currently experimental operations.

In a few problem patients a minilaparotomy is done through an abdominal incision under local anesthesia to approach the liver, the biliary tract, and the portal venous system. A liver biopsy is often necessary as a part of this procedure to make a correct diagnosis before initiation of appropriate treatment. If performed by a trained team, the patient is usually not harmed by this operation.

What are the clinician's needs in the area of liver disease?

Many drugs are of limited value in studies and treatment of the liver because of its unfavorable reaction to an increasing number of therapeutic and environmental agents. At best these reactions are diagnosed with uncertainty.

The lymphocyte transformation test holds promise to demonstrate such sensitivity *in vitro*. Briefly, the lymphocytes from the blood of a patient with a drug reaction, when placed in tissue culture with the drug, undergo transformation to a more primitive type, whereas the cells from control patients show little change. This may permit us to recognize halothane hepatitis in early forms before it becomes fatal.

With our increased knowledge and understanding of bile salt metabolism, we are on the verge of being able to prevent gallstones and cure with drugs those present. Simple and widely applicable blood tests of bile salt metabolism are needed. This will rival the alkaline phosphatase in the diagnosis of cholestasis and should permit us to know whether there is an element of bacterial infection in the bile ducts; it is likely that gallstone formers will be diagnosed and preventive measures taken.

An immunological test for short-incubation viral hepatitis is much needed. An earlier report from Italy of such an antigen has not been confirmed.

Other unmet needs in the management of liver disease are:

1. A test showing minimal involvement of the liver. Transaminase is useful only if the injury has been quite recent and if the transaminase stores of the liver were initially normal (not so in alcoholics); otherwise it fails. Scans have not persistently shown nodules 2 cm in diameter.

2. Blood tests that correlate with fibrosis and regeneration.

3. A specific blood test for alcoholic liver disease. This ailment is common in Europe and in America but is often permitted to reach an advanced stage largely because of inability to confirm or even suspect the diagnosis.

4. A simpler and safer means to diagnose surgically relievable obstruction of the bile duct. We must often rely on transhepatic cholangiography or laparotomy, but each is a major procedure.

5. A simple way to appraise functioning liver tissue in the patient with jaundice. This is badly needed to observe the response of liver disease to treatment. After several weeks of treatment, it is often impossible to determine if the patient is really improving or getting worse, and this can be a drawback.

6. A reliable, simple means to ascertain hepatic blood flow and the contributions of the hepatic artery and portal vein and their respective pressures. This would permit us to stage appropriate operations for portal hypertension and to avoid some complications.

SUMMARY

The state of the diagnostic art for the liver is good and is getting better each year. Therapy, however, has lagged and needs more attention from investigators than does diagnosis.

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DISCUSSION: LIVER AND PANCREAS

Viamonte: Focal and diffuse liver disease can be recognized and adequately assessed by the complementary use of imaging techniques and liver panangiography. Liver panangiography employs and combines hepatic or portal vein catheterization studies (manometry and angiography), direct or indirect splenoportography, and hepatic arteriography. It provides fundamental morphologic and hemodynamic information prior to treatment and also permits assessment of the physiologic effects of the surgical procedure used.

When portal hypertension is secondary to liver cirrhosis, prognosis and rational therapy require a careful assessment of the status of the liver damage and hemodynamic alterations. Only with such information can an effective choice between nonoperative and operative treatment be made. If surgery is to be carried out, preoperative studies are also helpful in the selection of the best surgical procedure. Surgical decompression of the portal system almost always cures the bleeding but may condemn the patient to an immediate or delayed death from liver failure. Observations indicate that the latter is likely to occur when the preshunt hepatic blood flow is markedly reduced, if the reduction of portal blood flow to the liver is profound (patient who preoperatively has a slight decrease in portal blood flow to the liver) or if the liver has not adapted to decreased portal blood flow through compensatory hepatic arterial circulation.

Imaging of the liver, evaluation of blood distribution in the liver, and estimation of hepatic blood flow are contributions of radioisotopic studies.

Likewise, celiacomesenteric arteriography allows for the morphologic definition of pancreatic diseases such as pseudocyst, chronic pancreatitis, carcinomas, and endocrine tumors. Angiography has its maximum contribution in the detection of endocrine tumors, the majority of which (over 75%) are hypervascular. Tumors as small as 1 cm or less can be detected by celiacomesenteric angiography.

When dealing with malignancies, the venous phase of the celiacomesenteric angiographic examination seems to offer the highest percentage of abnormalities. Clinical history, results of some laboratory examinations, imaging techniques of the pancreas, and celiacomesenteric arteriography are presently the best methods

for studying pancreatic disorders. Fiberoptic duodenoscopy and wirsungography are promising techniques that soon should add a new dimension for the evaluation of pancreatic disorders. I am sure that there are many questions from the audience.

Reba: In a retrospective analysis of our liver scans at Johns Hopkins, we found that the primary indication for liver scanning was hepatomegaly in at least 95% of the patients.¹ Yet we know that half the patients dying with metastatic involvement of the liver have a normal-size liver.

After a surgeon agreed to carefully examine the liver and perform a biopsy of any suspicious site, we performed a prospective analysis of liver scans in over 100 patients who were going to be operated on within 3 days of the scan examination.² As our single criterion for evidence of hepatic cancer, we selected the presence of clear-cut focal defect(s). Our results were very similar to those of Dr. Haynie. There were 29% false negatives. Of 30 patients found to have liver cancer, 8 had normal liver scans. Seven of the 8 had lesions less than 2.5 cm in diameter; only 1 had a lesion greater than 2.5 cm. Five of the 8 had normal liver size. So, if the liver is enlarged and the enlargement is due to cancer, you are more likely to see clear-cut focal defects.

We also looked at the sensitivity of liver scanning. The sensitivity was about 80%. In other words, we took all patients with clear-cut focal defects and divided them by the number of patients with cancer, multiplied by 100, and expressed the result in percent. Scan sensitivity compared favorably to elevated serum alkaline phosphatase. Serum alkaline phosphatase was about 85% sensitive, whereas the liver scans were nearly 80%. Only one patient with a clear-cut focal defect on the scan did not have cancer. Therefore only 5% of the scan studies gave false positives; so specificity was 95%. Like Dr. Haynie, we found that specificity for serum alkaline phosphatase was about 50% or less. You might increase this figure for alkaline phosphatase the way Dr. Iber suggests. The essential question is whether the lesion is a tumor, and if so, what is its extent. I would restate the aim another way: What can we do to increase specificity?

I would like to make one more comment about reporting positives and negatives, which seem to cause a lot of confusion in certain tests. When a scan is being interpreted, may I suggest the first word always be (you have a choice of two) normal or abnormal, followed by a qualifying statement. One example is: abnormal brain scan, almost certainly secondary to Paget's disease. That is, state the various diagnostic possibilities and, if possible, in some order of weighted priority, e.g., Paget's disease, 0.90; subdural hematoma, 0.10; tumor, <0.01.

¹ K. P. Poulouse, R. C. Reba, F. H. DeLand, et al., Role of Liver Scanning in the Preoperative Evaluation of Patients with Cancer, *Brit. Med. J.*, 4: 585-587 (1969).

² K. P. Poulouse, R. C. Reba, J. Cameron, and H. N. Wagner, Jr., The Value and Limitations of Liver Scanning for the Detection of Hepatic Metastasis in Patients with Cancer (in press).

Dr. Miale reported that 2 of 3 patients with diabetes mellitus have abnormal scans of the pancreas. Is there any relation to the age of the patient, duration of the disease, and therapy (i.e., oral hypoglycemic agents that act on the liver and pancreas, or insulin)? DeBlanc and Lomas³ reported that only 2 or 3 of 40 healthy men 20 to 45 years of age had an abnormal pancreas scan. However, since most of the patients for whom a pancreas scan is indicated are 50 years or older, what fraction of patients greater than 50 to 60 years of age, without apparent pancreatic disease, will have an abnormal pancreas scan? Can the defect seen in the midportion of the pancreas be explained by vascular compression from the aorta?

Miale: I will answer your last question first. First of all, the defect is not due to the aorta. The defect is due to an abnormality of the pancreas in that particular anatomical site which is related to the aorta. We proved this by injecting intravenously the bolus with sodium pertechnetate and simultaneously photographing the pancreas and the bolus at that site.

Regarding your question about diabetes, we are now correlating our data. Diabetes is more frequent in the higher decades of life. Diabetes has secondary effects on the exocrine pancreas and certainly produces vascular changes. It seems from our data thus far that at least two-thirds of our patients who have diabetes after the age of 60 have scans that reflect decreased pancreatic function. In other words, the anatomic outline of the pancreas is readily discerned, but the degree of concentration for that organ is not what we normally expect. This is not to say, however, that we have not seen perfectly normal pancreatic scans in a few diabetics whose disease is mild or well controlled. So the question really is: to what extent does the diabetes in the individual affect the exocrine function of the pancreas? And what age of the patient, duration of the diabetes, and degree of vascular disease associated with the diabetes may be factors affecting the pancreas? It seems that we are never going to be able to approach a perfect determination of what is normal and abnormal in the pancreas by so-called analog visualization alone.

I believe that we are nearly on the threshold of going into what Dr. Iber has alluded to earlier, mainly a computerized approach to the pancreas. As interesting as that is, I think that approach does not stress the most important point of all, for, when one evaluates a patient with a problem, there is no perfect single test you can choose for diagnosing anything. This is especially true with the pancreas. I think that the large variety of chemical, radiologic, and other diagnostic tests available simply reflects the fact that no one of them really proves or disproves a specific disease unless we get in there and perform a biopsy of tissue. However, we constantly face in the individual patient the problems of

³ Harold J. DeBlanc, Jr., and Frederick Lomas, The Normal Pancreas Scan: Criteria from a Prospective Study of Forty Normal Volunteers, submitted for publication.

risk, benefit, reliability, and discomfort. As clinicians we have to make choices as we go along. In my opinion the real value of studies such as the liver scans and pancreatic scans is that they will allow us to make choices and will direct the diagnostic work-up so the patient can be correctly selected for angiographic, duodenal intubation, or any of the other more-sophisticated procedures. It is all very well to say that the pancreatic scans are not positive, or rather do not show pancreatic disease, but that really is not the point. We do find lack of an abnormal scan in a normal individual with a normal pancreas. If you have a test that clearly indicates one does not have a pancreatic disease, I think this is an exceedingly valuable step forward in clinical diagnosis.

Schmidt: I would like to make a comment and also ask Dr. Miale a question. A couple of weeks ago I had a very interesting patient who weighed 250 lb. (I am a practicing radiologist.) The patient's history went like this: When he came for an upper G.I. series I asked him what kind of work he did. I am an engineer. What kind of engineer? Brewery engineer. What kind of trouble are you having? Maybe I have beer stones. What are beer stones? They are stones that form in the pancreas of people who do my kind of work. Sure enough he did have pancreatic stones in the films we took later; the largest of these was about 2 cm. He also had a poorly functioning gallbladder and a 3-cm gallstone, but I think his main problem was his pancreas. My question relates to your statement of the availability of a simple test which can exclude the presence of pancreatic disease. When you have pancreatic stones, are there any complications resulting when you try to do pancreatic scans? In a patient who shows pancreatic stones on a plain film of the abdomen, is a pancreatic scan likely to be successful and worthwhile?

Miale: I think not more than 3 to 4% of the patients that we have scanned had well-defined pancreatic calcification. This would not bother us or be a reason for not doing pancreatic studies because we still want to know: How well can the pancreas function? If it functions inadequately, we will be able to get at the facts merely by looking at the scans. Of course you can put a tube down that patient and obtain duodenal secretions to study pancreatic enzymes. But, if you ask the patient which test he would prefer, the scan or the duodenal intubation, the choice would be rather clear. Now the next question: Which of the two tests is the most reliable? Certainly the pancreozymin tests are reliable to a point, but they do not tell you everything either. They sometimes have a false-positive or false-negative value like the scan. However, when you get clear, normal data then you have a very fine probability that you are dealing with a patient who has a functioning pancreas regardless of the calcifications.

Baltaxe: I would just like to comment about Dr. Iber's presentation. I am an angiographer, and I do not share Dr. Iber's optimism. We reviewed 74 cases of patients with tumors of the liver, primary and secondary types. We tried to classify these tumors on the basis of the appearance of their vessels and to predict which tumors were malignant and which were primary or secondary. Hepatomas have a classical appearance in that they are very vascular.

Cholangioma might present an absolutely normal picture. A benign tumor such as a hamartoma may look exactly like a malignant tumor. Adenomas may also look malignant, but a scan would be helpful in such a case since adenomas usually have a positive uptake of radioactivity. As Dr. Viamonte said, all hepatomas are negative on phagocytic liver scans, but the benign adenoma that has malignant features on the angiogram shows positive uptake on the scan. I am very pleased when I can state that this tumor is a malignancy or this one is a primary tumor. However, I realize that I am guessing. It helps considerably to know that the patient has an underlying carcinoma of the colon, and I am supposed to look for metastases. I can state then that such lesions are metastases, but I cannot be more specific.

Calcifications of the pancreas are not unusual. I recall a report of a few years ago which stated that the disappearance of calcifications would indicate pancreatic carcinoma [D. H. Tucker and I. B. Moore, Vanishing Pancreatic Calcification in Chronic Pancreatitis; a Sign of Pancreatic Carcinoma, *New Engl. J. Med.*, 268: 31-33 (1963)]. We reported a case of a woman who had pancreatic calcifications that disappeared [H. A. Baltaxe and E. V. Leslie, Vanishing Pancreatic Calcifications, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, 99: 643-644 (1967)]. When she died from an unrelated pancreatic disorder, she did not have carcinoma of the pancreas.

Viamonte: I agree with Dr. Baltaxe about the nonspecificity of hepatic angiography. We may not be able to distinguish inflammatory lesions from noninflammatory disorders. There are also angiodyplasias that mimic malignancies by the angiographic appearances of the vessels.

Buonocore: I also would like to comment about the nonspecificity of arterial patterns in the liver and pancreas in the normal individual and in various disease states. During our presentations and discussions this morning, a very picturesque group of words has arisen like "corkscrew," "leafless tree," "stretched artery," and others that are really nonspecific for a given disease. We studied 200 patients who manifested no liver disease, and we tried to correlate the type of tortuosity as well as the location and size of the hepatic arteries with a given histologic pattern. We found only a correlation with the size of the liver. The larger the liver, the more stretched the arteries appeared; the smaller the liver, the more tortuous they were. Radiographic enhancement alone will add little to our understanding of the diagnosis of liver or pancreatic tumors. In my experience only one patient with increased vascularity determined by the angiogram was found to have an adenocarcinoma of the pancreas. A 2-cm adenocarcinoma rarely will produce symptoms. A number of studies have been performed which will help correlate our diagnostic approach to diseases of these organs, but it will not be radiographic enhancement, which provides too much detail and not enough information about physiology. So at this point I would like to lay to rest the statement made yesterday that radiographers are morphologists and that radioisotope people are physiologists. Maybe it is the

other way around because, once they start taking more than one picture, radiologists become physiologists also.

Ashburn: We should briefly mention another very simple procedure, a noninvasive technique for evaluating the liver, and that is ultrasonic scanning. In conjunction with Dr. George Leopold of our institution, we have performed over 100 diagnostic ultrasonic scans of the liver in combination with standard multiple views of radiocolloid imaging of the liver. We have been impressed with the improved detectability and, in many cases, specificity in determining whether the hepatic lesion is cystic or solid. Our impression so far is that the combined use of these two procedures is preferable to either one alone in our diagnostic approach. Both radiocolloid imaging of the liver and the ultrasonic scan can be done on an outpatient basis. I would suggest that ultrasonic techniques be kept in mind in the evaluation of liver disease by noninvasive methods.

Mulstein: Dr. Haynie, what percent of your patients screened for metastatic liver disease have neither an abnormal scan nor an abnormal liver-function test?

Haynie: In our experience it is a very small percentage. These figures are in my manuscript, and I believe only 2% of the cancer patients screened had neither a positive scan nor a positive liver-function test. In other words, in the patients who had cancer and were studied, 98% would have either an abnormal liver-function test or an abnormal scan.

Goswitz: I do not recall your mentioning anything, Dr. Viamonte, about the hazards or risks of splenoportography. Are there any contraindications to performing this procedure? How does the liver angiogram compare with liver-function tests in the evaluation of patients with liver cirrhosis, particularly in regard to their need for a portacaval shunt?

Viamonte: Since the decision for a surgical procedure has already been made in many cases, we need the simplest, quickest procedure in doing splenoportography. Splenoportography as an elective angiographic test is contraindicated in hemorrhagic diathesis, ascites, and liver failure, particularly if the patient has even mild jaundice.

The simplest technique with the lowest morbidity is indirect portography. Dr. Iber mentioned that the detail of the portal system is not good with this technique, but actually visualization of that system will depend on the size of the spleen. Most laboratories have injected at least 70 ml; some will use 100 ml, dependent on splenic size and the marked dilution of the contrast agent that will occur after injection. Certainly one would not inject this large volume into a peripheral vein, but it is really quite safe when injected into the splenic artery.

The local complications of the femoral approach are the most important and are related to the duration of the examination, the amount of manipulation, the size of the catheter, and the clinical condition of the patient, the morbidity being highest with severe hypertension and/or atherosclerosis and with wide pulse pressure. We use the smallest size catheter possible (No. 7F). As far as correlation between activity of liver disease and angiography, we could not find

any correlation between the activity or chronicity of liver disease and the angiographic appearance. We have observed the same type of liver vascularity, particularly arterial vascularity, in patients with inactive liver disease as well as in those who manifest active disease at the time of the study. Like other procedures angiography has certain advantages, indications, and limitations. I do not believe that angiography is intended for a functional diagnosis. Dr. Buonocore has had extensive experience in hepatic angiography, and maybe he disagrees with me. Dr. Buonocore, do you feel we can make a functional assessment of the liver by angiography?

Buonocore: No.

Viamonte: Thank you. In summary, I believe we should use the simplest procedure first, and, if we do not obtain the answers to our satisfaction, then we may proceed with more-complicated techniques, such as liver panangiography.

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BLOOD, MARROW, NODES, and SPLEEN

LYMPHOGRAPHY

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ABSTRACT

Diseases of lymph vessels and/or lymph nodes, particularly of the skeletal lymphatic system, can be adequately evaluated by hand, foot, neck, penile, and testicular lymphography. Radiographically silent lymph-node regions, such as most of the visceral lymphatic system, and the mediastinal nodes are inaccessible by injection of cutaneous lymphatics.

The technique often fails in certain types of lymphedema because of obstruction of the peripheral lymphatic channels. Isotopic studies in such situations are the only radiological means for establishing patency of deeper lymphatic channels and the presence or absence of regional nodes.

Diseased lymph nodes are characterized by alterations in their number, size, morphology, and architecture. Small filling defects dispersed throughout nodes suggest some types of lymphoma, such as Hodgkin's disease. However, there are no pathognomonic adenographic patterns in lymphography of a specific disease.

We do not expect isotopic studies to detect small filling defects and subtle changes in lymph-node architecture. As in other studies, the combination of radiographic opacification of the lymphatic system and imaging techniques is complementary. Lymphography remains the best radiologic method for anatomic delineation of the skeletal lymphatic system.

Lymphangiadenography is accomplished by the intralymphatic injection of an oily, radiopaque contrast agent followed by radiographic demonstration of lymph vessels and nodes.¹⁻³ Bilateral foot lymphography is the most popular technique for the in vivo demonstration of the inguinal, pelvic, and periaortic lymphatics (Figs. 1 to 4). A limitation of this technique is the inability to opacify lymph nodes adjacent to viscera and mediastinal nodes (Fig. 5). The latter may become opacified occasionally.

In patients with lymph-vessel pathology (aplasia, hypoplasia, or obliterative lymphangitis), it may be impossible to demonstrate radiologically the peripheral lymphatics. In such situations the intradermal injection of radiogold (¹⁹⁸Au) or

any other type of tagged large molecules that are selectively or predominantly absorbed via the lymphatic system is a useful technique for identifying the regional lymph nodes proximal to the injection site.

Lymphedema may be related to disease of the vessels (lymphangiopathic) or of the nodes (lymphadenopathic). Functional disorders of the lymphatic system may become manifested by chylous ascites, chylothorax, and various forms of chylous reflux. The mechanism and cause may be elucidated by lymphography.⁴

The most important contribution of lymphography is to aid in the study of *lymph-node pathology*. The immediate postinjection radiographs are used for the study of possible obstruction and/or displacement of lymphatic chains. It is important to analyze the flow pattern and compare immediate radiograms with delayed radiograms. Radiograms obtained 1, 2, or several days following the injection of contrast medium best outline the architecture of lymph nodes of the groin, pelvis, and periaortic regions. Position, number, size, morphology, and architecture of the opacified nodes are criteria used for identifying pathology in lymph nodes.

Increase in the size of nodes and changes in morphology may be observed with many neoplastic as well as nonneoplastic processes.⁵⁻⁷ Marginal defects in the lymph nodes may represent the hilar portion, inflammatory disease, or metastasis^{8,9} (Fig. 4). Relatively spared margins of nodes with disseminated filling defects or nodes with a coarse pattern may be seen with inflammatory processes and in lymphoproliferative disorders (Figs. 1 to 3). Lymph-node abnormalities smaller than 3 mm usually are not detected radiographically. Occasionally, magnification radiography and tomography may reveal abnormalities not observed on the conventional roentgenograms.

After foot lymphography, if pelvic or periaortic nodes appear to be involved, we have used needle aspiration biopsy under fluoroscopic control in an attempt to aspirate material from the site where the filling defect is observed in opacified nodes. When the nodes are in the pelvis, the paravascular approach of Ruttimann⁶ is utilized. When the nodes involved are to the left of the aortic chain, a translumbar approach with the patient prone is utilized (Viamonte technique). A patient rotating device or biplane fluoroscopy accurately delineates the position of the tip of the needle. When the nodes are to the right of the spine, the transvenous approach (Viamonte) is then employed. For the latter, a catheter is advanced into the inferior vena cava, and, when its tip position is perpendicular to the inner wall of the inferior vena cava and opposite the involved node, an intracatheter needle is passed which perforates the wall of the cava and is directed into the filling defect of the involved node. We have had no complications with the supra- and infradiaphragmatic needle aspiration of nodes. Bleeding and transient nerve anesthesia are usually unsequential complications.

Another radiologic examination, isotopic lymphography, complements lymphangiadenography.^{10,11} Scintiscanning of the lymph nodes with ¹⁹⁸Au

Fig. 1 Hodgkin's disease; unilateral study. Note diffuse involvement of right pelvic and periaortic nodes.

Fig. 2 Hodgkin's disease; unilateral study. Note opacification of right and left paravertebral nodes. Observe that the predominant involvement occurs on the right side.

Fig. 3 Hodgkin's disease; clinical stage 1. Note involvement of left aortic nodes. Between 20 and 40% of stage 1 Hodgkin's disease reveal involvement of nodes below the diaphragm.

Fig. 4 Metastatic left renal carcinoma. Observe enlarged, high left aortic nodes with characteristic marginal filling defects proven to be secondary to metastatic deposits from a left renal-cell carcinoma.

Fig. 5 Hodgkin's disease. Note bilateral paravertebral soft-tissue masses proven to be related to tumor (arrows). This area is usually not opacified by foot lymphography.

has been used for the evaluation and treatment of patients with lymphoma. A solution of colloidal particles of ^{198}Au is injected subcutaneously into the webbed space between the first and second toes of each foot. The colloid particles are engulfed by the histiocytes and transported through the usual lymphatic channels to the regional lymph nodes. Active motion of the lower extremities is usually followed by the detection of radioactivity in inguinal regions about 20 min after the injection. Localization and concentration of the isotope in lymph nodes depend on the patency of the lymph channels and the functional integrity of the lymph nodes. Radioactivity as recorded on the scintiscan reflects activity in lymph-node groups rather than in the individual lymph nodes. The total volume injected into each foot ranges from 0.75 to 1 ml depending on the specific activity of the ^{198}Au . Small particles from 5 to 15 μ should be used. A standard rectilinear scanner with a 3-in. crystal and a 19-hole collimator is used for scanning. Because of the short half-life of ^{198}Au , scanning is usually done at 24 hr. The scintiscanning can be repeated as often as necessary. The concentration of radioactivity is maximal in the draining nodes (those immediately proximal to the injection site) and gradually diminishes toward the more distant nodes. Abnormal scintiscans consist of diminished or absent radioactivity and/or displacement of the radioactivity. Mottled or patchy distribution of radioactivity reflects partial replacement of lymph nodes. Radioactivity occurs at unexpected sites when abnormal colloidal pathways fill nodes away from the pelvis and periaortic chain. The disadvantage of

scintiscanning is that it offers less morphologic information than lymphography. A repeat scan during an after-treatment may prove to be useful for evaluation of the radiation response. Scintiscanning of the patient with lymphoma is intended primarily as a rapid screening procedure.

Areas silent to lymphography have been demonstrated with certain isotopes, such as ^{67}Ga and ^{111}In . This technique has been of particular value in lymphomas. The affinity of certain tumors for some tagged materials makes isotopic lymphography a valuable complementary procedure.^{10,11}

Intravenously injected, tumor-seeking radionuclides, such as ^{111}In and ^{67}Ga (in the citrate or chloride form), have been used successfully in localizing the extent of various neoplastic processes. The most promising results have been obtained with the lymphomas, and indeed areas silent to lymphograms have been demonstrated to be involved with lymphomas.

Experimental animal lymphomas avidly concentrate indium and gallium, and sequential scans reflect the efficacy of such therapeutic agents as irradiation. Recently we have demonstrated with ^{67}Ga in a rat lymphosarcoma a striking regression of a tumor mass distant to the site of irradiation therapy (abscopal effect).

SUMMARY

Lymphography is of value for the detection of pathology of the lymph vessels, conditions of lymph reflux, and primary and secondary lymph-node disease. The discovery of unsuspected lymph-node pathology, the staging of a known lymphoma,¹² the assistance provided to the radiotherapist (placement of treatment portal), the response of treatment, and the early detection of recurrence are contributions of lymphography. Isotopic lymphography is used for diagnostic and therapeutic purposes. The nonspecific but valuable uptake by abnormal lymph nodes of such products as ^{67}Ga and particularly ^{111}In are promising complementary techniques for the radiologic assessment of lymph-node pathology.

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RADIOCOLLOID SCANNING

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ABSTRACT

With radioactive colloids one can label the reticuloendothelial (RE) system and thereby obtain an image of these tissues, particularly the liver, marrow, and spleen. Since the marrow sites of hemopoietic activity often parallel RE phagocytic activity, one can indirectly obtain information on hemopoiesis. In a variety of hemopoietic disorders, one can delineate expansion and extension of red marrow and demonstrate changes that occur as the disease progresses; this information may be useful to the clinician who decides on the type and amount of treatment. One can also show the extent of marrow destruction after radiotherapy and may demonstrate infiltrative lesions. The marrow scan has limited value in differential diagnosis. Images of the spleen, however, offer a more practical aid to the clinician in the differential diagnosis of a mass in the left side of the abdomen, determination of the size and position of the spleen, demonstration of the response to treatment, and the location of filling defects, particularly those from infarction. Imperfect radiopharmaceutical agents, instrumentation problems, and physiological conditions are the major factors that complicate and hinder interpretation of RE scans.

When one injects intravenously a suspension of colloidal sized particles (or microaggregates) of $1\ \mu\text{m}$ or less in diameter, the cells of the reticuloendothelial (RE) system remove them quickly. If the colloid particle is rendered radioactive, we have a convenient label of the RE system. Imaging the liver is the commonest application of radiocolloid scanning and has merited a separate paper in this symposium. Our own discussion will be limited to scanning the marrow and spleen.

In disorders of the interlinked hemopoietic, RE, and lymphatic systems, the marrow and spleen are usually both involved in the process; some specific questions can be asked about only one of these tissues. What questions can we answer with colloid scanning?

What is the distribution of the functional marrow in the skeleton, and is it expanded into the extremities?

- Is there increased or decreased labeling of the trunk marrow?
- Is there local or general destruction of the normal trunk marrow?
- Can we diagnose ectopic marrow?
- Is the spleen enlarged, atrophic, or absent?
- Has the spleen changed size under therapy?
- Does the spleen have defects that indicate infarct or neoplasm?

Armed with answers to these questions, along with other clinical and laboratory data, we then seek to interpret our findings for four purposes: (1) an aid in diagnosis, (2) an adjunct in planning treatment, (3) a tool in evaluating the response to therapy, and (4) an aid in prognosis.

With the benefit of adequate clinical trials, we must then face a more difficult set of decisions. We need to define the risk and the other costs to the patient and how these scans could modify his management. We also should ask whether there are other simpler or more reliable ways to get the same information.

EQUIPMENT AND AGENTS

One can obtain satisfactory images of the marrow and spleen with either rectilinear scanning equipment or stationary imaging devices, such as cameras or autofluoroscopes. At present the twin-headed whole-body scanner offers the most convenient way to obtain an image of anterior and posterior views in approximately 45 min of scanning time. With a scintillation camera, multiple views of the body are required in segments up to 12 in. in diameter and may take approximately the same total time. One can paste on a suitable outline of the body various views and rephotograph this collage for the scan record. For spleen scanning alone, a posterior and a left-lateral view are best, but, in the anterior scan of the liver, the splenic image can also be seen.

We have a narrow choice of available pharmaceutical agents even though many preparations have been tested over the past 10 years and new ones emerge each year for clinical trial. Most practitioners are obliged to use a commercially packaged thiosulfate solution to which is added ^{99m}Tc ; this mixture is boiled in acid to form a colloid, buffered, and again boiled. Dosages range from 3.5 to 10 mCi of ^{99m}Tc colloid, and the patient receives a low radiation dose because of the short half-life and the absence of beta particles. Colloidal ^{198}Au is also commercially available; the particles are superior in characteristics to the home-prepared thiosulfate colloid, but the ^{198}Au has an unacceptably high internal radiation dose for a general patient population. We have used 1 mCi of ^{198}Au per square meter of body surface for our investigative studies of the marrow, but we do not recommend it for general use. Gold-198 is acceptable for only limited kinds of patients with known proliferative disorders that will be treated with destructive or suppressive therapy; in these patients the therapeutic insult to the marrow will far exceed the dose required for scanning. For imaging

the spleen alone, the current agent of choice is ^{99m}Tc colloid, which gives a minimal radiation exposure. Sometimes alternatively one can use red cells damaged by heat or chemicals. The more popular method is ^{51}Cr labeling of heat-damaged erythrocytes; chemical damage with bromomercurihydroxypropane labeled with ^{197}Hg has also had some adherents, but questions concerning the chemical toxicity of the latter have inhibited its use and it is not currently on the market.

The details of scanning techniques are well established, and, suffice it to say, one must adhere to a well-standardized methodology or groups of patients or an individual patient cannot be compared at different stages in the disease. We have in recent papers given our views on the main problems related to imperfect radiopharmaceutical agents and other complex factors that affect the distribution of the colloid, such as changes in blood flow to the liver, spleen, and marrow or altered function of the RE cells.¹⁻²

NORMAL MARROW PATTERN

With radioactive colloids the adult's functional marrow image is confined to the trunk (Fig. 1a). One always sees the thoracic and lumbar vertebrae, pelvic bones, and usually the femoral and humeral heads. The cervical vertebrae, smaller in size, are frequently not apparent, nor are the ribs. Unfortunately the liver's Kupffer cells, dominating the RE system, take up the majority of the dose (80 to 90%), thereby obscuring the marrow of the midtrunk.

In normal children we have no real experience with marrow scanning, but we are confident that the well-known distribution of functional marrow in long bones would be shown. Adolescents (in this as in other situations) will be unpredictable since the marrow gradually assumes the adult pattern.

ABNORMAL MARROW PATTERNS

A number of groups have reported their clinical investigations, and we have listed some selected recent papers in Refs. 3 to 7.

The marrow responds to stress and exhibits hyperplasia, proliferating first in the normal trunk sites, then by expansion into the extremities; first the heads and proximal shafts of the femurs and humeri, then the knee and elbow regions, followed by the midshafts, and finally by uptake in the ankle regions but rarely in the wrists (Fig. 2a). Concurrently, the bones of the head become visible, including the cervical vertebrae, the skull and the facial bones, especially the mandible.

If one interprets a scan to have increased functional marrow in the trunk, it must be done gingerly because of variations in the display (Fig. 3b). On the other hand, the extension peripherally is clear-cut and moderately but not always symmetric. In extended marrows we find unexplained variations, particularly

Fig. 1a

Fig. 1b

Fig. 1a Marrow scan of a 72-year-old man with secondary polycythemia disease, under control, who had received five treatments with ^{32}P , which controlled his symptoms. The patient has a history of arteriosclerotic heart disease and emphysema, no enlarged spleen, no leukocytosis or thrombocytosis, and normal blood volume. The scan shows normal trunk distribution and a hint of extension into proximal femurs.

Fig. 1b Posterior view of a 45-year-old man with secondary polycythemia who also has arteriosclerotic heart disease and cirrhosis of the liver and a history of elevated red-blood-cell values for more than 15 years (treated by phlebotomy). The spleen is slightly enlarged, presumably from the cirrhosis. He has never had thrombocytosis or leukocytosis, and a red-cell mass was in the high normal range. The scan shows the normal trunk distribution but with abnormal extension into the shafts of the femur and humerus and also uptake in the head.

Fig. 1c Scan of a patient with polycythemia vera (active phase). A marrow image showing normal trunk uptake but with moderately pronounced extension in the extremities. The splenomegaly is noteworthy, and the liver is also somewhat enlarged. His red-blood-cell values at the time were not greatly elevated, but the red-cell mass was almost twice normal and there were elevated leukocyte values. His main complaint related to the enlarging spleen, a source of some concern to the clinicians who worried about impending secondary myelofibrosis. Six months later his disease had not advanced greatly except for further splenic enlargement.

Fig. 1c

around the knee joints, which customarily display the medial and lateral condylar widening. Sometimes these sites fail to participate in the hyperplasia for reasons unknown.

When the trunk marrow is involved in a diffuse disorder, particularly myelofibrosis (Figs. 4 and 5), the uptake is absent or is faint and patchy; patients able to compensate by activating their peripheral marrow will be labeled most prominently around the knee regions, and we have seen this occur in a variety of disorders, including acute leukemia, myeloma, and blast crisis of chronic granulocytic leukemia (CGL) (Fig. 2b). Some patients, however, fail to respond in this manner. In focal ablation by metastases, or radiation therapy (Fig. 3a), the marrow fails to take up the colloid and is seen as a "cold" area.⁸⁻¹²

We have seen increased labeling of the axial skeleton most prominently in polycythemia vera, Hodgkin's disease, and acute leukemia. We have also seen examples of "hypercellular" trunk marrow (apparent increased density on the scan) in CGL, secondary polycythemia, lymphosarcoma, and chronic lymphocytic leukemia but never in myelofibrosis.

Fig. 2a

Fig. 2b

Fig. 2a Scan of a 51-year-old man who had a 1-year history of chronic granulocytic leukemia that had been untreated except for low-dose splenic irradiation 9 months previously. Note the extension of marrow into the appendicular skeleton, pronounced splenomegaly, and enlarged liver.

Fig. 2b Scan of a 56-year-old woman in a blast crisis of granulocytic leukemia and secondary myelofibrosis. The chronic granulocytic leukemia had been controlled for 3 years by treatment with splenic irradiation and total-body irradiation. Note the absent uptake in the trunk and the massive splenomegaly. The extended marrow in extremities still shows some uptake. Compare this scan image with Fig. 4.

Fig. 3a **Fig. 3b**

Fig. 3a Scan of a 50-year-old woman with Hodgkin's disease who had been treated with extensive mantle and abdominal radiotherapy. This scan shows focal defects in the marrow and also one kind of pitfall in interpreting scans. Note the patchy defects in the lumbar spine, chest, midpelvis, and proximal femurs identifying the scope of marrow ablation. Note also extension of the marrow into the femoral shafts and visualization of the marrow in the head.

Fig. 3b Scan of the same patient as in Fig. 3a 18 months later. Beware of this scan. A light flasher recording the radioactivity on the photographic film was malfunctioning, which gives the impression of decreased uptake. Close inspection reveals about the same numbers of counts over marrow sites as in the earlier scan.

Fig. 4 Scan of a 47-year-old farmer who had a 5-year history of primary myelofibrosis treated with splenic irradiation $1\frac{1}{2}$ years earlier. During the 4 years between the first (a) and second (b) scan, his treatment included androgens, folic acid, steroids, and other agents to encourage stimulation of blood-cell production. His symptoms included abdominal pain, suggesting a splenic infarct. The scans show absent uptake in the marrow with enlarged spleen and probably normal-sized liver. Part b shows that after 4 years the liver and spleen have become massively enlarged. No splenic infarcts were demonstrable.

Fig. 5 Scan showing secondary myelofibrosis in a patient with chronic granulocytic leukemia. In part a the uptake is confined to a massively enlarged spleen and liver, and none is demonstrated in the pelvis. After treatment with two courses of low-dose-rate total-body irradiation totaling 300 R over a span of 15 weeks, the scan (part b) demonstrated a distinct uptake in the trunk marrow accompanied by reduction in splenic size. Although the hematologic depression was greater and more prolonged than expected, the patient obtained a hematologic remission which had lasted up to the time of writing, for 18 months after the treatment.

Extension into the extremities beyond the heads of the femurs and humeri can occur in polycythemia vera, CGL, chronic lymphocytic leukemia, acute leukemia, myelofibrosis, Hodgkin's disease, lymphosarcoma, and long-standing anemias. As a rule of thumb, the extension is greatest and more frequent in CGL (Fig. 2a), polycythemia vera (Fig. 1c), and acute lymphocytic leukemia.

In interpreting the RE scan, both the liver and spleen size should be considered as well as the uptake and distribution in the marrow. In primary and secondary myelofibrosis, we may find massive hepatosplenomegaly with essentially no marrow uptake, but this may not be diagnostic of the disorders for

we have also encountered on occasion a similar pattern in an associated blastic crisis of CGL (Fig. 2b).

THE SPLEEN

Without doubt imaging the spleen is a useful procedure for diagnosis and for measuring response to therapy. As part of a diagnostic work-up in myeloproliferative or lymphoproliferative disorders and hypersplenism from other causes, we want to know whether the spleen is enlarged. Occasionally we need help in determining whether an abdominal mass palpable on the left is spleen. Radiologists with plain films of the abdomen are prideful of their ability to visualize the spleen in more than 50% of the patients, and several studies have demonstrated that we can reliably estimate the size of the spleen by measuring its length on X-ray film.¹³⁻¹⁵ Yet the shadow of the spleen is sometimes obscure and the outline difficult to delineate, and catheterization and radiopaque media obviously are too cumbersome and costly to be ideal. Hence a radioisotopic method is a welcome new tool. A number of papers estimating splenic weight from radioisotope scans have appeared, perhaps the most recent by Larson et al.¹⁶ Spencer¹⁷ somewhat earlier approached the problem of estimating splenic volume from X rays and scans. In analyzing several equations based on lateral and posterior dimensions, Larson concluded that the posterior length from ^{99m}Tc colloid images would be the most practical single dimension for estimating weight. Sigel et al.,¹⁸ with scintillation-camera images, concluded also that the simplest and most practical approach was to measure the splenic height from a posterior view. Their criteria from camera images was as follows: 6 to 14 cm, normal; 15 to 18 cm, enlarged; 19 cm or larger, markedly enlarged. Because the size of the spleen (100 to 250 g) varies so widely in normal adults, correlates poorly with body size, and shrinks in advancing age,¹⁹ more complicated formulas for estimating its size may be unwarranted. The scan, then, is a simple way to measure response to therapy and document a shrinking spleen (Fig. 6).

Splenic scanning can aid in detecting asplenia or abnormally small organs, and Pearson, Spencer, and Cornelius²⁰ have described a state of "functional asplenia." In the latter situation some patients with sickle-cell anemia fail to visualize the spleen even though it is anatomically present. This failure can result either from shrunken spleens, which typically occur in sickle-cell anemia, or from defective function of the RE tissue within the organ.²¹ Locally impaired blood supply within the spleen without any true infarction can yield a pattern resembling infarction on the scan (Fig. 6).

After a splenectomy for hypersplenism, occasionally one can pick up an offending accessory spleen, although we have not had success in this procedure. With large doses of radioactive colloid, the RE tissues in the kidney may be visualized (Fig. 7) and in the absence of the spleen (surgical or congenital) could

Fig. 6 Scans of the spleen of a 45-year-old woman afflicted with lymphosarcoma who had a pronounced splenomegaly. In part a the image, an anterior view, is partially superimposed on the left lobe of the liver. Note the defects, which might be interpreted as infarcts. Three months later, after therapy with Cytosan and prednisone, the scan (part b) demonstrated the degree of splenic shrinkage (not of much value in managing this particular case). Focal defects persist, suggesting sites of infarction. However, at autopsy the spleen, although having some very small infarcts, had no wedge-shaped infarcts correlating with the scan image. True splenic infarcts show similar defects on the scan.

show up and be misinterpreted as splenic tissue. After posttraumatic splenectomy, splenosis has been demonstrable by scanning.²²

We can also show infarcts as filling defects, a useful tool in the troublesome problem of diagnosing the cause of left-upper abdominal pain, particularly in patients with spleens enlarged from one of the proliferative disorders (Fig. 8). In addition, scanning of the RE tissue has found its way into the protocols for staging Hodgkin's disease where information on splenomegaly or space-occupying lesions is needed. Table 1 puts scanning in the context of other procedures for answering clinical questions about splenic anatomic pathology.

Fig. 7 Posterior scan of the left upper quadrant in a patient with lymphosarcoma after splenectomy. Focal radioactivity mimicking spleen is in fact the left kidney. With a large dose for imaging the marrow and with the instrument set for high sensitivity, it is possible to see the small amount localizing in the kidney.

OF WHAT VALUE IS AN RE SCAN?

A perspective on this question may be difficult to reach. In a few kinds of problem cases, we find it helpful in making a diagnosis. Most notably, patients with primary myelofibrosis have a characteristic pattern of massive hepatosplenomegaly and absent or minimal uptake in the marrow. In patients with erythrocytosis and equivocal blood values, we gain support for a diagnosis of polycythemia vera if more colloid than usual concentrates in the axial skeleton

Fig. 8 Scan (a) of a 39-year-old man with chronic granulocytic leukemia in blastic crisis who suffered episodes of left abdominal pain which were suspected of being splenic infarcts. Note wedge-shaped defects in the enlarged spleen. The autopsy specimen [photograph (b)] confirmed the extensive infarction.

TABLE 1
SPLENIC ANATOMY

	Palpation	Surgery	Flat-film X ray	Contrast media	Radioisotopic scanning
Size, shape, and location	Limited precision	Considerable cost and risk	Precision sometimes limited	Cumber-some	Yes
Infarcts	No	Considerable cost and risk	No	Cumber-some	Yes (as focal defect)
Tumors	Not usually	Yes	Sometimes	Cumber-some	Yes (as focal defect)
Asplenia	No	Considerable cost and risk	No	Cumber-some	Yes
Accessory spleen	No	Yes	No	No	Has been demonstrated (Ref. 23)
Posttraumatic splenosis	No	Yes	No	No	Has been demonstrated (Ref. 22)

and extends into the extremities and the spleen is enlarged; but in secondary polycythemia the extension into the femurs usually will be absent or less pronounced (Fig. 1a). In truth, though, these are relative rather than pathognomonic differences; in general, we cannot name a specific disease from a total-body scan of a patient whose clinical story is unknown. We have reconciled ourselves to a low index of confidence in diagnosing a disease from a given total-body scan pattern.

Several groups⁹⁻¹² report success in locating osseous metastases; they believe that, if we are scanning the liver for metastases, we should include views of the marrow and look for focal defects. This finding, of course, would have a significant bearing on the choice of therapy and the prognosis.

When treatment is being planned, a colloid scan may on occasion sway a decision, especially if we find poor labeling of the marrow; with this knowledge we might proceed more cautiously than usual. In assessing beneficial responses to therapy, we find a more defined application. In greatly expanded and extended marrows (or in a marrow poorly delineated), the shift to a pattern closer to normal signals, with other observations, a beneficial response.

After local radiotherapy, marrow in the field will not concentrate colloid, and this fact is useful to properly interpret a scan where marrow infiltration is suspected. In extended field radiotherapy, especially for Hodgkin's disease, other lymphomas, and testicular tumors, the marrow scan vividly shows the degree of ablation,⁶⁻⁸ a factor to be weighed in planning any additional chemotherapy or radiotherapy. If the radiation dose is not too high, marrow regeneration can take

place, and a scan will demonstrate this change. As to its use in prognosis, the obvious application lies in revealing unsuspected osseous involvement by neoplasm. Table 2 contains an oversimplified summary of uses of RE scanning.

In comparing marrow scanning with other procedures (Table 2), we may establish its relative value. The direct approach to the marrow is to aspirate or biopsy samples. This approach is most useful in assessing the hemopoietic state, but relatively few sites are accessible, and the patient's tolerance for multiple aspirations is limited. The scan might give clues about optimum sites for a biopsy or reveal that an aspiration is from a nonrepresentative site.

TABLE 2
SOME USES OF RE SCANNING

	Differential diagnosis	Planning treatment	Beneficial response to R _x	Deleterious effects of R _x	Prognosis
Myeloproliferative states					
Acute granulocytic leukemia	0	0	±	0	0
Chronic granulocytic leukemia	±	+	+	0	+
Polycythemia vera	±	±	+	0	+
Myelofibrosis	+	0	+	0	0
Lymphoproliferative states					
Acute lymphocytic leukemia	0	0	±	0	0
Chronic lymphocytic leukemia	0	±	+	0	0
Lymphosarcoma	0	+	+	+	+
Hodgkin's disease	0	+	0	+	+
Secondary polycythemia	±	0	0	0	0
Hypersplenism	+	+	0	0	0
Bone metastases	+	+	0	0	+

The bone scan and bone X ray provide alternative, probably better, ways to find osseous lesions (metastases); finding such lesions with marrow scanning ought to be regarded as a dividend gained for little additional investment of scan time. Other hematologic procedures, including the standard ones, and the radioactive procedures with ⁵¹Cr labeling of erythrocytes, ⁵⁹Fe kinetics, leukokinetics with diisopropyl fluorophosphate (DFP)-32, and the like, provide their own special data on the hemopoietic organ. Generally speaking, we see no instance where the marrow scan will supplant these tests. Table 3 summarizes how to best obtain answers about the functional marrow.

TABLE 3
ANSWERS ABOUT THE FUNCTIONAL MARROW

	Aspiration or biopsy	X ray	Bone scan	Marrow scan	Hematological procedure, including isotopes
Hemopoietic state	Yes	No	No	No	Yes
Distribution in skeleton	Not practical	No	No	Yes*	No
Focal marrow ablation (radiation)	Limited in de- lineating extent	No	No	Yes	No
Focal marrow defects (tumor)	Use limited to known lesions	Yes	Yes	Yes	No
Cellularity of marrow	Yes, but sample may not be representative	No	No	Yes*	No
Local interference with blood supply	Not easy in some sites	Yes, but not early	No	Yes	No
Ectopic marrow	Sites hard to reach	No	No	†	Yes

*Good correlation usually but with noteworthy exceptions.

†has been demonstrated.

PITFALLS IN RE SCANNING

Earlier in this paper we have alluded to pitfalls at one or another point in the procedure. A compendium of these follows:

Colloid	Reproducibility of particle size and number not easily controlled, factors that enter into the distribution pattern.
Label	A small percentage of unbound label may produce concentrations of radioactivity in organs other than the RE system (salivary, thyroidal, gastric, colonic, renal, and bladder); the dose of radioactivity, of course, is also a variable.
Instrumentation	Printout: Variations in density may lead to a false impression of decreased or increased labeling of marrow. A change in collimation, scanner speed, or spectrometer setting may alter sensitivity, thereby

placing labeled marrow below the detection threshold.

Biologic

Correlation of RE activity with hemopoiesis: A dissociation may exist in certain disorders (e.g., aplastic anemia, red-cell aplasia, or treated Hodgkin's disease). Gross alteration in blood flow: Cirrhotics have much better visualization of marrow, even with small doses of radiocolloid.

SUMMARY

Marrow scans can delineate expansion and extension of functional marrow and show extent of marrow destruction and sites of infiltrative lesions. They have limited value in differential diagnosis but may be useful in selecting treatment. On the other hand, images of the spleen offer a more practical aid to the clinician; for example, in differential diagnosis of a mass on the left side of the abdomen, in estimating the size of the spleen, and in demonstrating focal interruptions in splenic blood supply as is seen in infarction or other space-occupying lesions.

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DYNAMIC RADIOISOTOPIC STUDIES IN CLINICAL HEMATOLOGY

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ABSTRACT

The radionuclides of iron, cobalt, and chromium are useful tools in providing information about the physiology of erythrocytes and their alteration in various disorders. Studies utilizing these radioisotopes help in the differential diagnosis of the macrocytic, normocytic, and microcytic anemias. In addition to the measurement of rate of red-cell formation and removal, sites of red-cell production and sequestration can be detected by body-surface monitoring for radioactivity. Disorders of overproduction, such as polycythemia, or underproduction, such as "refractory" anemias, may require more than one radioisotopic study to define the problem. In polycythemias concomitant but independent evaluations of red-cell mass and plasma volume are helpful in separating the various types. In marrow failure the destruction rate of red blood cells may be normal, but the utilization, turnover, and storage of iron are abnormal. Measurement of iron stored within the reticuloendothelial system can be evaluated with the nonerythropoietic iron turnover rate.

Radionuclides of hydrogen, carbon, selenium, sulfur, phosphorus, and chromium attached to various compounds have enabled scientists to study the physiology of granulocytes. Calculations of the rates of specific cell development in the marrow, total blood pool sizes, and blood disappearance time of granulocytes have all been possible with radioisotopic methods. This knowledge is germane to the therapy of various granulocytic disorders, especially leukemia, in which drug therapy is most effective when given to vulnerable cells. The ability to explain the cause of a thrombocytopenia or thrombocythemia would make clinical radioisotopic studies of the platelet more valuable. Radionuclides can determine platelet survival and sequestration; detection of platelet abnormalities by these procedures aids in the selection of treatment.

Until Huff and coworkers¹ published their paper on ferrokinetics in 1950, clinicians paid little attention to the diagnostic uses of radionuclides in hematology. With development of the ⁵¹Cr red-cell labeling technique for studying hemolysis and the ⁶⁰Co-vitamin B₁₂ urinary excretion test for malabsorption of B₁₂, the clinical applications of radionuclides to the hematologist became more apparent.^{2,3} With the availability of these radioactive

test materials to clinical medicine, physicians have greater access to physiologic information, leading to more precise diagnosis and better treatment for their patients.

The most frequent use of radionuclides in studying red-cell disorders is the evaluation of patients with anemias, subclassified morphologically into macrocytic, normocytic, or microcytic categories. Polycythemias are amenable to study with radionuclides to help distinguish the primary, secondary, or relative types, but usually these disorders present the clinician less diagnostic difficulty than the anemias.

MACROCYTIC ANEMIAS

The macrocytic anemias characterized by large erythrocytes [mean corpuscular volume (MCV) greater than $100 \mu\text{m}^3$] are usually caused by a deficiency of vitamin B_{12} or folic acid. The most useful test in elucidating the cause of B_{12} abnormalities is the ^{57}Co -cyanocobalamin absorption test. Table 1 cites the disorders responsible for macrocytic anemia classified according to the results of the absorption test. The four main categories are: (1) normal ^{57}Co - B_{12} absorption without intrinsic factor (IF, obtained from hog stomach), (2) normal absorption with hog IF, (3) impaired absorption without and with hog IF, and (4) normal absorption restored after appropriate treatment but not by hog IF.

Some patients with macrocytic anemia who have a normal absorption test without IF may have low serum ^{57}Co - B_{12} (normal: 100 to 760 pg/ml) and folate concentrations (normal: 5 to 20 mg/ml) that are diagnostically helpful; in these cases the defect may be a dietary deficiency, an increased requirement, or an impairment in utilization of the vitamins. Unfortunately these *in vitro* tests cannot pinpoint the specific defect but can only confirm or exclude a deficiency of vitamin B_{12} or folate.

Impaired B_{12} absorption without IF (8-hr plasma level less than 0.2% per 1% body weight or urine excretion less than 7%) and a normal result with it is diagnostic of IF deficiency. No other test is so specific for diagnosing this defect. The 6- to 8-hr plasma level of ^{57}Co - B_{12} can be more helpful than the urinary excretion test, particularly in those patients with renal insufficiency who have inadequate urine output and those with mental disturbances who do not cooperate in the collection of complete urine specimens.⁴ Patients with a deficiency of IF from whatever cause will not manifest a megaloblastic marrow unless anemia is evident, i.e., a venous hematocrit below 30 or thereabouts. Those who are not anemic may first show neurologic evidence of disease with posterior column changes manifested by abnormalities in gait and inability to maintain balance.

Patients in the third category whose basic defect is malabsorption will develop a folic acid or a vitamin B_{12} deficiency once their vitamin stores are depleted. Other nonradioisotopic tests are indicated to delineate various causes of malabsorption.

DIFFERENTIAL DIAGNOSIS OF MACROCYTIC ANEMIA

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- I. Normal $^{57}\text{CoB}_{12}$ absorption without hog IF:
 1. Folic acid deficiency:
 - a. Defective diet, e.g., in severe alcoholism.
 - b. Increased requirement
 - (1) Megaloblastic anemia of infancy or of pregnancy.
 - (2) Hematologic disease associated with hyperplastic bone marrow, e.g., leukemia or hemolytic anemia.
 - c. Impaired utilization (metabolic block)
 - (1) Chronic hepatic disease (enzyme deficiency).
 - (2) Antifolates, anticonvulsants, purine and pyrimidine antagonists.
 2. Vitamin B_{12} deficiency:
 - a. Dietary deficiency (inadequate intake of animal protein).
 - b. Increased requirement (chronic leukocytosis).
 - c. Inadequate utilization (chronic liver disease, deficiency of B_{12} -binding protein).
 - d. Inadequate retention (chronic liver disease).
 3. Vitamin C deficiency.
 4. Acute hemolytic anemias.
 5. Renal disease (collect urine at least 48 hr).
 - II. Normal absorption of $^{57}\text{CoB}_{12}$ with hog IF:
 1. Intrinsic factor (IF) deficiency (causes a secondary B_{12} deficiency):
 - a. Pernicious anemia (congenital and acquired).
 - b. Surgical resection of stomach.
 - c. Extensive carcinoma of stomach.
 - d. Severe gastric atrophy or gastritis.
 - III. Impaired absorption without and with hog IF:
 1. Folic acid and/or B_{12} deficiency eventually produced:
 - a. Malabsorption (note causes of untreated organic disease listed in IV, lymphoma).
 - b. Ileal bypass, fistulas of small bowel.
 - c. Sprue, nontropical or adult celiac disease (normal absorption after gluten-free diet).
 - d. Steatorrhea.
 - e. Regional ileitis.
 - f. Scleroderma.
 - g. Whipple's disease (lipodystrophy).
 - h. Extensive intestinal resection, particularly ileum.
 - i. Amyloidosis.
 - j. Prior ingestion of hog IF [Trinsicon (a product of Eli Lilly & Co.)]
 - IV. Normal absorption after appropriate treatment:
 1. Folic acid and/or B_{12} deficiency
 - a. Competition for the vitamin:
 - (1) Jejunal diverticula.
 - (2) Blind-loop syndrome.
 - (3) *Diphyllobothrium latum* (fish tapeworm) parasitic infestation.
 - b. Impaired absorption:
 - (1) Hypothyroidism and myxedema.
 - (2) Hyperthyroidism.
 - (3) Hog IF antibodies (normal with human gastric juice).
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Some disorders of folic acid or vitamin B₁₂ deficiency may have normal absorption after appropriate treatment of conditions in which there is competition for the vitamin or interference with its absorption. Examples are diverticula of the small intestine, infestation with the fish tapeworm, or a blind-loop syndrome. Hypo- and hyperthyroidism may interfere with vitamin B₁₂ absorption unless proper treatment is instituted.

NORMOCYTIC ANEMIAS

These anemias are characterized by no major change in the average size of the red cell and often no decrease in its hemoglobin content; they may result from: (1) suppression of marrow erythropoiesis, (2) an acute loss (hemorrhage) of red blood cells, (3) hemolysis, or (4) dilution of the blood.

TABLE 2
CALCULATION OF PLASMA IRON TURNOVER RATE

Factor	Normal value	Method of calculation
Serum iron, μg/100 ml	80 to 150	
Plasma volume, ml/kg	35 to 45	$\frac{\text{Counts/min/ml dose} \times \text{volume injected (ml)}}{\text{Counts/min/ml plasma } T_0 \times \text{body weight (kg)}}$
Plasma iron pool, mg	2.3 to 4.6	$\frac{\text{Serum iron (μg/ml)} \times \text{plasma volume (ml)}}{1000 (\mu\text{g/ml})}$
Plasma ⁵⁹ Fe clearance T _{1/2} , hr	1 to 2	
Fraction ⁵⁹ Fe cleared per hour (K)	0.34 to 0.68	$\frac{0.693 (\text{natural log of } 2)}{\text{Iron-59 clearance (hr)}}$
Plasma iron turnover rate, mg/day	25 to 40	K/hr x iron pool (mg) x 24 hr/day

Iron-59 is the radioisotope most useful for clinical studies to evaluate suppression of red-cell production in the marrow or nonproliferative erythropoiesis. The causes of impaired erythropoiesis may be inadequate stem-cell formation or defective stimulus to the marrow. By the radioactive iron method, a patient with failure of red-cell production will show a prolonged plasma ⁵⁹Fe clearance, poor utilization of iron by red cells, and a decreased red-blood-cell iron turnover rate (RBCITR). To obtain an accurate plasma iron turnover rate (PITR), the following data are required: serum iron, plasma volume, and plasma ⁵⁹Fe clearance (Table 2).

For an accurate RBCITR, three studies must be performed correctly: PITR, red-cell mass, and the utilization of iron for red-cell formation (Table 3).

TABLE 3
CALCULATION OF RED-BLOOD-CELL IRON TURNOVER RATE

Factor	Normal value	Method of calculation
Plasma iron turnover rate, mg/day	25 to 40	
Red-cell mass, ml/kg	25 to 35	$\frac{\text{Counts/min/ml dose} \times \text{volume injected (ml)}}{\text{Counts/min/ml RBC} \times \text{body weight (kg)}}$
Iron-59-RBC utilization, %	75 to 90	$\frac{\text{Counts/min/ml RBC} \times \text{RBC mass (ml)} \times 100}{\text{Total counts injected dose}}$
Red-cell iron turnover rate, mg/day	20 to 35	PITR $\times$ percent ^{59}Fe utilized (mg/day)

Nonproliferative erythropoiesis can be diagnosed from a marrow which has few or no red-cell precursors and a decreased erythroid/myeloid ratio. In the patient with a borderline abnormality, quantitation with ferrokinetics is necessary.

In acute hemorrhage, isotopic blood-volume tests are useful, although in clinical situations management is often based on serial hematocrits, vital sign evaluations, and clinical judgment.

Hemolysis, in the acute stage, will have increased numbers of young macrocytic red cells in the circulation if the marrow is compensating adequately. Hemolysis in the patient whose marrow is not compensating will lead to a normocytic anemia. Erythrokinetics is useful to distinguish a compensated from an uncompensated hemolytic anemia. In the former, the RBCITR is increased to a level that indicates the patient is in a steady state; erythrocyte production equals destruction. In the uncompensated state the destruction exceeds production, and the RBCITR does not equal the number of red cells being hemolyzed.

The ^{51}Cr -labeled red-cell method is the commonest study used in the clinical laboratory to quantitate hemolysis. If ^{51}Cr were the perfect erythrocyte-labeling agent, it would meet the following criteria: (1) tag the cells for the duration of their life-span or survival, (2) attach irreversibly to the cell and be easily and accurately measured, (3) label cells of all ages equally (random labeling) or cells of only a single age group (cohort labeling), (4) not be reutilized after cell death, and (5) not modify the cell morphologically or chemically. Unfortunately, an excess of chromate over $5\text{ }\mu\text{g}$ per milliliter of packed red cells will affect the enzyme, glutathione reductase, and may shorten the red-cell survival.⁵

Labeling of red cells with radioactive chromium enables us to determine the percentage of disappearance of ^{51}Cr red cells per day and to quantitate the

red-cell mass in the study of conditions involving blood dilution.⁶ The radionuclide labels cells of all ages. The half-time survival of ^{51}Cr -labeled red cells is 25 to 30 days. Normally the disappearance rate with this method is about 2% per day. Since ^{51}Cr elutes from the red blood cell normally at a rate of approximately 1% per day, the 2% disappearance minus the 1% elution rate would equal a percentage destruction rate of about 1% per day. The total red-blood-cell mass multiplied by this destruction rate yields the mass of red cells destroyed per day; in the adult the value is normally 20 to 25 ml/day. Hemolysis, of course, gives a higher value.

Sometimes we can use external monitoring studies to distinguish hemolysis due to extracellular defects from that due to intracellular defects. Measurements over the spleen show that the concentration of ^{51}Cr progressively increases in hemolysis due to the extrinsic defect of splenic sequestration [Fig. 1(a)]. All counts must be corrected for physical decay of the radionuclide, and any fluctuations in instrument sensitivity are corrected daily. If a severe, compensated hemolytic anemia is present, a ^{51}Cr survival study carried out simultaneously with a radioactive iron study will show a characteristic pattern over the organ of sequestration (spleen or liver) with a progressive rise in the ^{51}Cr and possibly the ^{59}Fe counting rate. In contrast, a normal patient would show a gradual decrease in counting rates over these organs.

The progressive accumulation of radiochromium in the spleen accompanying the enhanced disappearance of ^{51}Cr -labeled red cells in the blood indicates active red-blood-cell sequestration, as was first suggested by Jandl and coworkers⁷ in 1956. A rough numerical assessment, the index of sequestration, was suggested as a guide to the use of splenectomy. It is obtained by measuring the radioactivity over the spleen compared to the heart approximately $\frac{1}{2}$ hr after injection of the labeled red cells and subtracting this percent value from that percent figure obtained for the spleen over heart on the day that the half-time survival of the tagged erythrocytes is reached. The prediction of a beneficial result from splenectomy is most certain with severe sequestration, when the value is greater than 100. Other investigators, such as Schloesser et al.,⁸ compared the radioactivity over the spleen and liver following the infusion of ^{51}Cr -labeled erythrocytes. McCurdy and Rath⁹ in 1958 used a "splenic localization index" based on the maximum spleen/heart ratio after a period of equilibration. One of the better studies, which included careful follow-up of all patients, was that by Goldberg, Hutchison, and MacDonald,¹⁰ who studied 21 patients with hemolytic anemia before splenectomy. They believed a spleen/liver ratio of 2.3 or more on the day of the ^{51}Cr half-time survival in the blood was a reliable indication for splenectomy. A spleen/liver ratio that rises from the original day of the survival study to the day that the blood half-time is reached is probably a more favorable indication for splenectomy.

Thus the ^{51}Cr -labeled erythrocyte method is helpful in diagnosing the erythrocytic aspect of hypersplenism. This term, used rather loosely by some clini-

Fig. 1 Surface counting after intravenous injections of ^{51}Cr -labeled red cells and ^{59}Fe citrate in patients with and without certain hematologic disorders. (a) Splenic sequestration. (b) Iron-storage disease. (c) Splenic erythropoiesis. (d) Normal patient.

cians, should be used for patients who meet specific requirements as introduced by Jandl and Aster.¹¹ For the diagnosis they recommended the following requirements: (1) splenomegaly (a spleen scan may be necessary to demonstrate it); (2) blood cytopenia of erythrocytes, leukocytes, or platelets or either of the first two in combination with platelets; (3) if the erythrocytes are involved, random red-blood-cell destruction; and (4) marrow hyperplasia or at least normal cellularity (if the marrow is hypocellular, the diagnosis of hypersplenism is not justified). A final proof of the previous existence of hypersplenism is a beneficial response to splenectomy.

The ^{51}Cr -labeled red-cell method is also useful to distinguish an intracorporeal defect from an extracorporeal defect. If monitoring of the spleen and liver does not indicate sequestration, further analysis may be made by injecting some ^{51}Cr -labeled red cells from the patient into a normal recipient of compatible blood type. In such an instance a normal red-cell survival curve

would show that the anemic patient (donor) has an extracorporeal factor outside the liver or spleen which is responsible for his shortened survival.

In patients with hemorrhage, an assessment of the amount of blood lost per day during the time of the ^{51}Cr -labeled red-cell survival study should be determined. It is our custom to always collect stool samples for radioassay of ^{51}Cr activity during the period of the study. In patients who are simultaneously hemorrhaging and hemolyzing, subtraction of the average amount of red cells lost per day from the apparent amount destroyed per day in the blood permits the calculation of the true mean value of cells hemolyzed daily.

Hemorrhage and hemolysis are not the only possible causes for an apparently shortened red-cell survival. Dilution of the in vitro tagged red cells by blood transfusions or by increased erythrocyte production during this study could yield a steeper curve. Occasionally, a prolonged ^{51}Cr red-cell survival is seen during progression of the anemia in a patient with marrow failure who is not able to produce as many red blood cells as are leaving his circulation daily. This does not mean that his cells have a longer than normal survival but rather indicates the absence of the dilution of labeled cells with unlabeled, newly formed erythrocytes. Such a result may be found in the patient with aplastic anemia who has little or no hemolysis but badly impaired erythrocyte production.

MICROCYTIC ANEMIA

By far the commonest cause of microcytic anemia is iron deficiency, which is usually caused by chronic blood loss. We can detect and measure loss by assaying for radioactivity any sample, such as urine or feces, after the red cells have been labeled with ^{51}Cr . The equation used to determine the quantity of blood lost daily is:

$$\text{Red cells lost (ml/day)} = \frac{[^{51}\text{Cr red cells in specimen (counts/min as shown in radioassay)}]}{[^{51}\text{Cr red cells in circulating blood (counts/min/ml)]}$$

Besides iron deficiency, other examples of disorders with microcytic anemia are: pyridoxine-responsive anemia, thalassemia, lead intoxication, and hemoglobinopathies.

Radioactive iron is also useful in the physiologic evaluation of these microcytic anemias. In disorders of red-cell production, the two major categories are the proliferative and nonproliferative.^{1,2} The proliferative disorders are characterized by an increased PITS, and the nonproliferative, by a decreased rate. The PITS quantitates the iron that is leaving the plasma primarily for hemoglobin synthesis.

Proliferative disorders may be subclassified further into effective and ineffective erythropoiesis. To distinguish between the two, we measure the percentage of ^{59}Fe red-cell utilization (Table 4). This measurement multiplied by the Pitr determines the RBCITR, the rate that the iron enters the red cell. An increased RBCITR signifies effective erythropoiesis, and a decreased value,

TABLE 4
SIGNIFICANT RBC KINETIC DATA

Proliferative disorders	Pitr	Iron-59 utilization, %
Effective erythropoiesis		
Polycythemia vera	↑	↑
Compensated hemolysis or loss	↑	↑
Ineffective erythropoiesis		
Megaloblastic anemia (DNA synthesis)	↑	↓
Nonmegaloblastic (macrocytic anemia)	↑	N-↓
Iron-storage disorders	↑	↓
Hypochromic anemias	N-↑	↓*
Nonproliferative disorders		
Inadequate marrow stimulus	↓	↓
Defect in stem-cell formation	↓	↓

*Increase in iron-deficiency anemia.

ineffective. Examples of diseases manifesting effective erythropoiesis are polycythemia vera and compensated hemolytic or hemorrhagic disorders. Ineffective erythropoiesis, manifested by an increased Pitr, a decreased utilization of ^{59}Fe , and a decreased RBCITR, is seen especially in megaloblastic anemia, some macrocytic anemias, and iron-storage disease. Hypochromic microcytic anemias have a normal to increased Pitr, but, if iron deficiency is the cause of the anemia, the percentage utilization of ^{59}Fe is increased. Patients with iron deficiency clear iron from the plasma rapidly, incorporate it at an accelerated rate into red cells, and utilize 90 to 100% of the dose injected.

POLYCYTHEMIAS

Polycythemia is an increase in the number of red blood cells in the circulating blood due to increased marrow production. The erythroid/myeloid ratio along with an assessment of total cellularity of a marrow smear permits an estimate of total erythropoiesis, but it has limitations because morphologic features do not always indicate the rate of cell maturation and the marrow sample may be nonrepresentative.¹² To quantitate total erythropoiesis or the

potential for producing increased numbers of erythrocytes, one must determine the Pitr.¹³

If a proliferative disorder of the marrow is present and the underlying abnormality is characterized by effective erythropoiesis, an elevated reticulocyte count would be expected. Calculation of the RBCITR requires an accurate red-blood-cell mass and measurement of the radioiron utilization by erythrocytes. The RBCITR permits a quantitative determination of erythropoiesis. The fecal urobilinogen provides an index of destruction of erythrocytes, not only those in the circulation but also those in various stages of development in the marrow.

Patients with active polycythemia vera will manifest an elevated red-blood-cell mass, plasma volume, and total blood volume. Patients with secondary polycythemia, whether due to a tumor, cardiac or respiratory insufficiency (hypoxemia), or an endocrine or renal lesion, usually have an increased red-blood-cell mass, but the plasma volume is ordinarily not increased. Relative polycythemia is characterized by a normal red-blood-cell mass with a decreased plasma volume.

When we establish true erythrocytosis (an absolute increase in the number of erythrocytes), the possibility that it is secondary, compensatory for hypoxia, must be excluded by the demonstration of a normal arterial oxygen saturation and by the absence of an abnormal hemoglobin with impaired oxygen release or diminished oxygen-carrying capacity. Other nonradioisotopic procedures that may be necessary to differentiate polycythemia vera from secondary polycythemia are: (1) the platelet and leukocyte counts; (2) the presence or absence of splenomegaly; (3) the serum unsaturated B₁₂ capacity; (4) results of urinalysis; and (5) pyelograms, skull and chest X rays. The radiocolloid total-body scan is helpful in distinguishing an active polycythemia vera from secondary polycythemia. The radionuclides here are useful but are limited in their diagnostic specificity.

It is important to stress that the red-blood-cell mass and the plasma volume must be measured independently since the indirect determinations of either the red-cell mass from a measure of the plasma volume and venous hematocrit or of the plasma volume from the red-cell mass and plasmacrit are frequently inaccurate (Figs. 2 and 3). The primary reason for this inaccuracy is that the venous hematocrit/body hematocrit ratio of 0.9 is not constant and varies considerably under pathologic or physiologic conditions. Radioisotopes such as the preferable R¹²⁵ISA (radioiodinated serum albumin) or in certain cases ⁵⁹Fe (ferrous citrate) for measuring the plasma volume and ⁵¹Cr (sodium chromate) for measuring the red-cell mass are necessary. The ideal requirements of any radiopharmaceutical for measuring the blood volume are: (1) uniform distribution, (2) nontoxicity, (3) entrance into no metabolic pool, (4) confinement to the pool measured, and (5) an excretory pathway limited to the urinary tract.

Fig. 2 Comparison of the red-cell mass with venous hematocrit. Indirect estimations are usually larger than the direct method since total-body hematocrit is lower than the venous hematocrit.

Fig. 3 Comparison of plasma volume with venous hematocrit. Unlike the studies of red-cell mass, indirect measurements are usually lower than those obtained by directly studying the plasma volume. In 3 of 12 patients, the results by the ⁵⁹Fe method were higher than those studied by radioiodinated human serum albumin labeled with ¹²⁵I.

IRON-STORAGE DISORDERS

The iron-storage disorders include the following disease states: (1) idiopathic hemochromatosis; (2) transfusion hemosiderosis; (3) hemolytic iron overload due to infections, thalassemia, or refractory anemia; (4) dietary iron overload; and (5) medicinal iron overload.

Since the iron stores of reticuloendothelial (RE) tissue are nearly always increased in the sideroblastic anemias, classification would also include these diseases.¹⁴ The sideroblastic anemias are characterized by an anemia, either hypochromic or dimorphic with marrow erythroid hyperplasia, often with varying degrees of megaloblastic changes and with the presence of abnormal ringed sideroblasts. Ferrokinetic and erythrocyte-survival studies reveal an increased plasma iron turnover with subnormal red-cell iron incorporation and normal to slightly reduced red-cell survival.

Ferrokinetic studies are useful in evaluating iron-storage disorders since we find good correlation between the amount of iron in the RE stores and the nonerythropoietic iron turnover rate (NER). The NER is defined as the difference between the PITR and the RBCITR; more than 15 mg/day is consistent with increased stored iron, whereas less than 5 mg/day correlates with iron deficiency.

The question that arises is whether or not all patients demonstrating ineffective erythropoiesis have increased iron stores. The answer is yes. External monitoring at the body surface would be necessary to localize a given organ concentrating increased radioactive iron [Fig. 1(b)]. For example, some patients with acute hemolytic anemia may have little iron stored in the marrow but a pronounced increase of iron in the RE cells of the liver and spleen. In such an instance the pattern of the external counts of radioactivity over the liver and spleen would be consistent with iron-storage disease, but no similar pattern would be obtained from the external counts over the marrow.

Idiopathic or endogenous hemochromatosis is a hereditary disorder with increased absorption of iron. Absorption may be studied after giving 2 μ Ci of ⁵⁹Fe as ferric chloride orally together with 5 mg of aqueous ferrous sulfate and 50 mg of ascorbic acid in 20 ml of distilled water. Stools are collected for 7 days, and whole-body counts may be obtained. Normally between 5 and 30% is absorbed, whereas in hemochromatosis absorption is increased. Patients with iron-deficiency anemia will also have increased absorption determined best by whole-body counting, the method of choice for all studies of absorption.

EXTRAMEDULLARY HEMOPOIESIS AND SEQUESTRATION

External monitoring also aids in the detection of erythropoiesis, particularly extramedullary erythropoiesis (Tables 5 and 6). If this condition exists, an early

TABLE 5
EXTERNAL (BODY SURFACE) MONITORING
IN MEDULLARY ERYTHROPOIESIS

Patient	Disorder	Day 1 index	Gardner's index†	
		*Organ/heart	Spleen	Sacrum
I	Aplastic anemia	0.76	0.70	1.63
II	Rheumatoid disease, iron deficiency	1.19	0.90	2.51
III	AGL, ‡ tuberculosis	0.76	0.71	1.63
IV	Secondary polycythemia	0.88	1.04	1.41
V	Polycythemia rubra vera	1.24	0.86	2.05
VI	Hodgkin's disease	1.16	0.91	1.62
	Index for erythropoiesis	>1.75	>2	>2

*Either spleen or liver, whichever had the highest counting rate.

†Ratio of counts on day 1 to counts on day 5 over same organ.

‡Acute granulocytic leukemia.

TABLE 6
EXTERNAL (BODY SURFACE) MONITORING IN
EXTRAMEDULLARY ERYTHROPOIESIS

Patient	Disorder	Day 1 Index	Gardner's index*	
		Organ/heart	Spleen	Sacrum
A	Primary myelofibrosis	1.88	0.98	1.00
B	Primary myelofibrosis	2.09	1.07	1.22
C	Primary myelofibrosis	2.50	2.19	0.85
D	PRV, † secondary myelofibrosis	2.63	1.72	0.92
E	PRV, secondary myelofibrosis	2.34	1.38	2.09
F	AGL, ‡ secondary myelofibrosis	2.82	0.83 §	0.63
	Index for erythropoiesis	>1.75	>2	>2

*Ratio of counts on day 1 to counts on day 5 over same organ.

†Polycythemia rubra vera.

‡Acute granulocytic leukemia.

§ Liver ratio; patient's spleen absent due to splenectomy.

rise in the ^{59}Fe external count should occur over the site of erythropoiesis on the first day following intravenous injection [Fig. 1(c)], followed by a progressive decrease. In our experience a spleen/heart ratio or a liver/heart ratio greater than 1.75 on day 1 was consistent with the histologic diagnosis of extramedullary erythropoiesis. Gardner and Nathan¹⁵ used the index of the external count on day 1 over the ^{59}Fe external count on day 5 for the same organ. In their study of eight patients, they found an index greater than two to be consistent with extramedullary erythropoiesis.

Day 1 is chosen as our interval for assessing the index because it is then that ^{59}Fe activity will reach its peak as iron is incorporated into hemoglobin within the erythron. Unless iron storage is also present, the counting rate gradually decreases after day 1 since the ^{59}Fe now within the maturing erythrocytes is released into the circulation. In our experience with six cases of extramedullary erythropoiesis studied during the past 2 years, all had liver/heart or spleen/heart ratios on day 1 greater than 1.75. Except for two patients who had increased iron stored in the liver and spleen, the ratio decreased after day 1. We compared our index with Gardner and Nathan's "effective erythropoietic index" and found theirs too demanding and failing to make the diagnosis in three of our six patients. One advantage of our index is that detection of erythropoiesis can be made on day 1 rather than on day 5. The index is useful in detecting early the transition of one phase of a myeloproliferative disorder to another. It also substitutes for splenic aspirations or liver biopsies that have their hazards and limitations, particularly in patients who are thrombocytopenic or have myelofibrosis.

As mentioned earlier in the discussion under normocytic anemia, the prediction of a beneficial result from splenectomy is simple in patients who have pronounced sequestration and who manifest the other characteristics of hypersplenism. The borderline cases give us trouble and those who are suspected of having extramedullary erythropoiesis as well as splenic sequestration. A double radioisotopic study with ^{51}Cr -labeled red cells and an intravenous injection of ^{59}Fe may be needed. Corrections for the ^{59}Fe contribution to the ^{51}Cr counts are required if the clinician is to make an accurate interpretation.

LEUKOCYTE DISORDERS

The ability to use radioisotopic procedures for the study of leukocyte kinetics still remains, for the most part, a research tool. The failure to extend available techniques to "routine" laboratory use is due to problems of methodology rather than application. Perhaps the most significant single limiting factor is the lack of a radioisotope that will specifically label leukocytes; radionuclides currently used for labeling them also tag other blood elements. Thus tedious but feasible separation of the various blood components becomes necessary. The time, cost, and complexity of the procedure are factors that

influence its practicality. Nevertheless, with these methods some insight into the physiology of normal leukocytes has been achieved. This information could not have been obtained with any other present method.

Some of the radionuclides used are ^3H , ^{14}C , ^{35}S , ^{32}P , and ^{51}Cr (Refs. 16 and 17). Depending on the energy of emissions from the radioisotope, different studies can be performed. The weak beta-emitting isotopes that localize specific cells can be used for autoradiography. With tritiated thymidine or tritiated diisopropyl fluorophosphate (DFP), ^{14}C -labeled thymidine, and ^{35}S sodium sulfate, autoradiography of marrow can show uptake in specific cells. The more energetic radioisotopes suitable for scintillation counting provide a more sensitive method for quantitating radioisotope incorporation in a population of cells, but gamma-emitting isotopes are required for external monitoring of leukocyte distribution. Information obtained from one or all of these techniques can be combined to give some insight into the production, maturation, and death of leukocytes, of which only the granulocytic series is well-known. Depending on the chemical compound, there are differences in the site of attachment in the cell as well as in the type of cell labeled.

Compounds can be divided into cohort or random labels. Those which label a group of cells of uniform age, e.g., by being incorporated into nucleoprotein, are called cohort labels, whereas those which attach to cells of all ages are random labels. The thymidine compounds are cohort labels that are incorporated by the DNA-synthesizing myeloid precursors and by very few lymphocytes. Diisopropyl fluorophosphate binds randomly but irreversibly to cells that vary in their avidity for the compound. Because its binding depends on the presence of cholinesterase, this chemical does not attach to myeloblasts or lymphocytes. In bone-marrow studies, the DNA-synthesizing myeloid cells can be followed by determining the number of grains per cell, which parallels the amount of radioactivity per cell.¹⁸ The time required for cell division and maturation can be calculated from reduced average grain count in a particular cell line when measured over a specified interval. Thus can we learn the normal and abnormal generation and maturation times, important knowledge in understanding what happens to cell development in leukemia. With the increasing armamentarium of drugs for treatment of such diseases, knowledge of this type can enhance the selection of patterns of therapy. The finding that leukocytes in acute leukemia are not a rapidly proliferating pool of cells has direct bearing on the timing of administration of various mitotic inhibitors.

Radioisotopic studies mainly using DFP labeled with ^{32}P have revealed much about the survival of granulocytes in the vascular system.¹⁹ Granulocytes labeled in vitro and retransfused to the donor are lost at a surprisingly fast rate. On the average, half the labeled cells are lost in 7 hr. This fast utilization of granulocytes means that the total blood granulocyte pool must turn over about 2.5 times per day. It is no wonder that the normal myeloid/erythroid ratio in the bone marrow is fairly high. The granulocytes are removed from the blood

randomly as evidenced by the exponential loss of labeled cells. This means that granulocytes just released from the marrow may be moved into other tissues as quickly as those which have already spent some time in the circulation.

The ^{32}P -DFP studies have revealed that not all the intravascular granulocytes are measured by the usual white-blood-cell (WBC) count. By means of the isotope-dilution technique, at least 50% of the total blood granulocyte pool was found to be in a compartment referred to as the marginal granulocyte pool (MGP), where they move more slowly than those in the axial stream.¹⁹ Between these two compartments there is continual, free interchange of cells with a tendency for equilibrium to be maintained, normally consisting of about half the granulocytes in each pool. These marginated granulocytes can be easily shifted to the axial stream raising the WBC count quite rapidly. Epinephrine or exercise may cause such a shift; this explains why the WBC count may change dramatically after these procedures.

Indeed, persons apparently in good health may have a higher or lower than normal WBC count [Fig. 4(a)]. If the granulocyte pool sizes are measured, the total blood granulocyte pool may be normal with a greater shift to the marginal pool producing pseudoleukopenia [Fig. 4(b)] or with a greater shift to the circulating pool producing pseudoleukocytosis²⁰ [Fig. 4(c)]. This points out that the marginal-to-circulating pool need not be a 1:1 ratio. By the ^{32}P -DFP method, the reason for the elevated WBC count seen in patients who receive corticosteroids presumably has been found. It appears that the steroids slow down the rate of the egress of white blood cells from the vascular tree into tissue sites.²¹

Kinetic studies of lymphocytes have shown that the majority of the lymphocyte population does not incorporate tritiated thymidine. We can label DNA with ^{32}P , but isolation of DNA is a tedious procedure, and reutilization of the isotope is a problem.²² However, it is possible to label RNA using one of the radioactive-labeled amino acid precursors, such as leucine, guanine, or adenine. Gowans²³ has placed several pieces of valuable information into the puzzle of lymphocyte life-span in the circulation. Two groups of lymphocytes, one with a mean age of 3 to 4 days and the other with a mean age of 100 to 200 days, have been found. Evidence is mounting that the small lymphocyte, once thought to be a dormant, do-nothing cell, is, in reality, a vital do-everything cell—the pluripotential stem cell everyone has been searching for.

Lymphocytes tagged with ^{51}Cr (sodium chromate) can be monitored externally, but elution complicates interpretation and also influences the cell-survival curves.²⁴ Whole-body counts in our hands after the reinfusion of ^{51}Cr -tagged lymphocytes indicate that 10 to 90% of the radioactivity has left the body 48 hr later.²⁵

Progress has been slow, but significant information about leukocyte physiology has been accumulated, and many of the studies would not have been possible without radioisotopes.

Fig. 4 Representation of normal blood granulocyte pool (a); decreased circulating granulocyte pool, pseudoleukopenia (b); and increased circulating granulocyte pool, pseudoleukocytosis (c).

PLATELETS

It has been difficult to find a specific label for platelets, and their extreme fragility produces other complications. Early recognition of the need of a nonwetting surface in handling them helped to eliminate one of the problems. The awareness of the effects of temperature changes and anticoagulants on platelet survival came later.^{26,27}

Studies originally performed with cooling the blood and with sodium ethylenediaminetetraacetic acid (EDTA) as the anticoagulant gave different results when repeated without cooling and with acid-citrate-dextrose (ACD) solution. Electron microscopy established that temperatures below 10°C produce irreversible changes in the platelet morphology which, in turn, reduce platelet survival.²⁸ Damage to the platelets by EDTA was also demonstrated, and ACD acidified to a pH of 6.5 proved to be the anticoagulant of choice.²⁶

With the present radioisotopic methods, the average life-span of platelets in man is normally 10 days.²⁹ Similar values have been used. Some of the more commonly used radioisotopes are: ^{51}Cr (sodium chromate) (Ref. 30), ^{32}P (sodium phosphate) (Ref. 31), ^{32}P (diisopropylfluorophosphate) (Ref. 32), and ^{35}S (sodium sulfate) (Ref. 33). The advantage of a gamma-emitting radionuclide, such as ^{51}Cr , is the ability it provides to perform external monitoring of various organs. With detection of abnormal localization of the radionuclide in a particular organ, we could infer that excessive sequestration of platelets occurred in that site. Such evidence would help to determine whether surgical removal of the spleen might be beneficial. A shortened life-span of platelets shown by any of the preceding radioisotopes may indicate that increased utilization rather than decreased production is responsible for a low platelet count, but such information does not give a specific diagnosis.

Autoradiographic studies of megakaryocytes with a cohort label like ^{35}S (sodium sulfate) have enabled investigators to follow the maturation process in the marrow and calculate the generation time of the recognized states of development.³⁴ Such studies may eventually suggest ways to protect the megakaryocytes when cancer chemotherapeutic agents are used.

Separation of platelets from whole blood for transfusion to patients with thrombocytopenia has become an accepted and necessary procedure. Donor-recipient matches are based on the established ABO grouping of red blood cells. However, histocompatibility studies have confirmed that platelet antigens resemble white-blood-cell antigens more closely than red-blood-cell antigens.^{35,36} The need for finding an easy and quick-matching test for platelets is obvious. The cytotoxic effects of serum from recipients on in vitro tagged platelets from the donor may provide an answer for platelet compatibility.

In addition, long-term platelet preservation for transfusion will be a necessity in the future. Evaluation of preservation procedures may be facilitated by the use of radioisotopes.

SUMMARY

Radionuclide studies are useful diagnostic aids that help the clinical hematologist in the management of the complex problem. Their greatest shortcoming is their lack of specificity in making a precise diagnosis. Needed are better cell-labeling agents which would simplify methodology by not tagging other blood elements. The future for radionuclides in hematology looks bright, especially in the field of stem-cell production and kinetics.

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RADIONUCLIDES IN HEMATOLOGIC DIAGNOSIS: THEIR VALUE TO CLINICIANS

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ABSTRACT

Procedures employing radionuclides are useful in the diagnosis and management of hematologic disease, providing a valuable adjunct to the history, physical examination, and routine laboratory determinations. Most procedures requiring radionuclides are performed by introducing radioactive substances in vivo and then making observations to determine accumulation of radioactivity over surface projections of anatomical sites. Other in vivo observations may be directed to rate of disappearance of labeled material from the blood or appearance in circulating blood cells or urine. Other procedures utilizing nuclides are strictly in vitro wherein a labeled substance may be used as a chemical reagent that may be identified in laboratory reactions under cell-free or tissue-culture conditions.

Organ imaging procedures using radionuclides include identification of lymph nodes involved with Hodgkin's disease by radiogallium imaging. Disorders characterized by pathologic lesions or by changes in size of the spleen may be identified by scanning with ^{99m}Tc -sulfur colloid or heat-damaged erythrocytes labeled with ^{51}Cr . Radionuclides may be used as an adjunct in the differential diagnosis of anemia; tests to demonstrate absorption of orally administered radiocobalt-labeled vitamin B_{12} may distinguish between pernicious anemia, malabsorption syndrome, and the blind-loop syndrome. This test is effective, even though the patient's blood picture is influenced by transfusion or treatment. Procedures to demonstrate the rate of hemolysis as well as the accumulation of ^{51}Cr -labeled erythrocytes in the spleen are not only definitive for diagnostic purposes but also may be useful in the decision to do splenectomy.

Kinetic studies involving the disappearance rate of ^{59}Fe from plasma, followed by its appearance over surface projections of marrow, liver, and spleen and into circulating erythrocytes, are useful to distinguish between iron deficiency, bone-marrow insufficiency, hemolytic states, and other obscure forms of anemia. Blood-volume studies using ^{51}Cr -RBC and ^{125}I -human serum albumin are indispensable in the differential diagnosis of erythrocytosis.

The clinician who sees patients with blood diseases and encounters problems of diagnosis and management generally needs help from the laboratory. Satis-

factory solutions most frequently derive from procedures as commonplace as a thorough history, physical examination, and a simple, complete blood count. Occasionally, however, complex clinical situations require more sophisticated methods. In addition, procedures that vary in complexity are frequently used in the investigative approach to disease to explain and predict biologic events. The radionuclides provide one important type of assistance to the clinician and investigator. Most of the hematologically applicable procedures employing radionuclides require the *in vivo* administration of a labeled substance. Measurements are then made over anatomical locations where the labeled material may accumulate, or determinations are made of the disappearance rate of labeled materials from the blood, or their appearance in the circulating blood, or in urine. Some applications are strictly *in vitro* with an isotopically labeled substance used as an identifiable chemical reagent or as a substance that might be incorporated by biologically active cells or tissues under *in vitro* culture conditions.

LYMPHOMAS

Lymphangiography: Hodgkin's Disease

Attitudes toward the management of Hodgkin's disease have recently undergone radical alteration. Under certain circumstances it may be possible to cure Hodgkin's disease if it has not exceeded the bounds of a specific clinical stage. In preparation for a curative approach, the clinical stage must be known. Four clinical stages have been defined that correlate with the histologic classification and prognosis. In stages one and two, the disease is confined to one or more lymph-node areas located on the same side of the diaphragm. Such involvement is almost always located in the superior part of the body. In stage three the disease is limited to the lymphatic apparatus but occurs on both sides of the diaphragm. Because of this, prognosis for survival or cure is less than that for stages one and two. In stage four the disease escapes the limits of the lymphatic system to involve more than one parenchymal organ such as the spleen, liver, lung, kidney, and marrow. The stage is further subgraded A or B depending on the presence or absence of systemic symptoms such as chills, fever, night sweats, and weight loss. The physician must know the stage of disease for prognosis and to choose the most effective treatment. A number of procedures are available to determine the stage. Dr. Kniseley has referred to radiocolloid total-body scans to determine involvement of marrow, liver, or spleen. Dr. Viamonte has discussed percutaneous lymphangiography with radiopaque dyes (i.e., Lipiodol) which may visualize the extent of involvement of the lymph nodes on both sides of the diaphragm. Because of limitations in lymphangiography, some physicians consider a laparotomy necessary to identify more accurately the presence of Hodgkin's disease below the diaphragm. The

increasing use of laparotomy does not preclude lymphangiography because these procedures complement each other. In some instances the spleen may not be clinically enlarged and yet at laparotomy it may be demonstrably grossly involved. In all patients in whom laparotomy is planned, surgeons depend a great deal on lymphangiography to locate involved nodes. Collaboration with the radiologist in the operating room is extremely desirable for the selection of the nodes most likely to yield positive results.

Radiogallium Imaging

Earlier reports of Edwards and Hayes¹ demonstrated the effectiveness with which ^{67}Ga localizes in tissues affected with Hodgkin's disease. Their studies have led others to use the radiogallium imaging technique to locate lesions for staging.

Clinical staging is helpful because one may direct more intelligently a complete therapeutic attack on the entire area of involvement. Our experience regarding the comparative value of radiogallium imaging, lymphangiography, and laparotomy in establishing intra-abdominal Hodgkin's disease is limited, but, in a small recent series, seven patients presented with Hodgkin's disease for clinical staging. All seven had positive gallium scans. For two of the seven patients the staging was upgraded from two to three by the radiogallium imaging. Surgery indicated abdominal involvement in five instances and no abdominal involvement in two. Thus four patients were upgraded from stage two A to three A or four A after surgery; one was downgraded from three A to two A, and two remained the same.

Radionuclide Spleen Imaging

Disorders manifested by changes in size or pathologic lesions limited to spleen are frequently difficult to identify clinically. This is especially true of those instances in which the spleen is enlarged but blood and bone marrow show no morphologic changes leading to a diagnosis. In addition, in some patients with a mass in the left upper quadrant, it is necessary to distinguish between the spleen and some other organ.

Clinical data may be helpful in determining the etiologic factors involved in splenomegaly; a careful history and physical examination are obviously an important starting point. To this must be added the complete blood count, including red-cell indices, reticulocyte count, and platelet count. Following this the standard diagnostic bone-marrow examination by smear or biopsy may be valuable. To help distinguish between the spleen and kidney or other abdominal mass, an intravenous pyelogram is frequently used. If clinical hematologic or radiographic data fail to identify the cause of splenomegaly, then special procedures must be used. Splenic puncture for smear and biopsy is rarely used as a diagnostic aid; the information derived is limited to those instances in which

one finds definite morphologic alterations such as might be seen with lymphomas or with myeloid metaplasia. Moreover, splenic puncture and splenoportography are associated with some danger, especially in patients who have a bleeding tendency. These procedures should not be undertaken unless one is prepared to accept the risk of emergency splenectomy in the event of hemorrhage.

For these purposes, then, splenography by radionuclide imaging may be helpful. This may be accomplished by one of two methods. The patient's erythrocytes are labeled with $\text{Na}_2^{51}\text{CrO}_4$, subjected to heat-induced trauma, and injected intravenously, after which the spleen may be localized by point counting or by imaging. The second method involves radionuclide imaging following the intravenous injection of radiocolloid, the most common being ^{99m}Tc -sulfur colloid, which localizes in organs containing reticuloendothelial cells, the liver, spleen, bone marrow, and lymph nodes. The 140-keV gamma emission of ^{99m}Tc is suitable for external studies of the organs in which it localizes. In this way one can determine the anatomical location of spleen and liver, whether they are enlarged, whether filling defects are present, and whether accessory spleens are present. The following are clinical situations in which radionuclide spleen imaging was found to be useful clinically.

SPLENIC ABNORMALITIES AND DIFFERENTIAL DIAGNOSIS

Splenic Abscess

A 19-year-old man had an obscure fever and a tender mass in the left upper quadrant. A spleen scan with ^{99m}Tc -sulfur colloid was found to show defects in the center of an enlarged spleen. The presence of the fever, tenderness, and pain in the splenic area brought up the question of an infection. A laparotomy was performed and a splenic abscess was incised and drained with ultimate recovery. Though radiographic techniques can readily diagnose splenomegaly, the splenic substance can most easily be evaluated by the radionuclide imaging technique.

Spleen Location

A 15-year-old boy entered the hospital with epigastric distress and indigestion. An X-ray study of the abdomen disclosed a gas bubble on the right side interpreted as air in the stomach. A scan of the liver and spleen was made with ^{99m}Tc -sulfur colloid [Fig. 1(a)]. The image suggested that the liver was on the left and the spleen on the right. A fissure apparently separated the spleen from the liver, and the diagnosis suggested was situs inversus. The scan, however, was repeated with ^{51}Cr -labeled heat-treated red blood cells (RBC) [Fig. 1(b)];

Fig. 1 Liver and spleen scans of patient with pseudo-situs inversus.

(a) Liver and spleen scan using ^{99m}Tc -sulfur colloid. Apparent fissure separating liver and spleen.

(b) Spleen scan using ^{51}Cr -labeled heat-treated RBC. Apparent large lobe of liver proves to be elongated spleen. x, tip of xyphoid process. ©, umbilicus.

the activity was localized exclusively on the left side, and what had been thought to be the left lateral margin of the liver proved to be a large, elongated spleen. The patient proved to have an eventration of the right diaphragm with malposition of the liver and an esophageal hiatus hernia accounting for his symptoms.

Accessory Spleen

Figure 2 represents a patient who had had a splenectomy for traumatic splenic rupture. On a ^{99m}Tc -sulfur colloid liver scan, a small focus of activity in the lateral portion of the liver suggested an accessory spleen [Fig. 2(a)]. A scan was then done with heat-treated ^{51}Cr -labeled (RBC); the focus proved to be splenic and was interpreted as an accessory spleen [Fig. 2(b)]. This procedure has been applied with benefit to a patient with persistent thrombocytopenia following splenectomy for idiopathic thrombocytopenia purpura, and successful localization was followed by removal of accessory splenic tissue, resulting in clinical improvement.²

Pancreatic Pseudocyst

Figure 3 is a spleen scan from a 45-year-old woman. After injuring her abdomen in a fall, she was found to have a large mass in the left upper quadrant. The diagnostic investigation failed to demonstrate the nature of this mass. A ^{99m}Tc -sulfur colloid scan revealed the spleen to be crescent shaped and displaced inferiorly into the pelvis either by a massive subcapsular hematoma or by an extrinsic mass. A clinical interpretation was made of subcapsular hematoma of the spleen, and the patient was taken to surgery where a large pancreatic pseudocyst displacing a normal-size spleen inferiorly was discovered and treated. The pancreatic pseudocyst apparently developed as a result of recurrent pancreatitis in a chronic alcoholic. During an episode of drinking beer, she sustained the abdominal injury which called her physician's attention to the abdominal mass.

RED-CELL DISORDERS

Radionuclides in the Differential Diagnosis of Anemia

The differential diagnosis of anemia is usually determined by the history and physical examination, complete blood count, RBC indices, and, frequently, bone-marrow examination, serum iron, and iron binding capacity. At the end of a complete clinical examination, the identification of the etiological factor is frequently confirmed, but there are, of course, occasions when the diagnosis cannot be readily established, and, under these conditions, radionuclides offer a useful adjunct. In addition, the nuclear medicine laboratory is indispensable to

Fig. 2 Use of organ imaging to demonstrate accessory spleens.
 (a) Technetium-99m-sulfur colloid.
 (b) heat-treated ^{51}Cr -labeled RBC.

Fig. 3 Technetium-99m-sulfur colloid spleen scan showing displacement of spleen by pancreatic pseudocyst.

the clinical investigator who must clarify mechanisms of hematologic disease. Information derived from radionuclide procedures includes distribution, localization, and excretion of substrates, rate of production and rate of destruction of erythrocytes, and abnormal anatomical accumulations of labeled erythrocytes.

Vitamin B₁₂ Absorption

The physiologic principles of absorption, distribution, and excretion of vitamin B₁₂ have been used in the radionuclide Schilling test in the diagnosis of megaloblastic anemia.³ Vitamin B₁₂ enters the stomach by food ingestion and forms a complex with intrinsic factor. This intrinsic factor-B₁₂ complex is absorbed into the circulating blood from the ileum and carried by the circulating blood to the liver where it is stored. To demonstrate absorption of orally administered ⁵⁷Co-B₁₂, we most frequently use Schilling's procedure. This method is advantageous because radioactivity is demonstrated in the patient's urine. To do so we must saturate the patient's tissues with nonradioactive B₁₂ by giving an injection of 1000 µg of the vitamin at the time the dose of radioactive B₁₂ is given orally. The excessive (nonradioactive) B₁₂ which

saturates the tissues is immediately excreted in the urine and carries with it a portion of whatever radioactive B_{12} was absorbed through the gastrointestinal (GI) tract. Another procedure, not frequently used, consists in counting the radioactivity excreted in the stool; this represents B_{12} that is not absorbed.

Clinical Application

Patients with pernicious anemia have no intrinsic factor and for this reason cannot absorb vitamin B_{12} . In the Schilling test no radioactivity appears in the urine. Under such conditions we can further define the defect by repeating the $^{57}\text{Co}-B_{12}$ urinary excretion test after having simultaneously administered intrinsic-factor concentrate.³ If the patient does not have antibodies against intrinsic factor, the defect is corrected and radioactive B_{12} is now absorbed, some of which is excreted in the urine along with the saturating dose of B_{12} . In the presence of an intrinsic disorder of the intestines such as the malabsorption syndrome, the defect is not corrected by administration of intrinsic factor and the radioactive label does not appear in the urine. For the blind-loop syndrome, a loop of intestine is populated by bacteria which compete successfully with the host for the vitamin B_{12} in the diet, and correction of the apparent B_{12} absorptive defect occurs only after the administration of an oral antibiotic such as tetracycline.

The chief value for the Schilling $^{57}\text{Co}-B_{12}$ urinary excretion test is to identify and distinguish between pernicious anemia, malabsorption syndrome, and blind-loop syndrome. It may also help distinguish between B_{12} and folate deficiency. It is one of the few laboratory tests available that define a disease. Even if the peripheral blood and bone-marrow changes of pernicious anemia are corrected by parenteral treatment with vitamin B_{12} or with transfusions, the defect that characterizes this disease remains, and one can establish an accurate diagnosis even during phases of clinical remission. Thus, in a treated patient in whom an adequate diagnosis was never established, the Schilling test can clarify requirements for future therapy regardless of the hematologic state of the patient.

Hemolytic Anemias

The red-cell survival pattern in normal persons is linear, that is, red cells disappear from the peripheral blood in direct relation to their age. On the other hand, in hemolysis the red cells disappear exponentially in a random pattern with no relation to their age. Despite a built-in artifact that is present with respect to the ^{51}Cr label, this radionuclide is most commonly used to measure red-cell survival. About 1% of the ^{51}Cr label is eluted daily to result in a red-cell half-time of 25 to 35 days instead of 60 days as measured by other technics. The purist might feel compelled to correct this figure mathematically by applying a "fudge factor." However, we usually recognize that anything below this limit of 20 to 25 days is abnormal and represents hemolysis. Using the $^{51}\text{Cr}-\text{RBC}$

survival time, we may identify a form of hemolytic anemia characterized by intrinsically abnormal red cells and another associated with normal red cells destroyed by an extrinsic mechanism peculiar to the environment within the patient.⁴

Hereditary Spherocytosis

Distinction Between Various Forms of Hemolytic Anemia. The family history is the strongest means of identifying hereditary hemolytic anemia, such as hereditary spherocytosis. In this disorder the erythrocytes are intrinsically abnormal, that is, they have a shortened survival time in the patient's circulation, and, if they are given to a normal person who has a spleen, they also have a shortened survival time (Fig. 4a). On the other hand, if normal erythrocytes are given to a patient with hereditary spherocytosis, they survive normally. The role of the spleen in hereditary spherocytosis may be readily defined. To begin with, during the performance of the red-cell survival time with ^{51}Cr -RBC, external monitoring over the splenic area reveals accumulation of radioactivity which soon becomes two or three times greater than that over the precordial area (Fig. 4b). Second, if ^{51}Cr -RBC are given to a person who has had a splenectomy, then a normal survival curve is restored.

In other hereditary hemolytic diseases such as sickle-cell anemia (Fig. 5a), an exponential pattern of red-cell survival may be observed when a patient's labeled erythrocytes are given to normals, and a linear survival pattern is seen if normal erythrocytes are introduced into the patient's circulation. However, the pattern of organ distribution of radioactivity is different in sickle-cell anemia. In this disease the patient usually performs an autosplenectomy through repeated splenic infarctions. One can recognize this because of the appearance of Howell-Jolly bodies and target cells in the blood smear. It is no surprise that under these conditions splenic sequestration of ^{51}Cr -RBC does not occur. Indeed, radioactivity over this organ site is frequently below normal. Instead the liver seems to take over the main role in the destruction of red cells so that a major accumulation of radioactivity occurs at this organ site (Fig. 5b).

Acquired Hemolytic Anemia

The acquired hemolytic anemias are characterized by random destruction of basically normal erythrocytes by a deleterious factor outside the red cell. This may be chemical (e.g., arsine), bacterial (e.g., *Clostridium welchii*), parasitic (e.g., malaria), or autoantibody, as identified by the Coombs' antiglobulin test. The patient's own erythrocytes have a diminished survival time in his own circulation, as do normal erythrocytes introduced into the patient's circulation. If it were possible to introduce labeled erythrocytes from the patient into a normal circulation, we would probably observe a normal survival time. Thus the fundamental defect in acquired hemolytic anemia appears to be present in the environment to which red cells are exposed.

Fig. 4a Erythrocyte survival in patient with hereditary spherocytosis. Chromium-51-labeled RBC were used.

Fig. 4b Accumulation of radioactivity over spleen area in patient with hereditary spherocytosis.

Fig. 5a Erythrocyte survival in patient with sickle-cell anemia. Chromium-51-labeled RBC were used.

Fig. 5b Accumulation of radioactivity over hepatic area in sickle-cell anemia.

Mixed Hemolytic Anemia

Forms of hemolytic anemia have been recognized in which a hereditary defect is present in the patient's erythrocytes; this is not clinically evident until he is exposed to a noxious drug or chemical. Such a situation obtains in glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.⁵ This is a sex-linked disorder present in 10% of the random, black male population, which is generally unaccompanied by hematologic abnormality until the patient is treated with an oxidant drug. When he is stressed in this way, a profound hemolytic reaction takes place. Thus we have a combination of an hereditary defect with

Fig. 6 Erythrocyte survival in patient with carcinoma of ovary treated with irradiation. Transient hemolysis of autologous and isologous erythrocytes.

acquired hemolytic anemia. Another form of acquired intracorpuseular hemolytic anemia was reported recently by Burkert et al.⁶ An elderly woman had had a carcinoma of the ovary removed surgically; this was followed by therapeutic irradiation. The woman then developed an intense hemolytic anemia characterized by reticulocytosis, indirect hyperbilirubinemia, elevated fecal and urinary urobilinogen, hemosiderinuria, and hemoglobinemia. The Coombs' test was negative. The *in vitro* autohemolysis test was positive and corrected partially by glucose but not by adenosine triphosphate (ATP). When normal human erythrocytes were exposed to this patient's plasma and incubated *in vitro* in similar fashion, increased hemolysis was induced in them. The patient's own red cells labeled with ⁵¹Cr disappeared *in vivo* in a random fashion as expected. When given *in vivo* normal isologous red cells exposed *in vitro* to the patient's serum also disappeared randomly in both the patient's and the donor's circulation (Fig. 6). It was a matter of great interest that the patient's serum was found to have a substance that hemolyzed *in vitro* not only her own red

cells but also normal red cells. Accordingly, a remarkable correlation was demonstrated between in vitro autohemolysis and in vivo red-cell survival. After a period of observation, the patient's blood count reverted to normal, the autohemolysis disappeared, and the red-cell survival approached a normal pattern. The hemolytic factor could no longer be demonstrated.

Red-Cell Production Patterns

When radioactive iron is given,⁴ it disappears from the plasma at a specific rate so that normally half of it is gone in about 90 min. A day later the iron begins to appear in the circulating erythrocytes so that a peak of 80 to 90% of the dose is incorporated into circulating red cells in about 8 days. During the first 2 or 3 days after administration of ^{59}Fe , most of the iron is in the bone marrow; this can be demonstrated by external counting over a sacral area.

Under pathologic circumstances the plasma disappearance rate of iron might increase so that the half-life is greater than 120 min. This is seen whenever bone-marrow activity is curtailed as in hypoplastic anemia or anemia of renal disease. Contrariwise, iron might be cleared from the plasma very rapidly in the anemia of infection, hemolytic anemia, polycythemia vera, or iron deficiency (half-time of 60 min or less). An increased rate of incorporation into peripheral erythrocytes is seen in iron deficiency and in hemolytic anemia. Because of the increased destruction rate of red cells, a peak of radioactivity is never reached in hemolytic anemia. In severe hypoplastic anemia iron is hardly incorporated at all.

Since ^{59}Fe is a gamma emitter, it may also be used to demonstrate localization of iron during periods of active hematopoiesis. The first 24 hr is critical in making these observations. In myelofibrosis one would expect no early evidence of radioactivity over the sacrum but profound radioactivity over splenic and liver areas where active erythropoiesis is taking place. In aplastic anemia there is diminished surface radioactivity over both splenic and marrow areas. In hemolytic anemia increased radioactivity is observed early over the sacral area, and, with passage of time, radioactivity over the spleen becomes increased as sequestration takes place. In iron deficiency the major early indication of radioactivity will be found over the sacrum. Splenic radioactivity does not become significant because myeloid metaplasia and splenic sequestration are absent.

The ferrokinetic study is too formidable and expensive to be used routinely in the management of iron-deficiency anemia. However, there are times when the clinical diagnosis may be obscure or masked by treatment with parenteral iron. In such an event serum iron and iron binding capacity might be spuriously elevated. Also, deposition of iron-dextran complex in bone marrow might confuse interpretation of the iron stain on bone-marrow smears. If it becomes

important in such a patient to distinguish between iron deficiency and another disorder of heme synthesis, then a ferrokinetic study may be of value. The following case report illustrates the use of ferrokinetics in difficult diagnostic states.

Occult Hemorrhage—Diagnostic Problem

A 37-year-old woman was referred to us by her physician because of two syncopal attacks. She was hospitalized at a private hospital, found to be anemic, and was given six transfusions. Her physician saw her 2 months later and found her to be weak, tired, and pale, and he gave her injections of iron-dextran and vitamin B₁₂. A blood count showed hemoglobin, 8 g/100 ml; hematocrit, 26%; RBC, 2.48 m/cm³; with mean corpuscular volume, 104 μ m³; mean corpuscular hemoglobin, 32 μ g; and mean corpuscular hemoglobin concentration, 31%. The indices were not helpful in identifying the kind of anemia. The white-cell and platelet counts were normal, and the reticulocyte count was 5.4%. The initial bone-marrow smear was hypoplastic with tissue mast cells and absent stainable iron. After the injection of iron-dextran, the serum iron was 174 μ g/100 ml and the iron binding capacity 213 μ g/100 ml. Once again the bone marrow showed no stainable iron. In December 1961 she was hospitalized by her private physician for further studies. Physical findings continued to be negative. Her blood counts were normal with hemoglobin, 13.4 g/100 ml; and hematocrit, 42%. Her serum iron and total-iron binding capacity remained 170 and 342 μ g/100 ml, respectively. However, there was again a total absence of iron in the bone marrow. Four studies of the stools for occult blood were negative. X rays of the GI tract were negative. Chromium-51-RBC survival time showed a half-time of 39 days. Radioactivity in the stool was negative. A ferrokinetic study at this point disclosed a radioactive-plasma clearance rate of 20 min (Fig. 7a). Almost 100% of the total dose of ⁵⁹Fe was incorporated into circulating erythrocytes in 5 days (Fig. 7b), corroborating the diagnosis of iron deficiency. She remained asymptomatic for 3 years. Suddenly in 1964 she developed a precipitous anemia once more. Her stool was tarry black and contained blood. For the first time a GI series showed a filling defect in the jejunum. At surgery a leiomyoma was found with ulceration resulting in GI bleeding. Radionuclide testing in this patient confirmed the diagnosis of iron deficiency; its course had been obscured by parenteral iron administration and intermittent bleeding.

Other Helpful Applications of Ferrokinetic Studies

In myelofibrosis with myeloid metaplasia of the spleen and liver, the bone marrow fails to produce blood cells because of replacement with fibrous tissue. In compensatory response the spleen and liver revert to their fetal function of producing blood cells. Accordingly in this disorder ⁵⁹Fe persists in the plasma and is incorporated incompletely into circulating erythrocytes (Figs. 8a and 8b).

Fig. 7a Plasma clearance pattern of ^{59}Fe in patient with iron-deficiency anemia.

Fig. 7b Erythrocyte reappearance of ^{59}Fe in patient with iron-deficiency anemia.

In addition, examination over various organ sites shows a failure to demonstrate radioactivity over the sacral area but increased spleen/precordial and liver/precordial radioactive ratios soon after the radionuclide is given, representing an accumulation of iron in areas of active erythropoiesis (Fig. 8c).

Thalassemia major (Cooley's anemia) is characterized by the delayed synthesis of the beta-polypeptide chains of hemoglobin with an accompanying retardation in hematopoiesis. The red cells produced in this disorder are inadequate and are readily hemolyzed. Accordingly we have a combination of hemolysis and inadequate red-cell production. This is reflected in the radionuclide studies that show diminished RBC survival time with ^{51}Cr -RBC, together with limited incorporation of ^{59}Fe into RBC (Figs. 9a and 9b).

Hypoplastic Anemia

Hypoplastic anemia sometimes develops after the administration of chloramphenicol. The incorporation of radioactive iron into circulating erythrocytes during hypoplastic states is below normal (Fig. 10a). Three years after the patient illustrated had developed bone-marrow depression, she continued to be anemic, developed jaundice, and the question of hemolytic anemia arose. Survival time of ^{51}Cr -RBC was greatly diminished (Fig. 10b). When this patient's red cells were incubated with sugar water, they readily hemolyzed. Furthermore, the acid hemolysin tests were positive. The patient was determined to have paroxysmal nocturnal hemoglobinemia which developed during the course of recovery from hypoplastic anemia. Pancytopenia is an important and vexing clinical problem. Diminished incorporation of ^{59}Fe to red cells in a patient with pancytopenia suggests functional marrow inadequacy. Unfortunately this procedure per se does not identify the type of etiologic mechanism for pancytopenia. Such a blood picture and ferrokinetic pattern might occur in aplastic anemia. It might also be seen in preleukemic states, a difficult diagnosis to establish. Preleukemic leukemia involves those patients who have pancytopenia but who do not yet have "blasts" in their bone marrow sufficient to enable us to diagnose leukemia. These patients are destined to develop leukemia but have no diagnostic morphologic marrow changes when they are first seen. The diminished incorporation of radioactive iron seen in early stages is not specific enough to permit this diagnosis, which can only be made in retrospect.

Anemia of Infection

Procedures using radionuclides for ferrokinetic studies are generally not needed to establish the diagnosis of anemia of infection. In this condition the presence of chronic infection dominates the clinical picture. Incidentally such a patient is often found to have mild normocytic and normochromic anemia, a morphologically normal bone marrow with increased stainable iron, a low serum iron, and a low iron binding capacity. Ferrokinetic study frequently shows rapid

Fig. 8a Plasma clearance rate of ^{59}Fe in patient with myelofibrosis.

Fig. 8b Reappearance rate of ^{59}Fe -RBC in patient with myelofibrosis.

Fig. 8c Ratio of ^{59}Fe activity in a patient with myelofibrosis as monitored from the body surface over sites of various organs.

disappearance of ^{59}Fe from plasma with diminished rate and percentage of incorporation into circulating erythrocytes (Figs. 11a and 11b).

Polycythemic States

Polycythemia vera is a myeloproliferative disorder characterized by splenomegaly, increased numbers of circulating erythrocytes, leukocytes, and platelets, an extremely generalized hyperplastic bone marrow, and absence of hypoxia. In this disorder blood-volume studies made with simultaneous ^{51}Cr -RBC and human serum albumin labeled with ^{125}I (^{125}I HSA) disclose elevated total blood volume, red-cell volume, and plasma volume.

Polycythemia vera is frequently confused with relative, or "stress," erythrocytosis, a common variety of erythrocytosis seen in hard-driving younger men who often have slight obesity, mild hypertension, peptic ulcer, and gallstones. Very frequently such patients have high red-cell counts but normal numbers of leukocytes and platelets and their spleens are not generally enlarged

Fig. 9a Survival of RBC in patient with Cooley's anemia.

Fig. 9b Reappearance rate of ^{59}Fe -RBC in patient with Cooley's anemia.

Fig. 10a Reappearance rate of ^{59}Fe -RBC in patient with chloramphenicol-induced hypoplastic anemia.

Fig. 10b Hemolytic anemia (paroxysmal nocturnal hemoglobinuria) developing in patient after "recovery" from hypoplastic anemia.

Fig. 11a Plasma clearance rate of ^{59}Fe in patient with anemia of infection.

Fig. 11b Reappearance rate of ^{59}Fe -RBC in patient with anemia of infection.

Fig. 12 Blood, erythrocyte, and plasma volume data in the polycythemic states.

or their marrow hyperplastic. This group is readily distinguished from polycythemia vera on the basis of the blood-volume test which shows a normal or slightly increased red-cell volume but a decreased plasma volume, resulting in relative or spurious polycythemia. The apparent common denominator which characterizes most of these patients is their tendency to smoke cigarettes heavily, resulting in chronic hypoxia because of elevated carbon monoxide blood levels. An accurate blood-volume study using both ^{51}Cr -RBC and ^{125}I HSA is considered indispensable in distinguishing between polycythemia vera and stress erythrocytosis (Fig. 12).

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DISCUSSION: BLOOD, MARROW, NODES, AND SPLEEN

Goswitz: In view of recent trends in the treatment of Hodgkin's disease calling for laparotomy and early splenectomy, I would like to have Dr. Viamonte comment about the need for lymphangiography in this group of patients. Also, what is the incidence of false-positive and false-negative studies using this technique in the study of patients with lymphoma?

Viamonte: I would like to comment about laparotomy and tell you how the Hodgkin's Cooperative Study group feels about laparotomy and splenectomy in determining with accuracy involvement of the spleen in Hodgkin's disease. Twenty-five percent of spleens involved clinically when studied carefully histologically after laparotomy will contain Hodgkin's disease. Conversely, approximately 50% of spleens found enlarged on physical examination will not contain Hodgkin's disease when examined pathologically. Of lesser value as a result of laparotomy is the evaluation of lymph nodes not surveyed by the lower lymphangiogram and the liver. The surgical inspection for abdominal nodes, even when directed by the radiologist, is not 100%. All lymph nodes cannot be removed, and nodes that are difficult to remove surgically for pathologic confirmation are the ones most frequently involved: the high para-aortic nodes.

The most frequently involved areas in lymphangiography of Hodgkin's disease are the higher aortic or retropancreatic nodes, and these are not accessible to the surgeon; so biopsies or removal of them for study are incomplete. A negative laparotomy does not always disprove the lymphographic findings. Quite often we see on postoperative films the same nodes that appeared abnormal, indicating they were not removed. So operative radiography is advised. Lymphography and laparotomy are complementary procedures.

The demonstration of liver involvement by laparotomy is uncommon and in the order of 5% or less for all persons with no consideration of extension of disease. The demonstration of liver disease rises to approximately 15% in the presence of clinical involvement of retroperitoneal lymph nodes and spleen. Some believe that the mode of spread of Hodgkin's disease in the abdomen is to the spleen first before it reaches the liver.

Peritoneoscopy performed by some has a similar yield of positive liver biopsy and is an alternative to laparotomy for the demonstration of Hodgkin's disease in the liver.

Finally, in view of the possible complications of exploratory laparotomy and splenectomy, if the therapeutic philosophy for an individual patient is to limit radiotherapy only to known sites of disease that are affected in patients with stages I and II disease only, then it is justified. The procedure is desirable but not required to exclude the involvement of liver in those patients who have high aortic nodes or have liver involvement. For those who have para-aortic nodes or marked splenomegaly, peritoneoscopy with liver biopsy are suitable alternatives to surgery. Laparotomy is not required or justified if the risk for liver involvement is minimal, and the therapeutic philosophy for individual patients is to treat para-aortic and retroperitoneal nodes even in the absence of abdominal disease.

I believe lymphangiography is a simple guideline to the assessment of retroperitoneal disease and the yield is quite high. I have shown you examples of false positives and false negatives. In patients with Hodgkin's disease, if the lymphogram shows abnormal nodes, chances are over 90% that the radiologist will be correct, and these nodes may be confirmed at some time during the course of the disease or at laparotomy to be histologically positive. On the other hand, if the lymphogram is negative, the majority of these nodes sampled at laparotomy will show no evidence of Hodgkin's disease. We know too that in the early stages of Hodgkin's disease the lymphogram can be absolutely normal. Also, mesenteric and splenic nodes are not visualized by lymphography. Dr. Ralph Johnson has stated the fact that some cases that I reviewed at NIH and called negative that subsequently turned out to be positive does not deny the accuracy of the lymphogram. Why? Because we know that some patients with initially negative retroperitoneal nodes during the course of the disease later will develop enlarged nodes. We cannot prove one way or another if those nodes were diseased when initially interpreted or if the disease spread in the interval. Dr. Kaplan (H. S. Kaplan, Clinical Evaluation and Radiotherapeutic Management of Hodgkin's Disease and the Malignant Lymphomas, *New Engl. J. Med.*, 278: 892-899 (1968)) believes that a mode of spread of the disease from the neck to the juxta-aortic nodes is via the thoracic duct. Dr. Vera Peters believes that the mixed-cell types with left supraclavicular node involvement have a greater chance for developing abdominal disease, and she believes that laparotomy will be helpful in those institutions where they do not systemically irradiate below the diaphragm. Laparotomy may be useful when the lymphogram is negative. The radicalist who prefers extensive radiotherapy will irradiate the abdomen regardless of what laparotomy shows, in which case laparotomy would not be absolutely necessary.

Goswitz: What is the correlation between positive imaging studies and activity of the disease following treatment of lymphomas? Will the negative scan unequivocally indicate that the disease is stable or has been controlled?

Viamonte: I do not have a figure of the correlation between imaging and lymphography during the course of the disease. In Miami we have patients with negative chest films and lymphogram but with a positive mediastinum on scanning, with subsequently positive nodes at pathology. Imaging may be helpful especially for the assessment of a group of nodes not demonstrated by lymphography. We have found conversion from positive to negative with ^{67}Ga or $^{113\text{m}}\text{In}$ studies which correlates to the histology. We do not have comparative data in the human, so I cannot speak authoritatively.

Edwards: In regard to lymphography, sometimes we worry about complications, particularly emboli to the lung. This can be serious since we have had one death. Emboli to the brain might even be a serious disaster. I was wondering if in your work-up you try to exclude people who might have a right-to-left shunt. You mentioned also that you thought lymphography should be done under X-ray monitoring. Do you limit your procedures to a certain volume of dye, or do you stop injection when the dye reaches a certain level? In what percentage of studies do you actually demonstrate nodes at the level of T-10, T-11, or higher?

Viamonte: We have seen very few patients (in over 4000 examinations about three cases) with brain embolization. One person took about 1½ months to recover. Another lady became psychotic (she had married twice), and, when she was recovering, she remembered her first husband but not her second husband. Eventually she recovered completely and her memory returned to normal. A brain scan initially revealed a diffuse abnormality, and we were at first very worried. This transient psychological disturbance was the only problem we encountered. She was calling her second husband by the name of her first husband, and he was very upset.

In regard to your question about the contrast material and total volume, one should use less volume if there is minimal leak at the injection site. It also depends on the size of the patient: the smaller the individual, the less volume used. Third, volume depends on the nature of the disease we are evaluating. The larger the nodes, particularly in some lymphomas, the greater the volume of contrast to be used. I have injected 40 cm³ into one patient who had giant-size nodes due to follicular lymphoma. In adults we seldom inject more than 6 to 8 ml in each foot. When the mid-aortic nodes are visualized, we stop the injection. After injecting a couple of milliliters, we radiograph the injection site (to rule out inadvertent venous injection), and, after 4 ml, we take a film of the pelvis to detect possible obstruction as manifested by collateral circulation in the groin or pelvis. If seen, we will stop the injection. When we see the thoracic duct, that means we have injected too much. When contrast is seen at L-3, 2 hr later, particularly after the patient has been walking, if we take another film we see more proximal nodes. Very infrequently we see mediastinal nodes. Often, however, we see supraclavicular nodes because of the normal, frequent anatomic connections between these nodes and the terminal portion of the thoracic duct.

Goswitz: Since lymph nodes in the upper retroperitoneal space near the diaphragm and the first lumbar vertebra are so poorly detected by lymphography, would anterior venocavography be a better method to use for evaluation of these nodes?

Viamonte: Venography is indicated sometimes. Perhaps we should do it more often. Despite a normal intravenous pyelogram (IVP) (no displacement of the right ureter or right kidney) and a normal lymphogram, cavography may show evidence of nodal involvement. Presently we do not do cavography routinely and do it only when we suspect disease on the right side of the spine based on the IVP or lymphographic findings.

Brill: Radioactive isotopes of iron are better indicators of red-cell production and iron storage and turnover than are the colloidal agents used for marrow scanning. We are eagerly awaiting the day when large amounts of ^{52}Fe will be available at a low cost for patient studies. Until that day arrives, I believe we will obtain better diagnostic information on marrow function using ^{59}Fe than can be obtained with the radiocolloids, including both kinetic analysis of plasma clearance and red-cell incorporation along with imaging the whole-body distribution of radioiron for an index of marrow distribution and/or iron storage depots. The group at Donner Laboratory has conducted studies using Hal Anger's 64-crystal scanning system [P. Ronai, H. S. Winchell, H. O. Anger, and J. Lawrence, Whole Body Scanning of ^{59}Fe for Evaluating Body Distribution of Erythropoietic Marrow, Splenic Sequestration of Red Cells and Hepatic Deposition of Iron, *J. Nuclear Med.*, 10: 469-474 (1969)]. At Vanderbilt University we have conducted approximately 100 whole-body ^{59}Fe scans in several normal subjects and in selected disease states. The essential feature of our system, which is a well-shielded dual-opposed 5- by 4-in. NaI (Tl) crystal scanner (coupled to a computer), is the low-resolution, high-sensitivity collimators we use for the mapping of low doses of high-energy gamma emitters. The collimators are approximately 7 in. long with a 5-in.-diameter opening next to the crystal and a 2-in. opening next to the patient. An image of the geometric mean of the counts collected by the top and bottom detectors is obtained in approximately 15 min when patients are scanned 3 hr. After the intravenous (I.V.) administration of 10 μCi of ^{59}Fe , these scans clearly illustrate the pattern of ^{59}Fe distribution and have been of great help to the clinician. An example of a normal scan is shown in Fig. 1 where the images collected by the top and bottom detectors are shown separately and an image of the geometric mean is shown superimposed on a transmission scan from the same patient. Figure 2 shows a few examples we have collected from several patients with different hematologic diseases.

The point I am trying to make goes beyond marrow scanning. We have avoided the use of high-energy gamma emitters for scanning studies because of difficulties in collimation. These arise when we try to obtain high-resolution images. When low-resolution images will suffice, high-energy tracers can be used to great advantage.

Fig. 1 Normal ^{59}Fe scan 1 day following $10\ \mu\text{Ci}$ intravenously. Unprocessed data collected from the lower (a) and upper (b) 5-in. NaI detectors. The geometric mean of counts collected in homologous cells of the 64×64 image are overlaid with a transmission image (c) above the computer-smoothed geometric mean image (d).

Fig. 2 Abnormal ^{59}Fe scans.

(a) Refractory anemia.

(b) Hemolytic anemia.

(c) Chronic myelogenous leukemia with myelofibrosis. Extramedullary hematopoiesis in liver, spleen, and knees.

(d) Follicular lymphoma with splenomegaly.

Goswitz: The ^{59}Fe whole-body imaging would provide us with more information about red-cell production sites than the radiocolloid reticulo-endothelial (RE) scan. However, with the ^{59}Fe imaging technique alone, I do not see how we can distinguish effective erythropoiesis from ineffective erythropoiesis, particularly in those patients with iron-storage disorders. I would think the blood-sample collections and the organ monitoring are still needed to provide more specific information about erythropoiesis. In my estimation the radiocolloid RE scan would be preferred to ^{59}Fe whole-body imaging to study patients with myeloproliferative diseases.

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ENDOCRINES

RADIOGRAPHIC ASSESSMENT OF ENDOCRINE GLANDS

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ABSTRACT

The endocrine glands are not readily demonstrable by routine radiographic means. Angiography has been helpful in visualizing some of these glands directly. The indirect assessment of these glands, however, is much easier. The very complex manifestations of endocrine disorders are all demonstrable by their effect on either the skeletal or the soft-tissue system. In this paper I have attempted to describe the different radiologic methods that can be used to study endocrine disorders. The description of each specific disorder is incomplete, and the reader is referred to the classical papers describing each entity.

The radiographic visualization of endocrine glands is rather difficult. These structures are not radiopaque because they have the same density as their surrounding soft tissues. The adrenal gland is the only one of those organs which at times is embedded in enough fat to permit its direct radiographic visualization. On the other hand, endocrine disorders produce changes that affect the skeleton and the soft tissues, and the result of these disorders may be easily detected by X ray. Furthermore, enlargement of endocrine glands can affect surrounding structures, and they, in turn, can be opacified by barium or contrast medium. For instance, the downward displacement of the kidney might indicate the presence of an adrenal tumor.

The radiologic assessment of endocrine glands will therefore be done in two parts: (1) the direct assessment, which consists in visualizing the organ itself (either because it is calcified, surrounded by fat, or opacified during angiography); and (2) the indirect assessment, which consists in the study of the organs surrounding an enlarged endocrine gland or the study of the metabolic disorders and their effect on bony and soft-tissue structures.

NEUROENDOCRINE SYSTEM

The hypothalamus, the pituitary, and the pineal glands are probably the prime control organs of hormonal secretion. These three structures are difficult to visualize directly. Indeed the pineal gland, which calcifies in approximately 55% of cases after the age of 25, is the only intracranial gland that can be seen directly by X ray with some consistency. The downward, dorsad, or sideward displacement of this structure, which indicates the presence of an intracranial mass, can be detected on a skull X-ray series.

The hypothalamus and the pituitary gland, on the other hand, usually do not calcify (calcification of the pituitary gland has been reported in rare instances). Angiography usually does not help to visualize these intracranial glands because they are fairly avascular; therefore, only indirect assessment is possible.

Fig. 1 (a) Radiographic appearance of a normal sella turcica.

(b) Sella turcica of a patient with a chromophobe adenoma. Note the typical appearance of a double contour sella with posterior displacement and erosion of the posterior clinoid process (arrow). The sella is widened and its volume increased.

All three glands are in close relation to either bony structures, important intracranial vessels, or the ventricular system of the brain. Thus, when tumors of these structures are suspected, we have the choice of using several diagnostic tools. The simplest one for diagnosing the pituitary gland is the assessment of the sella turcica. The size of the sella turcica is very close to that of the pituitary gland. Normal measurements of the sella by skull films are available.¹ In cases of hyperpituitarism caused by a pituitary tumor, the sella turcica may become eroded (Fig. 1). Interpretation of sellar abnormalities is relatively easy, and these abnormalities may represent one of the first indicators of a neuroendocrine

disorder. All these tumors may produce increased intracranial pressure, which, in turn, may cause pressure atrophy of the sella turcica and widening of the cranial sutures in the young.

The pneumoencephalogram helps to detect intracranial masses, particularly those of the posterior fossa. Hypothalamic tumors may extend to the posterior fossa or displace structures in that area. Pinealomas are best diagnosed by pneumoencephalography. In children tumors of the pineal gland have been associated with precocious sexual maturity. Most often glial tumors are thought to produce this disorder.²

The exact endocrine function of the pineal gland in man is not known, but in animals it has been shown that the pineal gland serves as a biologic clock system.³ In Fig. 2 there is an example of such a tumor, demonstrated by its

Fig. 2 Lateral tomogram of a pneumoencephalogram of a patient with a pinealoma. Observe the solid soft-tissue mass (arrow) pressing on the posterior aspect of the third ventricle.

effect on the posterior portion of the third ventricle. The introduction of air into the ventricular system combined with tomography allows excellent visualization of these lesions. Because tumors of the endocrine glands are often avascular, cerebral angiograms are not as useful; however, these masses produce displacement of some of the major intracranial vessels. Thus pituitary tumors

spread the carotid siphon. Tumors of the hypothalamus can also be diagnosed either by pneumoencephalography or by carotid angiography.

Disorders of the neuroendocrine system produce numerous metabolic changes that are relatively easy to diagnose roentgenologically. The radiographic appearance of acromegaly and gigantism are well known (enlargement of the paranasal sinuses and of the sella turcica, increased heel thickness, etc.). All endocrine glands are controlled by the hypothalamus, and some of the resulting skeletal and soft-tissue disorders will be mentioned more specifically under each of the following paragraphs.

THYROID GLAND

Direct radiologic assessment of the thyroid gland can be obtained when the gland is either calcified or opacified during selective angiography. Calcification of the thyroid gland is not rare; the presence of calcium, however, has no diagnostic significance. Angiography, on the other hand, has been found rather useful, particularly for the assessment of goiters.

The blood supply of the thyroid gland occurs via the inferior thyroid artery, which is a branch of the thyrocervical trunk, and the superior thyroid artery, a branch of the external carotid artery. Selective catheterization of the thyrocervical trunk and more specifically of the inferior thyroid artery is not difficult. Some investigators recommend simultaneous injection to the inferior thyroid and the superior thyroid arteries.⁴ The approach to the superior thyroid artery is either by a direct needle puncture of the carotid artery and the subsequent introduction of a small catheter into the external carotid artery or by catheterization of this vessel from the femoral artery. Goiters due to hyperthyroidism are vascular and blush during angiography (Fig. 3). This type of examination has been found particularly helpful when the isotopic scan reveals a "cold nodule." Schmidt⁵ has shown that the angiogram may reveal a highly vascular carcinoma, whereas the scan may not be conclusive. In this country angiography of the thyroid gland has not been widely accepted because of the ease with which the isotopic examinations can be performed and the risks of the angiographic method.

The indirect assessment of the thyroid gland is perhaps easier and more readily available. Enlargement of the thyroid gland produces displacement of the trachea and of the surrounding vascular structures. The venous structures, i.e., the innominate and jugular veins, are displaced by an enlarged thyroid gland (Fig. 4). Once a thyroid mass has been shown, its pathology must be identified. The metabolic effects of hyper- and hypothyroidism are well known and can be easily assessed radiographically; however, it is more difficult to exclude the presence of a carcinoma.

Hypothyroidism causes retarded development of the individual vertebral bodies, which, in turn, results in kyphosis.⁶ This hypoplasia produces the

Fig. 3 (a) Left subclavian angiogram demonstrating a hyperactive benign thyroid nodule (arrow).

(b) The flow through the gland is increased. See the rapid venous return indicated by the early appearance of a draining vein (arrow).

so-called "bullet shaped" vertebral bodies. Multiple dense centers of ossification in the child are practically pathognomonic of hypothyroidism⁷ (Fig. 5). The cardiovascular system may be affected also: pericardial effusion,⁸ cardiac enlargement, and early atherosclerosis often are encountered.

Hyperthyroidism causes early epiphyseal closure in children. In the adult it may produce osteoporosis. In the cardiovascular system it may result in high output failure, cardiomegaly, and increased ventricular pulsations.

PARATHYROID GLAND

Direct angiographic visualization of the parathyroid gland is successful only occasionally when a blush of the gland or vascular displacement are obtained. In this fashion some have demonstrated adenomas located in odd places like the mediastinum.⁹ In those instances the adenomas were either supplied by the inferior thyroid artery, the internal mammary artery, or other anomalous vessels. Their visualization is extremely important for the surgeon, who otherwise has to perform extensive dissections of the mediastinum. Five percent of parathyroid tumors are calcified, and some of those have been seen on plain films.¹⁰

Fig. 4 Substernal extension of a thyroid tumor. Note the lateral displacement of the trachea (arrow) and the downward displacement of the left innominate vein.

Indirect demonstration of parathyroid adenomas has been reported. Usually located between the thoracic inlet and the root of the aorta, these rather small tumors occasionally produce an impression on the barium column of the esophagus.¹¹ Selective arteriograms have been used widely as a diagnostic test for the detection of parathyroid adenomas.¹² Displacement of adjoining arteries, such as the inferior thyroid artery, can be due to a parathyroid adenoma. The inferior thyroid artery forms a constant loop around the lower parathyroid gland, and enlargement of this structure is associated with widening and splaying of this loop. Opacification of the inferior thyroid arteries is essential since they represent the main blood supply of the parathyroid glands. Pneumomediastinography has been used mostly outside this country, but its value is doubtful.

The metabolic disorders created by hyperparathyroidism and their radiologic appearance have been well described elsewhere.^{13,14} Thirty or forty percent of patients with hyperparathyroidism have bone lesions radiographically detectable. The earliest and most characteristic lesions are seen in the hands, where subperiosteal reabsorption at the radial margin of the middle phalange occurs

Fig. 5 Epiphyseal dysgenesis in a 12-year-old patient with hypothyroidism. Note the multiple dense centers of ossification in the femoral head epiphysis (arrows).

(Fig. 6). Involvement of the distal end of the clavicles often has been attributed to secondary hyperparathyroidism.¹⁵ The lamina dura may become eroded; this is also an early sign of hyperparathyroidism but is quite nonspecific. Dental films should be obtained when hyperparathyroidism is to be excluded. Osteosclerosis, especially about the vertebral bodies ("rugger jersey" appearance), has been associated particularly with secondary hyperparathyroidism. Soft-tissue calcifications, nephrocalcinosis, and kidney stones often are found. A high incidence of peptic ulcers has been described.

Hypoparathyroidism, on the other hand, may produce calcification of the basal ganglia¹⁶ (Fig. 7) and generalized increased bone density.

ADRENAL GLAND

This is the endocrine gland that can be visualized best directly. There are multiple radiologic methods that provide direct demonstration of this organ.

The adrenal gland often is surrounded by a considerable amount of fat which makes it detectable by X ray. Calcification of the adrenal gland is not unusual and often is associated with tuberculosis, Addison's disease, and primary carcinoma. Adrenal cysts may also calcify. Retroperitoneal air, CO₂ or NO₂, insufflation has been used extensively for the examination of this organ.¹⁷ The presacral, retrorectal route is usually used to introduce up to 1500 cm³ of gas. With the patient in the knee/chest position, the gas dissects through the retroperitoneal space and surrounds the adrenal gland making it radiologically visible. The examination often is combined with tomography (Fig. 8). This

Fig. 6 (a) Anteroposterior view of a finger of a patient with hyperparathyroidism. The arrow points to an area of subperiosteal cortical resorption. Note the lacelike appearance of the bone beneath the periosteum (arrow).

(b) Same patient after adequate therapy. See the normal appearance of the cortex (arrow).

method has been somewhat abandoned lately because the correlation of radiographic and pathologic findings has not always been accurate. Fat may adhere to the gland, and the picture obtained in the radiograph may not only represent the gland but also the surrounding fat. Angiography has replaced the former method because it offers a view of the inner architecture of the gland (Fig. 9).

Arteriography¹⁸ and venography¹⁹ are very useful for the assessment of adrenal tumors. The blood supply to the adrenal gland occurs through three main vessels. The inferior adrenal artery arises from the renal artery. The middle adrenal artery is a branch that arises directly from the aorta, whereas the

Fig. 7 Lateral tomogram of a child with hypoparathyroidism. The white arrow points to the calcification of the basal ganglia. The black arrow shows calcification of the dentate nuclei, which is of no significance.

Fig. 8 Retroperitoneal air insufflation of a patient with bilateral adrenal hyperplasia. The arrows outline the tomographic appearance of the gland.

Fig. 9 Bilateral selective venogram. See the normal size and normal architecture of both glands.

superior adrenal artery is a branch of the inferior phrenic artery. All three of these vessels can be selectively catheterized, and injection of contrast into them may demonstrate tumors of the adrenal gland (Fig. 10). Very vascular adrenal tumors, like pheochromocytomas, may be demonstrated by flush aortograms. Angiography in cases of pheochromocytomas is not without risk and should be performed with the patient premedicated in the same fashion as for surgery and with Regitine readily available for immediate intravenous infusion. Angiography allows us to localize the tumor and to rule out multiple tumors.

Adrenal venography has also been very helpful in identifying adrenal masses (Fig. 11). The right adrenal vein drains directly into the inferior vena cava, whereas the left adrenal vein enters the left renal vein. Selective catheterization of these vessels is technically fairly easy, and injection of contrast into them opacifies the adrenal gland. This method has been quite successful in demonstrating adrenal adenomas (Fig. 12) and bilateral adrenal hyperplasia (Fig. 13). This examination carries a certain risk. If the injection is done too forcefully, one may "blow out" the adrenal gland. Thrombosis of the adrenal vein has also been reported.²⁰

PANCREAS

Direct visualization of the pancreas may be obtained occasionally by angiography. During selective celiac arteriography, the gland may blush and its outline may be seen; however, pathologic processes usually are not identified in this fashion. Pancreatitis may cause diabetes and calcifications of the gland.

Fig. 10 Selective inferior phrenic arteriogram demonstrating the "tumor vasculature" of a malignant mesenchymoma of the adrenal gland.

Fig. 11 Selective left adrenal venogram demonstrating stretching of veins around a large mass representing an adrenal cyst.

Fig. 12 Selective left adrenal venogram of a 30-year-old patient with a history of hypertension. Note the presence of a 3-cm mass which at surgery was found to be an adrenal adenoma.

Fig. 13 Bilateral selective adrenal venogram. Note that both glands are enlarged but that their venous pattern is not disturbed. This represents a case of bilateral adrenal hyperplasia.

These can be seen easily on a radiograph of the abdomen. Altogether the pancreas, however, is a silent organ and is difficult to assess radiographically. Vascular tumors, such as insulinomas, and Zollinger–Ellison tumors, can be visualized by selective celiac angiography (Fig. 14). Malignant endocrine tumors of the pancreas can be also diagnosed by selective angiography.

The indirect manifestations of the Zollinger–Ellison syndrome producing changes in the gastrointestinal tract have been described by Nelson.²¹

Fig. 14 Selective splenic arteriogram that demonstrates a rounded vascular mass in the area of the tail of the pancreas (arrow). At surgery an insulinoma was removed.

SEX GLANDS

Testes

The radiologic examination of the testes is not necessary because of the ease of the physical examination. On the other hand, malignant testicular tumors may produce distant metastases, particularly to the lungs (Fig. 15). Lymphangiography is used widely to demonstrate retroperitoneal involvement by testicular tumors. These metastases replace and destroy partially some of the retroperitoneal lymph nodes. However, when a nodule is completely replaced, it cannot be identified by lymphangiography. The mediastinal involvement by testicular tumors is well known. Examination of the mediastinum is best done by tomography.

Fig. 15 Multiple lung metastasis caused by a seminoma of the testicle.

Ovaries

Ovarian tumors can be diagnosed by plain film radiography. These tumors at times may be so large that they displace bowel and are visualized on radiographs of the abdomen. The presence of calcifications and particularly of teeth in such masses is pathognomonic for ovarian dermoid tumors. Pneumoperitoneography may be useful for detecting ovarian tumors.²²

Hysterosalpingography has also been useful in demonstrating ovarian tumors.²³ It consists in the introduction of an oily contrast medium into the uterus. When the Fallopian tubes are patent, the contrast spills into the pelvis and surrounds the ovaries. The Stein—Leventhal syndrome may be diagnosed by this technique.

Angiography has only a limited value for the assessment of the ovaries. Pelvic angiography does not visualize the ovaries but demonstrates the uterus. Displacement of the uterus by an ovarian tumor can thus be seen; this facilitates the identification of some pelvic tumors. Selective catheterization of ovarian arteries is technically difficult and has not been used widely.

On the other hand, ovarian venography has recently been done to assess the ovarian-vein syndrome.²⁴ The left ovarian vein enters the left renal vein, whereas the right ovarian vein usually enters the inferior vena cava. Injection of those veins demonstrates incompetence of the valves and may explain venous congestion of the pelvis. Jacobs²⁵ also has used selective gonadal venography to diagnose various ovarian or testicular disorders.

Chromosome abnormalities produce a lack of sex differentiation (Turner's and Klinefelter's syndromes). These conditions display typical skeletal changes. It is beyond the scope of this paper to describe the radiographic findings of these rare syndromes. For example, Fig. 16 reveals shortening of the fourth metacarpal bone, which suggests the presence of a chromosomal abnormality.

Fig. 16 Anteroposterior view of the hand of a patient with Turner's syndrome. Note the short fourth metacarpal bone (arrow). A line drawn from the top of the third metacarpal to the top of the fifth metacarpal should touch or transect the top of the fourth metacarpal. This is not the case here.

CONCLUSION AND SUMMARY

The radiographic examination of endocrine glands has been discussed. The assessment is usually done in two parts.

1. The direct approach: visualizing the organ itself.

2. The indirect approach: studying the organs neighboring the enlarged gland or the metabolic disorders caused by them.

Direct visualization is obtained either when the gland is calcified, surrounded by fat, or angiographically opacified. Indirect assessment is possible because the abnormal levels of secretion by these malfunctioning glands produce typical radiographic images of the soft tissues and bones. The study of each gland was discussed separately. The adrenal gland was found to be the most amenable to radiologic assessment.

The radiologic study at best produces an anatomic representation of the organ without any physiologic data. This shortcoming is particularly acute in the study of the thyroid gland. In the last few years, angiographic methods have somewhat overcome this deficiency. Angiography demonstrates blood flow, which is related to function; furthermore, blood samples obtained during the procedure can be analyzed for hormone levels. The radiographic appearance of the vessels during angiography often allows us to distinguish a benign from a malignant process.

EDITOR'S NOTE

This is an excellent review on radiographic assessment of endocrine gland pathology by the radiologist. It does not indicate the value of sampling venous drainage from the parathyroid glands. This is accomplished by superselective catheterization of the several veins that drain the parathyroid glands by bioassay assessment of parathyroid hormone.

*An excellent reference that should be listed in all reviews of radiology of the endocrine tumors is *The Endocrine*, by Howard L. Steinbach and H. Minagi, which is one of the volumes of the collection *Atlas of Tumor Radiology*, Year Book Medical Publishers, Inc., Chicago, Ill., 1969.*

Selective studies of the ovarian veins are not stressed. Ovarian venography and sampling of blood from the ovarian veins are complementary procedures that have been extensively used for assessing pelvic tumors and, particularly, for the study of endocrinological disorders that may be gonadal or adrenal in origin. Sampling of blood from veins draining the adrenal and gonadal organs is a complementary useful procedure.

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DIAGNOSIS OF ENDOCRINE DISORDERS BY RADIOISOTOPIC METHODS

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ABSTRACT

The principles of competitive protein-binding assay have now been applied to the measurement of almost all hormonal substances. Such assays may be subdivided into three major categories: radioimmunoassays, radioreceptor assays, and assays utilizing serum-binding proteins. For radioimmunoassays, the binding protein is an antibody, and such antibodies may now be prepared against all hormonal substances regardless of size. Generally, hormones with molecular weights less than 2 to 4000 are conjugated to larger carrier proteins for production of antisera. The radioreceptor assay uses the specific receptor protein present in cell membranes for polypeptide hormones and cytosol or nuclear binding proteins for steroid hormones. Although radioimmunoassays may cross-react with any substance bearing immunological similarity to the hormone to be measured and may not react to biologically active hormones from another species, radioreceptor assays measure with any substance having biological activity regardless of species or tissue origin. Thus each type of competitive protein-binding assay has its own particular advantages and disadvantages for use. Competitive protein-binding assays have the advantages of great sensitivity and generally simplicity of use; several hundred samples may be measured a day.

Although the application of competitive protein-binding assays to experimental biology and to clinical medicine has increased our knowledge of physiology of endocrine control systems, their use has, in general, not simplified clinical diagnoses. As a matter of fact, in almost all spheres their use has shown that measurement of a single blood sample is not sufficient to indicate the status of glandular function in that subject. Thus extensive perturbation tests for glandular function, requiring several carefully timed blood specimens, are necessary. Furthermore, in some instances several different perturbation tests must be done. Last, since perturbation tests require extensive knowledge of the control systems both in the normal individual and in the individual with various disease states, the clinician must now have extensive knowledge of this physiology to apply such tests.

COMPETITIVE PROTEIN-BINDING ASSAYS

The heart of clinical as well as experimental endocrinology has been the quantitation of hormones. In the earliest days this was done by observing target-organ response after glandular ablation or glandular extract administration. Later, specific bioassays were developed for polypeptide hormones and chemical assays for steroid hormones and thyronines. Except for thyronines in the diagnosis of human disease, these measurements were usually performed on 24-hr urine collections. Thus a whole generation of clinical endocrinologists has utilized the measurement of 24-hr urinary 17-ketosteroids, 17-hydroxysteroids, gonadotropins, and estriol for assistance in diagnosis. Such studies were in essence an integrated assessment of total 24-hr excretion; normal values were established, and patients with lower or higher values were usually diagnosed as having deficiency states or excessive production states. As will be seen later, the concepts on which such statements of normality or abnormality were made may not be generally used when hormones are measured by current radioisotopic techniques in serum. Indeed, for the sophisticated clinical endocrinologist using urinary excretion as the sole means of studying physiology, problems arose. A reliable collection of total 24-hr urine, a seemingly simple procedure, proved to be difficult in most hospitals. Alterations in excretion not associated with endocrine disease were defined. Thus 17-ketosteroid excretion was found to decrease markedly with fasting,¹ and a low excretion was not, therefore, diagnostic of adrenal insufficiency.* Similarly, excretion of cortisol metabolites was found to be low in patients with hypothyroidism and increased in patients with hyperthyroidism, even though no disease of adrenal function existed.² Last, unusual situations were described in which one steroid was converted to another and the latter excreted into urine without equilibrating in blood. Thus androstenedione was found to be converted to testosterone and a significant proportion of the testosterone excreted in urine without contributing to blood testosterone.³

Although many bioassays were too insensitive to be applied to blood measurements, this was not always true; for example, bioassays of blood insulin-like substances, adrenocorticotrophic hormone (ACTH), vasopressin, prolactin, and thyroid-stimulating hormone (TSH) were performed on extracts of blood. However, such assays were tedious (ACTH, TSH, and prolactin) or questions arose as to specificity (insulin and prolactin). For all these methods applied to urine or blood, there were limitations in numbers of samples capable of being studied.

*In women 17-ketosteroids arise almost entirely from adrenal secretion. In men testicular secretions also contribute to 17-ketosteroid excretion. Thus in women 17-ketosteroid excretion might be a good indicator of adrenal function if such considerations as this did not limit its reliability.

A great advance in sensitivity and specificity occurred with the development of double-isotope derivative methods of measuring steroids, which permitted reliable quantitation of steroids in blood from normal human subjects. This technique was gratifyingly applied for research purposes, producing considerable advances in knowledge of physiology and pathophysiology. However, this isotopic technique was even more cumbersome than earlier bioassay or chemical methods and was not easily adapted to routine patient diagnosis; only a few samples could be processed in a week's work.

In the 1950's Berson and Yalow began studying the dynamics of labeled insulin in various *in vitro* and *in vivo* systems⁴ and in 1959 published a radioimmunoassay method for porcine⁵ and human insulin.⁶ This paper marked the onset of development and application of radioimmunoassay or as subsequently termed to include other types of assays, competitive protein-binding assays. These types of assays had several advantages over all previous hormone-measurement systems: decreased cost, greater ease of performance, ability to quantify hundreds of samples simultaneously or in unextracted serum or plasma, and greater sensitivity. As examples, it is worth noting that growth hormone (GH), luteinizing hormone (LH), or follicle-stimulating hormone (FSH) had never been quantified from blood of normal animals or humans before the development of radioimmunoassays for these hormones. Also, in 1959 Unger et al.⁷ described a radioimmunoassay for glucagon. In 1960 Ekins⁸ described an assay for thyroxine using serum thyroxine-binding globulin as binding protein and Yalow and Berson⁹ and Grodsky and Forsham¹⁰ described radioimmunoassays for human insulin. In 1961 Rothenberg¹¹ and Barakat and Ekins¹² described assays for vitamin B₁₂ using a B₁₂-receptor protein. Subsequent to 1961, assays have been described for almost every known hormone, and they have been extensively applied to clinical practice.

However, for the clinician as well as the experimental endocrinologist, use of these assays resulted in a new set of problems. As stated before, measurement of hormones in a 24-hr urine in essence integrated secretion over this period. Measurement of a hormone in a small aliquot of blood gives a value at a single time. Since concentrations of most hormones⁴ fluctuate greatly, simply obtaining a single sample for hormone measurement frequently does not permit an accurate statement of glandular function. Whereas the clinician needs to know only the simplest physiology to permit interpretation of urinary hormone excretion data using blood measurements, he must be aware of the latest information about control of the particular hormone. Furthermore, most often he must obtain several carefully timed samples of blood for hormone determination, usually during specifically induced perturbations of the hormonal control system. Although competitive protein-binding assays for clinical diagnosis entail a number of problems, they arise, in general, not from the assay systems themselves but from our own limited knowledge of the physiology of control systems for the given hormone.

Discussion of the techniques of development and characterization of competitive protein-binding assays is beyond the aims of this paper; however, all aspects of this methodology have been recently reviewed as part of a workshop on competitive protein-binding assays held at Harbor Hospital.¹³ In essence, three components and four steps are required: (1) a well-characterized specific binding protein, (2) high-specific activity undamaged radiolabeled hormone, (3) a well-characterized method of separating protein-bound from "free" or nonbound hormone, and (4) a suitable reference preparation. Characteristics of the binding protein that must be comprehended include: "titer," specificity, affinity of binding, and stability. Characteristics of the labeled hormone that

Fig. 1 Schematic representation of the principles of all competitive protein-binding assays. It is possible to use several types of binding proteins (see Table 1). As the amount of unlabeled hormone (hormone to be measured) increases, the fraction of labeled hormone that is protein bound decreases.

must be known include degree of purity and of reactivity with the binding protein and stability in known and unknown samples to be assayed. Features of the method of separation of bound and free hormone that must be understood include change of characteristics with time, specificity for bound or free hormone, and the magnitude of controls. Characteristics of the reference preparation that must be comprehended include its stability, widespread availability, and certainty that it reacts identically to the unknown samples to be assayed. Figure 1 schematically presents the principles involved in competitive protein-binding assays.

The specific binding protein used in radioimmunoassays is an antibody. Whereas it was commonly conceived that substances smaller than molecular weights of about 10,000 were not immunogenic, Roth et al.¹⁴ showed that a vasopressin (M.W., 1092) when unconjugated was capable of producing antibodies. Furthermore, by conjugating smaller haptens to larger carrier proteins, antisera may be produced against most organic substances. Recently, with the use of conjugation techniques, studies from our laboratories at Harbor Hospital, as well as from others, have led to development of radioimmunoassays for triiodothyronine,¹⁵ progesterone,¹⁶ 17-hydroxyprogesterone,¹⁷ thyroxine,¹⁸ and vasopressin.¹⁹ However, a variety of other types of receptor

proteins (besides antibodies) may also be used for competitive protein-binding assays. Table 1 lists various types that have been used. Extensive knowledge of the properties of receptor proteins must be considered in use and selection for specific assay purposes.

TABLE 1
SPECIFIC BINDING PROTEINS USED IN
COMPETITIVE PROTEIN-BINDING ASSAYS

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1. Antibodies
a. Produced against unconjugated immunogens (assays for TSH, LH, FSH, GH, prolactin, insulin, parathormone, ACTH, etc.).
b. Produced against conjugated haptens (assays for estradiol, progesterone, testosterone, aldosterone, triiodothyronine, thyroxine, gastrin, etc.).
2. Tissue-receptor proteins
a. Membrane bound (assays for ACTH).
b. Cytosol or nuclear receptors (assays for estradiol and testosterone).
3. Circulating blood-binding proteins (assays for cortisol, thyroxine, and progesterone).
-

The clinical endocrinologist must have some knowledge of the potential use and limitations of each competitive protein-binding assay system. Because of the large number of assays, many for each hormone, it is not possible to acquaint the reader with each one. Instead, we shall take a specific example and describe problems that have arisen:

Radioimmunoassay of Human LH and FSH

Figures 2a and 2b depict a dose-response curve for human LH and FSH in the radioimmunoassays for these hormones as performed in our laboratory. Both of these assays as developed in our laboratory have been shown to be precise, specific, and sensitive for human LH and FSH. It is worth noting that neither assay reacts to biologically potent LH or FSH from species other than human. However, human chorionic gonadotropin (HCG) and gonadotropin extracted from teratocarcinomas of the pineal gland, ovary, testis, liver, and mediastinum, as well as from some carcinomas of the lung and all gestational neoplasms in the human, react in the LH radioimmunoassay.^{20,21} Table 2 shows the mean and range of values of serum LH and FSH seen in normal subjects and determined in these assays. Note the great overlap in LH and FSH determinations from prepubertal children and sexually mature men and the variation in concentrations observed in normal women.

Explanation of some of these findings may be gained from consideration of some additional data. Figure 3, taken from our recent publication,²² depicts daily LH and FSH, estradiol, progesterone, and 17-hydroxyprogesterone determinations throughout the normal menstrual cycle. Without detailed discussion of control of reproduction in women, let us state that this is a

Fig. 2a Semilog dose-response curve for the radioimmunoassay for human FSH in our laboratory. Antiserum dilution, 1:30,000. Dose of human FSH given in terms of the second urinary International Reference Preparation (IRP) of Human Menopausal Gonadotropin (HMG) (IRP-HMG No. 2). Routine sensitivity of this assay is approximately 2.5 international milliunits per milliliter of serum.

Fig. 2b Semilog dose-response curve for the radioimmunoassay for human LH in our laboratory. IRP-HMG No. 2 is impure, containing both LH and FSH, and serves as the reference for it also. Also shown is a dose-response curve for serum from a postmenopausal woman (PM), constructed from about 1 ml of serum. Note the slight differences in these dose-response curves. For this reason, using this anti-human chorionic gonadotropin (HCG) antiserum, the IRP-HMG is not an optimal reference. We thus use a reference pool of menopausal serum.

TABLE 2
SERUM LH AND FSH CONCENTRATIONS IN NORMAL SUBJECTS

Sex and gonadal status	Mean LH, mIU/ml	N*	SEM†	SD‡	Mean FSH, mIU/ml	N	SEM	SD
Prepubertal children								
Stage I puberty	4.7	38	0.3	2.0	4.9	32	0.4	2.5
Sexually mature men								
Ages 19 to 40	11.3	735	1.9	5.1	11.1	735	1.7	4.6
Sexually mature women								
Follicular phase	12.7	80	0.5	4.9	9.8	80	0.4	3.4
Midcycle surge	68.4	19	7.6	31.1	16.5	21	1.0	4.5
Luteal phase	10.0	95	0.5	4.6	6.3	95	0.3	3.0
Postmenopausal women	71.6	45	4.3	28.5	19.0	23	10.6	51.0

*N, number studied.

†SEM, standard error of the mean.

‡SD, standard deviation.

multifaceted and highly interdigitated system, involving dynamic interaction and sequential signaling from hypothalamus to pituitary to ovary several times during each cycle. For the normal menstrual cycle to proceed, smooth functioning of all portions of the system schematically depicted in Fig. 4 is required. Thus amenorrhea may occur without total absence of gonadotropins; i.e., amenorrhea usually occurs with normal or high normal concentrations of gonadotropins in blood. Of particular importance is the positive feedback that exists in women; increasing estradiol and possibly 17-hydroxyprogesterone concentrations increase LH and FSH secretion to result in the midcycle ovulation peak. Estrogen alone administered to normal women (and possibly to some hypogonadal individuals) may increase LH secretion rather than inhibit it. This fact is further illustrated later. What are normal values of LH and FSH (or of estradiol or progesterone) in women? It is obvious from these data that the values vary tremendously from day to day. During the luteal phase LH and FSH concentrations are similar to those observed in prepubertal children or in hypopituitary adults. During midcycle, LH is similar to that observed in castrate women or men; during the follicular phase, LH and FSH concentrations are similar to those observed in normal men. Figure 5 schematically integrates hormonal fluctuations during the menstrual cycle.^{2,3} Figure 6 schematically summarizes data from several of our studies describing the fluctuations in LH and FSH during treatment with various types of oral contraceptives.^{2,4-6} These illustrate the great variations observed during different contraceptive treatment, the differences in different types of contraceptives, and the fact that estrogens administered to normal women do not uniformly suppress LH secretion, but, in fact, may stimulate it.

Fig. 3 Mean (dark line) and standard error of the mean (SEM) (shaded area) of LH, progesterone, FSH, estradiol, and 17-hydroxyprogesterone measured daily in normal women throughout the menstrual cycle. All values centered on the day of the LH surge (indicated as day zero). [From G. Abraham, W. D. Odell, R. S. Swerdloff, and K. Hopper, *J. Clin. Endocrinol. Metab.*, 34(2): 312 (1972).

Fig. 4 Schematic presentation of mean concentrations of LH, FSH, estradiol, progesterone, and 17-hydroxyprogesterone during the normal menstrual cycle. The small preovulatory rise in progesterone depicted in Fig. 3 (by using a log scale) is not shown here. (From W. D. Odell and D. L. Moyer, *Physiology of Reproduction*, p. 65, The C. V. Mosby Company, St. Louis, Mo., 1971.)

Castration of normal women or the menopausal state is associated with increase in both FSH and LH concentrations. Generally, as shown in Table 1, FSH is more elevated than LH when both are stated in terms of the IRP-HMG No. 2. On an average, FSH and LH concentrations in normal men are relatively stable from day to day and at different times of day. In careful study we have been unable to determine any significant changes with time of day.²⁷ However, others have observed a minor fluctuation in FSH with time of day; Saxena et al.²⁸ and Faiman and Ryan²⁹ reported that FSH was higher in the morning than in the evening. Franchimont³⁰ and Swerdloff and Odell²⁷ failed to detect alterations in LH and FSH with time of day. The small fluctuations reported by some do not alter FSH sufficiently; evening concentrations on populations of

Fig. 5 Schematic presentation of the relations among the central nervous system, pituitary, and ovary.

men show great overlap with morning concentrations. However, in other studies we determined LH and FSH concentrations during sleep in normal men with indwelling catheters and correlated these with sleep stage. Very minor but significant increases in FSH, but not LH, were observed during stages 2 and 3 of sleep.³¹

These statements do not imply that LH and FSH determinations may not vary randomly from time of day to time of day; this they certainly do. Differences of 100% are common when multiple determinations are made on the same individual. However, in our experience systematic, rhythmic alterations are not observed. Figures 7a and 7b give two examples of LH and FSH measured at frequent time intervals in the same man. Examination of these figures also shows why a randomly obtained serum sample might not permit separation of

prepubertal from adult subjects. However, mean concentrations obtained from several samples from an adult man would differ from mean values obtained from a child.

With this background of concentrations in normal men, women, and children, let us turn to consideration of a few disease categories. Table 3 shows some data. Hypopituitary patients or patients with isolated hypogonadotropic hypogonadism have mean concentrations indistinguishable from normal prepubertal children. Note, however, that in a single individual the variation is such that overlaps exist with adult patients who have no gonadal disease. If one obtained multiple serial samples from a single individual and determined the mean value, greater reliability of assigning the correct gonadal status might be achieved by comparison to a simultaneously multiple-determined reference pool from a normal population. This kind of study has not been done on large numbers of individuals in our laboratory and has not been reported from the laboratory of others. Stated in another way, we have not observed a hypopituitary individual or prepubertal child who consistently had LH and FSH concentrations indistinguishable from those consistently found in normal men or women during the follicular phase.

Routinely, serum LH and FSH measured in a single blood sample is useful in only two clinical situations. With great accuracy, primary gonadal failure in either sex may be differentiated from gonadal failure caused by hypothalamic-pituitary causes. Second, gonadotropin-producing neoplasms may be diagnosed readily since even relatively inefficient tumor production results in higher concentrations in the LH assay than those observed in any castrate individual. However, as indicated, normal men or women may not reliably be differentiated from "hypogonadotropic" men or women. As a mean or average, populations of hypopituitary individuals differ from normal, but so much overlap exists that in any single patient such differentiation is unreliable. Thus, if he is to get any help from a single LH or FSH measurement, the clinician must return to firm and careful clinical assessment. In the clinical examination of a patient with hypogonadism, a high serum LH and FSH indicates testicular or ovarian failure;

Fig. 6 Schematic presentation of the fluctuations of serum LH and FSH during the normal menstrual cycle and during treatment with three types of oral contraceptives:

- 1. Combined estrogen and progesterone administered daily for 20 days.**
- 2. Estrogen administered alone for 15 days and followed by combined estrogen and progesterone for 5 days.**
- 3. Progesterone administered alone.**

The frequency LH peaks observed with ethnodial diacetate varies with dosage administered with doses over 1 mg/day; both LH and FSH are suppressed. (Based on data from W. D. Odell and D. L. Moyer, *Physiology of Reproduction*, The C. V. Mosby Company, St. Louis, Mo., 1971.)

Fig. 7a Measurement of serum LH and FSH at 30-min intervals during normal sleep in a eugonadal man. Stages of sleep determined as rapid-eye-movement (REM) sleep, fast-wave sleep (stages 1 and 2), and slow-wave sleep (stages 3 and 4). [From R. Rubin, A. Kales, R. Adler, T. Fagan, and W. Odell, Gonadotropin Secretion During Sleep in Normal Adult Men, *Science*, 175: 197 (1972).]

Fig. 7b Same man as in Fig. 7a. Samples were obtained through a 10-ft-long tubing connected to a venous catheter. [From R. Rubin, A. Kales, R. Adler, T. Fagan, and W. Odell, Gonadotropin Secretion During Sleep in Normal Adult Men, *Science*, 175: 197 (1972).]

TABLE 3
SERUM LH AND FSH CONCENTRATIONS IN SOME DISEASE STATES

Sex and gonadal status	Mean LH, mIU/ml	N	SEM	SD	Mean FSH, mIU/ml	N	SEM	SD
Hypogonadotropic hypogonadism*	5.9	17	0.5	1.9				
Klinefelter's syndrome	58.6	14	10.4	37.6	30.7	9	5.1	15.2
Precocious puberty	10.3		1.3	4.9				

*Isolated gonadotropin insufficiency and hypopituitarism with hypogonadism.

normal or low LH and FSH indicates a hypothalamic-pituitary defect. As is true for other hormone assessment using competitive protein-binding assays, perturbation of the control system must be performed to gain further information. In 1967 we³² first reported that Clomid* increased serum LH in normal men, and since then we have used Clomid to assist in evaluation of gonadal states in both sexes. A dose of 50 mg of Clomid every 8 hr per day for 5 to 7 days causes progressive small increases in LH and FSH. Figure 8 depicts the mean and standard error of response of normal subjects to clomiphene administration. If samples are measured daily, this test may serve as a functional test of hypothalamic-pituitary function in patients with an equivocal diagnosis and normal or low LH and FSH concentrations. In patients with hypothalamic-pituitary dysfunction,³³ Clomid does not cause an increase in serum LH or FSH. It is not useful nor needed to diagnose hypergonadotropic states (normal menopause or castration in either sex). When administered to women this drug may mimic the early follicular-phase FSH increase and initiate follicle growth to start the sequence of ovarian events which result in ovulation, corpus luteum growth, and, some 28 days later, menses. Although the same LH and FSH rise occurs during drug administration in men, no ovary or appropriately responsive hypothalamus exists to result in the multiple resultant events observed in women.

In summary, based on a single LH and FSH determination, it is commonly not possible to accurately assign the correct gonadal status, and multiple independent determination of serial samples from the same individual increases accuracy in hypogonadotropic states. If clinical judgment is also utilized, this is not necessary. Ryan et al.³⁴ have recently published data similar to those reported herein concerning clinical use of LH and FSH assays.

The principles that emerge from discussion of the clinical use of LH and FSH assays are applicable to almost every hormone measurement system. Each of the

*Clomid (clomiphene citrate), trade name of the Wm. S. Merrell Company, Cincinnati, Ohio.

Fig. 8 Mean serum LH in eight men during 3 control days and 7 treatment days with 50 mg of clomiphene three times daily. The dark line indicates the mean and the shaded area the SEM.

hormones with perhaps the single exception of the thyronines (thyroxine and triiodothyronine) has greatly varying blood concentrations. Usually, but not always, multiple blood samples and perturbations tests are required. Reflect that the adult patient with the onset of diabetes may not be differentiated from normals on the basis of single insulin determinations,³⁵ that a growth hormone (GH) in a child may not be differentiated from that of a normal adult on the basis of a single determination,³⁶ of serum growth hormone that men with gynecomastia may not be distinguished from normal men on the basis of an estradiol determination,³⁷ and that hirsute women may not be separated from normal women on the basis of a single testosterone determination.³⁸ In each of these and many other circumstances, the physician using the assay must be familiar with details of endocrine physiology and pathophysiology pertaining to the particular glandular system. Obviously it is not possible to indicate all the information required to use each assay appropriately for a given clinical purpose in a brief discussion such as this. The following general guidelines may be offered:

1. Be intimately aware of the reliable historical and physical findings which should be present in a particular endocrine disorder.
2. Understand the normal physiology of that particular hormonal system.
3. Understand the various perturbation or functional tests available and choose those appropriate for diagnosis.

4. Perform this test under carefully controlled conditions and send samples to a reliable laboratory with known quality controls.

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IN VITRO TESTS OF THYROID FUNCTION: PRINCIPLES OF USE

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ABSTRACT

Principles that serve as a basis for the use of in vitro thyroid-function tests are discussed. Emphasis is placed on the limitations of the many procedures now available. Newer tests are compared with the serum-protein-bound iodine that serves as a prototype. The indications, advantages, and limitations of triiodothyronine (T_3) resin uptake, butanol-extractable iodine, thyroxine-by-column chromatography, and thyroxine by competitive binding measurements are reviewed. Physicians may find the serum-free thyroxine concentration of value in estimating the thyroid function. As a result of the newly discovered importance of T_3 in health and disease, clinicians require that some measure of serum concentration of this hormone be available. Problems in nomenclature of the broad variety of tests hopefully will be reduced or eliminated by current efforts toward standardization of both names and abbreviations.

Physicians today have at their disposal a broad array of laboratory procedures to facilitate the diagnosis of thyroid dysfunction. Although these tests provide opportunities to rather precisely define thyroid disease, the measurements obtained, by nature of their number and variety, may bring about more confusion than help to the busy practitioner who has not understood their limitations. Some principles in the uses of these tests will be discussed, with particular emphasis on the value of each in diagnosis. (Hyperthyroidism and hypothyroidism are the clinical states to be detected, but in this discussion they will be used along with euthyroidism as reference points.)

ESTIMATIONS OF TOTAL OR BOUND T_4 IN SERUM

The serum-protein-bound-iodine (PBI) determination, although frequently influenced in spurious ways, has through years of use become a prototype for in vitro tests of thyroid function. In normal sera the PBI consists almost entirely of

thyroxine (T_4), and it is a reasonable estimate of the concentration of this hormone. Because of its limitations in many clinical situations, the PBI is being replaced by newer laboratory measures; however, by examining the factors affecting the PBI (Table 1), one can better appreciate the problems with respect to interpretation of all in vitro thyroid-function tests:

TABLE 1
FACTORS INFLUENCING THE SERUM-PROTEIN-BOUND IODINE

-
A.	Factors that alter the serum T_4 level and consequently the PBI:
1.	Changes in the binding of T_4 by serum proteins.
2.	Administration of thyroid hormone preparations: desiccated thyroid, T_4 , triiodo-
thyronine (T_3), combinations of T_4 and T_3 .
3.	Hyperthyroidism and hypothyroidism.
B.	Factors that interfere with the technique of PBI determination:
1.	Iodine: iodides and iodine compounds.
2.	Heavy metals: gold salts and mercurial diuretics.
-

Changes in the Binding of T_4 by Serum Proteins

Although serum proteins bind nearly all the circulating T_4 , the fraction of the hormone that reaches the tissues is free or unbound. The two fractions of T_4 , free and bound, are in equilibrium, but the former exists at less than 1/1000 the concentration of the latter.

The binding of T_4 is complex and involves three species of proteins. For purposes of explanation, thyroxine-binding globulin (TBG) may be used to represent all the binding proteins. A useful equation is:

$$[T_4] [TBG] = K [T_4 - TBG]$$

where $[T_4]$ = concentration of the free T_4

$[TBG]$ = concentration of protein binding sites not occupied by T_4

K = constant

$[T_4 - TBG]$ = concentration of T_4 bound to protein

In terms of iodine, $[T_4 - TBG]$ equals the PBI. Then the equation may be written:

$$[T_4] [TBG] = K \text{ PBI}$$

If $[T_4]$ is the physiologically active fraction of T_4 , that which controls the metabolism of tissues and plays a central role in the hypothalamus-pituitary-thyroid feedback system, the $[T_4]$ of an euthyroid individual is, by definition,

in the normal range.* One can then predict from the equation that high levels of TBG in the euthyroid subject possessing a normal feedback system will be associated with an elevated PBI (and total T_4), and, conversely, a low TBG will be accompanied by a reduced PBI (and total T_4). However, in both cases the [T_4] and metabolic status of the patient are normal.

When a resin that binds thyroid hormones is added to serum, an equilibrium for T_4 between serum proteins and the resin is established. This equilibrium can be estimated by adding to the mixture a trace quantity of labeled hormone, which is traditionally ^{131}I -labeled T_3 . Although T_4 and T_3 have different binding affinities, each binds to the same sites on resin and proteins. The fraction or percent of total ^{131}I - T_3 bound to resin is determined by counting radioactivity after the serum has been washed from the resin. This is the T_3 resin uptake. With most resins now used, the equilibria established for euthyroid sera result in T_3 resin uptakes that vary about a mean of approximately 30%. The actual uptake value for any given serum may be related to that obtained simultaneously from pooled control serum, and the final result can be expressed as percentage of control. This additional calculation allows expression of a normal range that deviates on either side of 100%; the measurements are thereby more stable from day to day and thus are more accurate.

The T_3 resin uptake percentages correlate well with thyroid function, but they are not estimates of serum T_4 . Rather, the test values are reciprocally related to the number of unoccupied hormone binding sites on the serum proteins. Because the T_3 resin uptake does not measure serum T_4 , under some circumstances results of the former test may be altered differently from those of the latter test.

The T_3 resin uptake is portrayed in various clinical conditions in Fig. 1. As shown in the figure, in hyperthyroidism and hypothyroidism the PBI (and T_4) and T_3 resin uptake values deviate from the normal in the same direction. However, when the binding of thyroid hormones by proteins in serum (TBG concentration) is increased, the serum PBI (and T_4) levels are elevated, as predicted from the preceding equation, but the T_3 resin uptake percentage is low. Although the number of occupied binding sites is then increased, the number of unoccupied sites is also augmented, and the equilibrium in the T_3 resin uptake is shifted away from the resin (Fig. 1, example 4).

The obverse obtains when the protein binding of hormone in serum is decreased (Fig. 1, example 5): the PBI (and T_4) value is low, and the T_3 resin uptake measurement is high. Although the mechanism is different, the consequence of interference in the protein binding of T_4 by drugs, such as diphenylhydantoin, is, in terms of PBI (and T_4) and T_3 resin uptake results, the same as that from decreased TBG (Fig. 1, example 6).

*As with most rules in biology, this concept is not invariably true. See the discussions under Estimations of Free T_4 in Serum and Estimation of T_3 in Serum.

Fig. 1 Portrayals of T_3 resin uptake tests in various clinical situations. [From J. C. Sisson, Principles of, and Pitfalls in, Thyroid Function Tests, *J. Nucl. Med.*, 6: 887 (1965).]

TABLE 2
SITUATIONS IN WHICH THE BINDING OF
THYROXINE BY SERUM PROTEINS IS ALTERED

A. Increased binding	
1.	Pregnancy. ¹
2.	Estrogen therapy. ^{1,2}
3.	Hepatitis. ¹
4.	Inherited (sex-linked recessive). ³
B. Decreased binding	
1.	Androgen or anabolic hormone therapies. ^{1,4}
2.	Nephrosis (urine loss of protein). ¹
3.	Late cirrhosis (underproduction of protein).
4.	Inherited (sex-linked recessive). ⁵
C. Interference with binding (effectively decreased binding)	
1.	Diphenylhydantoin therapy. ⁶
2.	Salicylate therapy (mild effect). ⁷

Table 2 lists the commonly encountered conditions leading to increased and decreased binding of thyroid hormones by serum proteins. The production of the major binding protein appears to be controlled by a sex-linked gene, and familial increases and decreases in this protein are much more striking in the man than in the heterozygous woman.^{3,5} Although abnormal TBG concentrations distort the results of the in vitro thyroid-function tests previously discussed, such alterations in serum proteins, in themselves, do not cause disease.

The PBI (and T_4) and T_3 resin uptake values that result from changes in the binding proteins diverge from normal in opposite directions with approximately the same magnitude. Because the alterations are opposing and nearly equal for euthyroid individuals, the product (PBI or $T_4 \times T_3$ resin uptake) will be stable in spite of wide variations in the serum proteins.

In a number of laboratories, this binding product has been found a useful gauge of thyroid function when interpretation of the result from an individual test was difficult or impossible. Use of this concept is demonstrated for two periods of pregnancy in Table 3.

TABLE 3*
EFFECT OF PREGNANCY ON THE PBI, T_3 TEST, AND PBI $\times$ T_3 PRODUCT

Test	Control			Pregnant (13 weeks) [†]			Pregnant (30 weeks) [‡]		
	Mean	±SD	Range	Mean	±SD	Range	Mean	±SD	Range
Age, years	24.8		19-39	23.7		17-30	23.9		17-30
PBI, μ g/100 ml	6.0	1.3	3.6-8.8	8.4†	1.8	4.7-11.4	10.5†	1.8	7.8-13.4
T_3 test (fraction of pooled serum value)	0.94	0.08	0.81-1.09	0.78‡	0.09	0.67-0.95	0.59†	0.04	0.54-0.64
PBI $\times$ T_3 product	5.58	1.11	3.92-7.66	6.42	1.14	3.7-8.00	6.22	1.11	4.52-8.58

*From J. C. Sisson et al., Serum Protein-Bound Iodine and Resin Uptake of Triiodothyronine During Normal Pregnancy, *Mich. Med. Cent. J.*, 33: 231 (1967).

†Differs from control by student "t" test: $P < 0.001$.

‡Differs from control by student "t" test: $P < 0.01$.

Administration of Thyroid Hormones

The normal human thyroid gland secretes both T_4 and T_3 . Because the latter has so little affinity for serum proteins in vivo, the PBI value reflects virtually only the T_4 concentration. (For further discussion of the physiologic principles involved in the secretion of T_4 and T_3 , see the section on the Estimation of T_3 in Serum). Administration of thyroid hormones will result in one of three general types of changes in serum hormones: (1) in patients with myxedema, the administered hormone(s) will be the only hormones in serum, although some conversion of T_4 to T_3 outside the thyroid gland may occur (see below); (2) in euthyroidism, with increasing doses of exogenous hormones, endogenous hormonogenesis is progressively suppressed until at maintenance quantities serum hormone(s) are almost entirely derived from the medication; and (3) in hyperthyroidism or in euthyroid patients with unsuppressible thyroid function, exogenous and endogenous hormones are additive in the serum. No attention will be given here to the third condition.*

*Suppressibility of the thyroid function is probably best evaluated by using the thyroidal radioiodine uptake as the parameter.

Because T_3 is poorly bound to serum proteins and exists in serum in low quantities relative to T_4 , therapy with the former hormone is associated with a decline in PBI and T_4 to very low levels. Conversely, thyroxine treatment is associated with a rise in PBI and T_4 values since the normally secreted T_3 component of serum hormones is absent. Therapies with combinations of T_4 and T_3 , including that in desiccated thyroid, will produce physiologic PBI and T_4 values. A summary of anticipated results in PBI from various regimens is given in Table 4. Changes in the T_3 resin uptake after the administration of hormones have not been so completely evaluated and appear to be more capricious than those in the PBI measurement.¹¹

TABLE 4
EFFECTS ON THE SERUM PBI OR T_4 VALUES OF
PREPARATIONS OF THYROID HORMONES ADMINISTERED
IN MAINTENANCE DOSAGE TO HYPOTHYROID OR
EUTHYROID SUBJECTS

Hormone preparation	Daily dosage, mg	PBI or T_4 values	References
Desiccated thyroid	180	Normal	8
L-thyroxine	0.3	High normal	8
L-triiodothyronine	0.075	to high	
		Very low, close to zero	9
Combinations			
Euthroid (Warner-Chilcott)			
L-thyroxine	0.18		
L-triiodothyronine	0.05	Normal	16
Thyrolar (Armour)			
L-thyroxine	0.15		
L-triiodothyronine	0.0375	Normal	

Although clinical situations may be suggested from the PBI or T_4 concentrations, the determination of the patient's status requires a careful history and physical examination. In this regard it should be noted that quantities of T_4 and T_3 contained in the maintenance dose (recommended by the manufacturer) of Euthroid* are more than half the established human requirements of each component. Although the PBI resulting from this dose of Euthroid is in the normal range,¹⁰ the amount of hormones may be excessive for some patients.

* (liotrix) Warner-Chilcott.

Technical Interferences in the Determination of PBI

Iodine, in the forms of iodides and iodine compounds, is ubiquitous in a hospital setting and elsewhere. Spuriously high PBI measurements quickly follow the administration of iodine-containing materials. Mercury, usually given in the form of a diuretic, and gold, injected as salts for the treatment of rheumatoid arthritis, interfere with the color reaction for iodine in the analysis of the PBI, resulting in falsely low values. After the injection of gold salts, the PBI value for a patient was near zero for at least 44 days.^{1,2}

Over the years many efforts have been directed toward eliminating these artifacts that distort the otherwise valid PBI measurement. Although affected by neither iodine nor heavy metals, the T_3 resin uptake does not measure serum hormone, and, for the preceding reasons, it is frequently necessary to have both a T_3 resin uptake value and a serum T_4 estimation.

Determinations in serum of butanol-extractable iodine or T_4 by column chromatography give answers that are free of some of the artifacts found in measuring the PBI, but some iodine compounds, especially the cholecystographic contrast media, also vitiate these newer estimates of serum T_4 .

More recently, serum T_4 has been determined by competitive binding analysis. Since the final assay in this test does not depend on a color reaction for iodine, interferences from the presence of iodine or heavy metals are absent. Competitive binding analysis makes use of the principles involved on the T_3 resin uptake; as the T_4 concentration is increased in this analytic system, the resin uptake predictably rises. Since the capacity of the resin to bind T_4 far exceeds that of the serum proteins, additions of T_4 to the mixture shift the equilibrium toward the resin. Thus a control (normal) serum or binding protein solution, a resin, and a radiolabeled hormone indicator (usually $^{125}\text{I}-T_4$) are incubated together as a basic system. The subsequent percentage of radioactive hormone taken up by the resin is measured.

A dose-response curve is inscribed by adding known quantities of T_4 to the basic system (Fig. 2). Thyroxine is extracted from a volume of the patient's serum and added as an unknown to the basic system; the resulting resin uptake is related to the established dose-response curve to give the quantity of T_4 in the aliquot of serum.

Alcoholic extractions of T_4 from serum proteins have been incomplete because they have required a tedious evaporation step that was frequently difficult for technicians to reproduce. However, with practice and the use of a recovery factor, results have been satisfactory. Improvements in the efficiency and ease of T_4 extraction from serum have been reported when an alkaline pH and a resin column were used.^{1,3}

In many institutions competitive binding analysis, which is specific for thyroxine and unaffected by the presence of iodine or heavy metals, is replacing all other procedures for estimating this serum hormone. The values obtained by this method can be used in conjunction with T_3 resin uptake percentages

obtained from the same serum to evaluate thyroid function in the presence of increases and decreases in the binding of serum proteins.¹⁴

Recently, serum T_4 was measured by a radioimmunoassay. After injections of thyroglobulin into rabbits, proteins that specifically bind T_4 were produced which gave the essential binding ingredient for such an assay.¹⁵ A radioimmuno-

Fig. 2 Scheme of dose-response curve for measuring thyroxine by competitive binding analysis. Thyroxine extracted from a patient's serum could be added as unknown to the basic analytic system and the quantity determined by relating the resulting resin uptake to the dose-response curve. [From J. C. Sisson, *The Use of In Vitro Tests of Thyroid Function*, *Laboratory Scope*, 3: 10 (1970).]

assay will not likely be more specific than competitive binding analysis for T_4 , but with further use it is possible that the former may become a more convenient and/or precise test than the latter.

ESTIMATIONS OF FREE T_4 IN SERUM

In theory, the small free or unbound fraction of circulating T_4 acts on tissues and determines the metabolic state of the individual. Although generally correct, this theory is too simple, and many factors play a role in the cell-hormone interaction. However, the free T_4 concentration is an important and possibly a major determinant of hormone effects. One might anticipate,

then, that the measurement of this minute fraction of serum T_4 would provide the best index of an individual's thyroidal status.

Unfortunately, free T_4 in serum is difficult to determine, and the usual case of thyroid dysfunction is more accurately defined by estimating the total T_4 in serum by competitive binding analysis. Further, the free T_4 concentration is increased in circumstances unrelated to thyroid function. During acute illness or after trauma, the equilibria between free and bound serum hormone are altered. Particularly confusing is the rise in serum concentration of free T_4 in patients who are ill since during sickness the physician most needs laboratory help for diagnosis.

However, free T_4 concentrations rarely exceed twice the upper normal range as a consequence of nonthyroidal illness, whereas values much greater than this are frequently recorded for hyperthyroid patients.^{16,17} When multiple factors may be operating on the binding of T_4 to serum proteins and where it is difficult to be certain of the net effect even by using the diagnostic adjuncts already described, the determination of free thyroxine concentration may be helpful, especially in identifying hyperthyroidism. The validity of this concept has been demonstrated in patients with cirrhosis of the liver, where production of binding proteins, estrogen effects, poor nutrition, and other variables may act to distort T_3 resin uptakes and serum T_4 assays.¹⁸ Of course, measurement of free T_4 concentrations will continue to be important in investigations of physiologic and pathologic hormone economies.

ESTIMATION OF T_3 IN SERUM

The structure of T_4 was first reported in 1926, but another 25 years were required before the second thyroid hormone, T_3 , was detected in human serum. Although second in discovery, T_3 is by no means second in physiologic importance.

Because serum concentrations of T_3 are so low, reliable assays were not developed until the past few years. Knowledge of T_3 synthesis and metabolism, therefore, has been limited compared with that of T_4 . Several concepts now seem clear: (1) T_3 contains one less iodine atom than T_4 ; (2) in effects on tissues, T_3 is three to four times more potent than T_4 per unit of weight; (3) T_3 is poorly bound to serum proteins so that not only is the serum concentration relatively low, but (4) T_3 is metabolized in peripheral tissues more rapidly than T_4 .

Other concepts are still evolving: Depending on the type of assay used, the mean serum T_3 level may be as low as 98 ng/100 ml (Ref. 19) or as high as 450 ng/100 ml (Ref. 20), giving T_3/T_4 ratios of 1/30 to 1/60. Approximately 31% of serum T_3 arises from extrathyroidal deiodination of T_4 (Refs. 21 and 22). It is as yet uncertain whether T_4 acts directly on tissues or requires conversion to T_3 for effect; the normal rate of T_3 secretion by the human thyroid is, using the

minimum estimate, one-fourth that of T_4 , which gives the four-times-more-potent T_3 at least equal physiologic importance.¹⁹

Most disturbances of thyroid function affect the secretions of T_3 and T_4 about equally, and in these circumstances estimates of serum T_4 suffice for diagnostic purposes. Occasionally, the ratio of serum T_3 to T_4 is abnormal, and the relation of serum T_4 concentration, which does not measure serum T_3 , to clinical status is invalid.

The detection of deviant T_3/T_4 ratios in serum requires an accurate measurement of T_3 as well as of T_4 . Although technically difficult to perform, various types of serum T_3 assays have been reported: (a) gas chromatographic identification and quantification (a method never fully described²⁰), (b) separation of T_3 from T_4 by column¹⁹ or paper²³ chromatography and subsequent measurement of the former hormone by competitive binding analysis, and (c) radioimmunoassay using T_3 binding antibodies from rabbits that have been immunized in various ways. Refinements in the last two techniques make them the most promising for future use as routine clinical procedures.

TABLE 5

SITUATIONS ASSOCIATED WITH CHANGES IN THE SERUM T_3/T_4 RATIO

-
- A. Increased T_3/T_4 ²⁵⁻²⁷
1. Hyperthyroidism present (T_3 thyrotoxicosis), PBI or T_4 value normal or low:
 - a. Graves' disease.
 - b. Toxic adenoma.
 - c. Administration of large quantities of T_3 .
 2. Euthyroidism present (normal to elevated serum T_3 levels)^{23,27}
 - a. Spontaneous.
 - b. After therapy for hyperthyroidism.
 - c. Iodine deficiency (especially endemic goiter areas).
 - d. Administration of maintenance quantities of T_3 .
- B. Decreased T_3/T_4
1. Administration of T_4 (although some T_4 is converted to T_3 , the serum ratio is relatively low).
 2. Spontaneous (none known).
-

After noting the first four concepts of T_3 and T_4 metabolism recorded above, it is easy to visualize that increased production of T_3 relative to T_4 during iodine deprivation would have a teleologic basis. A rise in T_3/T_4 may be in response to increased thyrotropin stimulation of thyroid tissue. However, other explanations of abnormal T_3/T_4 secretions by the thyroid gland are lacking. Situations in which abnormal serum T_3/T_4 ratios are encountered are listed in Table 5. The frequency of the various disorders of T_3/T_4 secretion, although probably low, cannot be determined at this time since the use of T_3 assays is not widespread. It seems clear that estimates of serum T_3 , if not developed as screening procedures, will become indispensable adjuncts to the already available laboratory aids in the measurement of thyroid function.

It is well to remember that the diagnosis of hyperthyroidism should be made primarily in clinical grounds; laboratory tests should provide confirmatory evidence. For hyperthyroidism related to excessive secretion of T_3 but not T_4 (T_3 thyrotoxicosis), confirmation is difficult to obtain in the laboratory. By definition the serum PBI and T_4 levels are normal or low, and the T_3 resin uptake may also be normal. Thyroidal uptakes of ^{131}I may be elevated but, in some cases, may be within the normal range. However, all patients with this type of hyperthyroidism have manifested unsuppressible thyroid function when thyroid hormones are given. Demonstration of an abnormal suppression is almost a *sine qua non* to the recognition of this disorder. Finally, the serum T_3 concentration must be elevated to verify the diagnosis, but high values of T_3 in themselves are insufficient evidence of hyperthyroidism. If T_4 for some reason is absent in a patient and normal metabolism is maintained by T_3 , the serum levels of the latter would be abnormally high in compensation for the lack of the former hormone. The precise concentration of serum T_3 relative to any given quantity of serum T_4 that will be associated with clinical hyperthyroidism is unknown. Thus the presence of hyperthyroidism should be established on clinical grounds and the laboratory tests used as corroborative data and to elucidate the mechanisms.

ASSAY OF SERUM T_4

A consequence of primary hypothyroidism is a rise in the concentration of thyroid-stimulating hormone (TSH) in the serum. The radioimmunoassay of serum TSH is now quite precise for elevated serum levels, and measurements of this hormone are possibly the most sensitive laboratory indicators of primary failure of thyroid hormonogenesis.²⁸ It remains to be seen whether the assay of TSH, which is one step further removed from the clinical state than are determinations of serum thyroid hormones, will become the test for routine confirmation of primary hypothyroidism. In any event serum TSH values will be indispensable aids for the separation of patients with primary and secondary (pituitary) hypothyroidism. Combined with the injection of the newly discovered thyrotropin releasing hormone, estimates of serum TSH will be helpful in localizing pituitary and hypothalamic lesions.²⁹

Although subnormal levels of TSH cannot yet be detected accurately, in the future the range of the radioimmunoassay may be extended. With such an improvement one could evaluate the efficacy of thyroid-hormone administration in suppressing TSH secretion for the management of goiter or thyroid cancer.

NOMENCLATURE

Currently used names and abbreviations of the wide variety of tests for thyroid hormones in serum confuse and dismay even experts in thyroidology. A

committee appointed by the American Thyroid Association is proposing a standard nomenclature for such tests. The nomenclature will divide the tests for serum hormones into three groups: (1) those which measure, in final analysis, iodine concentration; (2) those which measure the concentration of serum hormones by other methods; and (3) those which estimate the inverse of unoccupied T_4 binding sites in serum proteins. The abbreviations suggested will not only be unique for each test but also descriptive of the procedure used. Hopefully these efforts will both clarify terminology and prod physicians to ponder the potential and the limitations of tests they order to help diagnose thyroid dysfunction.

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SOME NEW ISOTOPIC PROCEDURES AND TECHNIQUES FOR ENDOCRINE DIAGNOSIS

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ABSTRACT

Data are presented on ^{131}I -19-iodocholesterol in the diagnosis of adrenal disease in 27 patients, using an Anger camera and/or a rectilinear scanner. This method gives a great deal of information on the functional state of the adrenals and the actual diagnosis of many adrenal diseases. It is less difficult to use as a screening procedure than the usual hormonal work-up. It is the only method for direct visualization in patients with a hyperfunctioning remnant after one or more adrenalectomies for Cushing's syndrome, in the presence of a known sensitivity to contrast media, and when the venography fails to visualize the adrenal. The venogram at present can image primary aldosterone-secreting tumors as small as 5 mm in diameter, and the Anger camera cannot image tumors discretely less than 2 cm in diameter.

Almost all diagnostic scanning procedures are dependent on the lesion not concentrating radioactivity as well as normal tissue. Brain scanning is the principal exception to this statement. Even here, however, the diagnostic concentration of radionuclide is not significantly above that found in normal tissues other than the brain.

Ten years ago we formalized a program to develop radio-labeled medicinals that would concentrate diagnostically and therapeutically in organs and in cancers of these organs. We have also attempted to develop radiation-detection and -measurement instrumentation to detect cancer primaries or metastases as small as 2 mm in diameter at a depth of 10 cm in the tissue. Recently these two efforts have come to fruition in the ^{125}I -chloroquine analog in the diagnosis of melanomas¹⁻⁴ and ^{131}I -19-iodocholesterol in the diagnosis of adrenal disease.⁵⁻¹¹

In this paper we will present a comparison of isotope procedures in relation to other diagnostic measures in the diagnosis of adrenal disease.

Cholesterol is the principal precursor of adrenocortical steroids. The total cholesterol content of dog and human adrenals has been reported as 2 to 6% of the total wet weight. Beierwaltes et al.⁵ gave ^{14}C -cholesterol to dogs and demonstrated that the percent of it taken up by the adrenal cortex of the dog was similar to the percent of ^{131}I (as Na^{131}I) taken up by the thyroid of the human being. Counsell et al.⁶ demonstrated that ^{125}I -19-iodocholesterol could be synthesized with satisfactory specific concentration and stability. Blair et al.⁷ demonstrated that ^{125}I -19-iodocholesterol concentrated in the dog adrenal almost as well as ^{14}C -cholesterol.

The ^{125}I -19-iodocholesterol disappeared more rapidly from the liver than from the adrenal glands, resulting in adrenal/liver radioactivity concentration ratios of 168 in ACTH-treated animals 6 to 8 days after administration of the tracer dose. The uptake of the radioiodocholesterol in the dog adrenal gland was sufficient for visualization with the scanner and the gamma camera.

The successful imaging of the adrenal in a patient with Cushing's syndrome⁸ as well as in patients with normal adrenal function^{9,10} and in primary aldosteronism¹¹ has been reported.

The diagnostic efficacy of the procedure has now been studied in 27 patients.

METHODS

Iodine-131-19-iodocholesterol was administered intravenously to 27 patients in doses of 650 to 2000 μCi (0.75 to 30 mg) as previously described.⁹ Imaging of the adrenals was usually attempted at 3 to 10 days with an Anger camera and a 5 in. crystal photoscanner.⁹ A percent uptake of the administered dose in the adrenals was determined in 37 patients, using our previously published method.¹⁰

In addition, a new technique of "progressive background erase" was used to develop criteria for diagnosing primary aldosterone-secreting tumors. A series of pictures from the cathode-ray-tube display of a 64 by 64 matrix of a 4096-channel analyzer was taken by raising the "Z-level threshold" to obliterate the areas of lower counting rate so that only one matrix point remained visible over the adrenal with the lower counting rate.

RESULTS

Patients Without Adrenal Disease

As shown in Table 1, the adrenal glands were visualized in seven patients with no adrenocortical disease, and the uptake ranged from 0.10 to 0.28%.

TABLE 1
SUMMARY OF ^{131}I -IODOCHOLESTEROL SCANS (AUG. 17, 1971)

Condition	No. of patients	Condition	No. of patients
Normals	7	Virilizing syndrome	2
Cushing's syndrome	10	Stein-Leventhal syndrome (1)	
ACTH excess (3)		Adrenocortical carcinoma (1)	
Remnants (4)		(producing testosterone)	
Adrenocortical carcinoma (2)		Adrenal medullary tumors	2
Adenoma (1)		Neuroblastoma (1)	
Hypoadrenalism	1	Pheochromocytoma (1)	
Hypopituitarism (1)		Aldosteronism	5
[secondary to pituitary adenoma		Tumors (4)	
(on hydrocortisone)]		Nodular hyperplasia (1)	

Patient No. 1, a 36-year-old woman, underwent left radical nephrectomy for carcinoma of the left kidney. Only the right adrenal gland was visualized after radioiodocholesterol had been administered intravenously (Fig. 1).

Patient No. 2, a 50-year-old man, had carcinoma of a congenitally single right kidney. A simple right nephrectomy was performed, and, because he was to be placed on a hemodialysis program in preparation for a kidney transplant and would not be able to excrete much of the labeled material, a reduced dose of 750 μCi of radioiodocholesterol was administered. Four days later both adrenal glands were visualized with the gamma camera. Figure 2 shows the adrenals in their expected location. Radioactivity in the lower left portion of the picture is in the colon.

CUSHING'S SYNDROME

ACTH Excess

Table 1 shows that of 10 patients with Cushing's syndrome, both adrenals imaged readily in all 3 patients whose disease was due to excess of adrenocorticotrophic hormone (ACTH). The total uptake for both adrenals ranged from 0.57 to 1.18%.

Patient No. 3 had a 10-year history of Cushing's syndrome, and laboratory studies strongly suggested autonomous oversecretion of pituitary ACTH as its cause. Confirmation of this diagnosis was attempted with bilateral retrograde venography; however, a normal-size adrenal was demonstrated on the right side only. The left adrenal venogram was unsuccessful, and after the procedure the patient had flank and abdominal pains and hematuria. Figure 3 shows a posterior rectilinear photoscan of the patient's adrenal area performed 3 days after

Fig. 1 Scan of a 36-year-old woman (patient No. 1) after a left radical nephrectomy for carcinoma of the left kidney. Only the right adrenal is visualized.

Fig. 2 Scan of a 50-year-old man (patient No. 2) 4 days after a tracer dose of ^{131}I -19-iodocholesterol and 5 days after a simple right nephrectomy for a carcinomatous congenitally single right kidney. Both adrenals image normally.

Fig. 3 Posterior view of adrenal area of patient No. 3 with rectilinear photoscan; scan showing kidney localization superimposed.

Fig. 4 Posterior view of adrenal area, patient No. 4: (a) Anger-camera scintiphoto. (b) Polaroid picture taken from multichannel analyzer cathode-ray-tube display.

administration of a dose of 2000 μCi (30 mg) of radioiodocholesterol. Without moving the patient kidney localization was performed with ^{197}Hg -chlormerodrin and the outline of each kidney transferred to the adrenal scan to show the anatomic relation of the adrenals to the kidneys. The diagnosis of Cushing's syndrome from ACTH excess was thus confirmed by demonstrating that both adrenal glands were of approximately equal size and that each concentrated the radioactivity equally well. The patient then received X-ray therapy to the pituitary gland.

Patient No. 4 was a 65-year-old woman who also had Cushing's syndrome secondary to ACTH excess. Figure 4(a) is a gamma-camera picture of the adrenals; Fig. 4(b) is the Polaroid picture of the same area obtained from the cathode-ray-tube display.

Fig. 5 Rectilinear photoscan of right adrenal remnant in patient No. 5 with ^{131}I -Hippuran kidney localization superimposed. The dark areas medial and lateral to the upper pole of the right kidney are film marks from the two superimposed scans.

Adrenal Remnants

Four patients with persistent steroid excess after bilateral total adrenalectomy were shown to have adrenal remnants on the right side only. The percent uptake ranged from 0.52 to 0.62.

Patient No. 5 was a 44-year-old woman with a 20-year history of persistent Cushing's syndrome after bilateral subtotal adrenalectomy, total adrenalectomy, and pituitary irradiation. She was explored bilaterally for adrenal remnant tissue without success and was being treated with *o,p'*-DDD [1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)-ethane] when the dose of radioiodocholesterol was administered. Within 48 hr after administration of 2000 μCi (1.8 mg) of radioiodocholesterol, an area of markedly increased radioactivity concentration was noted in the region of the right adrenal. With a combined adrenal scan and kidney localization study, Fig. 5 shows the area of increased radioactivity concentration to be located above the upper pole of the right kidney.

Adrenocortical Carcinoma

Two patients with adrenocortical carcinoma demonstrated no visualization of the involved adrenal and showed suppression of the contralateral gland.

Adrenocortical Adenoma

A right adrenal adenoma was correctly imaged in one patient with Cushing's syndrome. Patient No. 6 was an 18-year-old girl with a 2-year history of

Cushing's syndrome. She was referred to the University of Michigan Medical Center for retrograde venography to confirm the presence of an adrenal cortical tumor. Bilateral retrograde venography [Figs. 6(a) and (b)] demonstrated a tumor on the right adrenal gland and a small atrophic left adrenal gland. She received 1870 μCi (4 mg) of radioiodocholesterol. Figures 6(c) and (d) show a single area of increased radioactivity concentration in the right adrenal area. On a rectilinear scan performed with a 3-in.-focus, $\frac{1}{4}$ -in.-resolution, high-energy collimator, the area measured 3.5 by 3.0 cm. There was no indication of radioactivity being concentrated in the region of the left adrenal, a result compatible with functional suppression of that gland. At surgery an adrenal adenoma was removed from the right gland which measured 3.5 by 3.0 by 2.7 cm and weighed 12.6 g. The uptake in vivo was 1.2% at 8 days and 1.6% in the excised adenoma at 10 days.

All patients with Cushing's syndrome not due to adrenocortical carcinoma showed a higher uptake (0.52 to 1.2%) than patients without adrenal disease (0.10 to 0.28%) (see Fig. 7).

Hypoadrenocortical Activity

No uptake was found in the adrenals of the patient with hypopituitarism on hydrocortisone medication.

VIRILIZATION

The percent uptake was in the normal range in two patients with virilization; both adrenals visualized normally in the one with Stein-Leventhal syndrome, whereas only the normal adrenal visualized in the one with an adrenocortical carcinoma producing testosterone.

ADRENAL MEDULLARY DISEASE

Neuroblastoma

Patient No. 7 had a mass in the mediastinum which was discovered at the age of $3\frac{1}{2}$ months. This was removed and reported to be a neuroblastoma. Calcifications were observed in the area of the right adrenal. Figure 8(a) shows the gamma-camera scintiphoto of the liver and adrenal area from the posterior view after 1000 μCi (2 mg) of radioiodocholesterol. Increased radioactivity appears in the region of the left adrenal, but no discernible adrenal concentration appears on the right. The image was obtained at the relatively early interval of 72 hr after administration of the dose, and radioactivity is seen in the liver at this time. Although this radioactivity concentrated in the liver might obscure somewhat the adrenal on the right side, it would not completely prevent the recognition of one that had normal uptake of the labeled material. Here none

Fig. 6 Adrenal venogram of patient No. 6 showing (a) tumor on right adrenal gland and (b) atrophic left adrenal gland. Rectilinear photoscan showing adenoma of right adrenal gland (c) 3 days and (d) 9 days after dose. L-1, lumbar-1. [Parts c and d are from L. M. Lieberman, W. H. Beierwaltes, A. N. Ansari, and H. Nishiyami, Visualization of Human Adrenal Glands with ^{131}I -19-Iodocholesterol in the Diagnosis of Adrenal Disease, *New Engl. J. Med.*, 285: 1390 (December 1971).

was seen. Normally the radioactivity disappears from the liver with time, leaving any uptake in the right adrenal gland clearly defined. In this patient surgery was performed within a few hours of the imaging, and an atrophic right adrenal gland was resected which was described as containing calcium. The normal architecture was disrupted, but no neuroblastoma tissue was found.

At 10 days after the dose and 7 days after surgery, the left adrenal radioactivity is even more apparent [Fig. 8(b)]. At this time the radioactivity concentrated in the liver has decreased markedly.

Patient No. 8 was a 43-year-old man with a 12-year history of hypertension. Preoperative imaging of the adrenals after the administration of radioiodocholesterol revealed that only the right adrenal concentrated the radioactivity

Fig. 7 Graph showing percent uptake of ^{131}I -19-iodocholesterol on the ordinate and time (in days) on the abscissa in 10 patients. The range of uptake in all patients with Cushing's syndrome is above the range of uptake in all patients without adrenal disease.

(see Fig. 9). At operation a pheochromocytoma that was 7.5 by 5 by 5 cm was resected from the left side. The tumor had compressed the normal adrenal cortex to a 1- to 2-mm rim.

PRIMARY ALDOSTERONISM

Of the five patients with clinical and laboratory evidence of primary aldosteronism, four had both radioiodocholesterol and venography localizing procedures and all were found to have tumors at operation. Both techniques correctly indicated the size of the lesion. The fifth patient had no venogram because of sensitivity to contrast media. She had bilateral, nodular adrenocortical hyperplasia.

All the tumor patients were demonstrated to have the hypokalemic form of primary aldosteronism with low plasma-renin activity and high aldosterone excretion. The one with bilateral hyperplasia was normokalemic.

We present here two patients, one with a large, easily imaged tumor and one with two tumors 1 cm or less in diameter.

Patient No. 9 had hypertension for 3 years with systolic pressures from 165 to 170 and diastolic from 104 to 120. Figure 10(a) shows his venogram, positive for a 22-mm tumor in the superior pole of the left adrenal cortex. Figure 10(c)

Fig. 8 Anger-camera scintiphoto of posterior liver and adrenal area in patient No. 7 showing left adrenal and liver activity (a) at 72 hr after 1000 μ Ci (2 mg) of radioiodocholesterol and (b) at 10 days after the dose and 7 days after right adrenal-gland resection. Liver concentration markedly decreased.

Fig. 9 (a) Anger-camera scintiphoto and (b) cathode-ray-tube display showing imaging of right adrenal only in a patient with a pheochromocytoma in the left adrenal measuring 7.5 by 5 by 5 cm (patient No. 8). Extraneous shadows produced by radioactivity in bowel.

shows an image positive for a tumor of approximately 2 cm in diameter in the superior pole of the left adrenal cortex. The percent uptake on the left was 0.18, and on the right, 0.10. The progressive background-erase showed 17 matrix points persisting on the left and only 1 persisting on the right. At surgery a 2-cm-diameter tumor was found in the expected location. The radioactivity assay was 0.45 μ Ci/g in the tumor and 0.58 μ Ci/g in the left adrenal.

Patient No. 10 was a 54-year-old man with an 18-year history of hypertension. His systolic blood pressure had ranged from 170 to 180, his diastolic, from 115 to 170. Figure 11(a) shows an adrenal venogram positive on

the left for one 6-mm tumor, one 10-mm tumor, and possibly another 6- to 8-mm lesion. The radiologic diagnosis was "probably tumor on left." The scan, shown in Fig. 11(b), was positive on the left in that it showed a zone of increased radioactivity, but the discrete tumor was not visualized. At 9 days the percent uptake on the left was 0.21, and on the right, 0.15. Progressive background erase showed six matrix spots on the left to one on the right.

At surgery a 5-mm tumor was found in the upper left and a 10-mm tumor in the left midportion. The radioassay showed 0.29% of the dose per gram in tumor No. 1, 0.49% in tumor No. 2, 0.2% in the uninvolved adrenal on that side, and 0.002% in deep muscle.

PROGRESSIVE BACKGROUND ERASE

Table 2 summarizes the scan, percent uptake (difference between the two adrenals), and progressive-background-erase (PBE) results in five patients with proved primary or idiopathic aldosteronism. In all tumor cases the scan identified the adrenal that was the site of excessive aldosterone production. The PBE values in the tumor cases appear as more definitive than the differences in percent uptake by the two glands.

TABLE 2
SCAN, PERCENT UPTAKE (DIFFERENCE), AND PBE

Aldosteronism	Scan	Difference in percent uptake	PBE
4 tumors	+ 4/4	0.10 (0.06 to 0.16)	31.5:1*
1 nodular hyperplasia	+	0.07	4:1

*Individual values are 17:1, 6:1, 46:1, and 57:1.

RELATION OF IODOCHOLESTEROL SCAN AND PBE TO BIOCHEMICAL DATA AND VENOGRAM

Value of Scan and Percent Uptake Alone as a Screen

The adrenal scan and percent uptake give a good deal of information on the pathologic anatomy and functional state of the adrenals. The advantages of these two procedures are simplicity and absence of morbidity, attributes required in a screening test for adrenal disease.

Our studies⁹ have shown that the whole-body biological half-life for ¹³¹I-19-iodocholesterol is 3.15 days, and the effective half-life, 2.26 days. The total-body absorbed dose from the ¹³¹I is 0.97 rad/mCi, assuming a 110-lb patient.

(a)

(b)

Fig. 10 (a) Venogram showing primary aldosterone tumor in left adrenal gland of patient No. 9. (b) Anger-camera scintiphoto and (c) cathode-ray-tube display showing same-size tumor in the same location as that in part (a). [Part c is from J. W. Conn, W. H. Beierwaltes, L. M. Lieberman, A. N. Ansari, E. L. Cohen, J. J. Bookstein, and K. R. Herwig, Primary Aldosteronism: Preoperative Tumor Visualization by Scintillation Scanning, *J. Clin. Endocrinol. Metab.*, 33: 715 (1971).]

The total absorbed radiation dose to the adrenal and gonads is not yet known.

Relative Value in Primary Aldosterone Tumors

Current techniques for localizing the characteristically small aldosterone-producing tumor are (1) selective adrenal venography and (2) determination of aldosterone concentrations in adrenal venous blood obtained by catheter techniques.¹¹ There are, however, some very practical disadvantages inherent in adrenal venography.¹¹ First, it requires a person highly skilled in the techniques of adrenal catheterization. Second, rupture of tiny medullary vessels in the course of the procedure may lead to morbidity and occasionally to functional loss of that adrenal gland. Although the total of such complications is small, it precludes the use of adrenal venography for screening purposes. Third, about 5% of patients needing venography give a history of alarming reactions during previous intravenous pyelography which contraindicates the procedure.

Determination of aldosterone concentration in adrenal venous blood, although theoretically the best approach, requires the same skill with the catheter as that indicated for adrenal venography.¹¹ The venogram can image primary aldosterone tumors of the adrenal cortex as small as 5 mm in diameter. The inherent resolution of the Anger camera is 1.4 cm, but higher resolution can be obtained with less definition.

A PROSPECTIVE VIEW

We are looking forward to use of our two new image-intensifier cameras.^{12,13} They have an inherent resolution of 16 to 32 line pairs per millimeter. If the new cameras can image tumors as small as 2 mm in diameter, a great stride forward will be made. Recently a collimator that will allow resolution of 2 mm with our image-intensifier camera was developed in our laboratory.

For the time being, when the aldosterone-secreting tumor is <1 cm in diameter, the tumor can be diagnosed by a total uptake of <0.47%, a scan showing one adrenal to be larger than the other, and a PBE of more than five matrix points on one side when only one point remains over the opposite adrenal gland.

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APPENDIX

Dr. Baltaxe has admirably summarized the Radiologic Assessment of Endocrine Glands. It is helpful to remember his point that the assessment is made in three ways: direct radiographic visualization, displacement or alteration of adjacent organs, and evaluation of changes produced elsewhere by the excessive or subnormal output of hormone by the endocrine gland in question.

Clearly, the radiologic assessment of the pathologic anatomy, anatomical relations, and the effect of the hormones in other tissues is much further developed and more complete than the radionuclide assessment. Radionuclides, however, have been of great help in providing knowledge of the pathologic anatomy of the thyroid and the adrenal glands and the function of most endocrine glands.

The principal areas where isotopic methods are used daily are:

Organ	Radionuclide	Efficacy
Pituitary		
Tumor imaging	^{99m}Tc	Poor
Radioimmunoassay of hormones	^{125}I	Excellent
Craniopharyngioma imaging	^{99m}Tc	Good
Hypothalamic tumor imaging	^{99m}Tc	Poor
Thyroid		
Nodular goiter and carcinoma imaging	^{99m}Tc , ^{125}I , ^{131}I	Excellent
Percent uptake	^{125}I , ^{131}I	Excellent
TSH stimulation	^{125}I , ^{131}I	Excellent
TSH suppression	^{125}I , ^{131}I	Excellent
KClO ₄ discharge	^{125}I , ^{131}I	Excellent
Hormonal output		
Murphy-Pattee T ₄	^{125}I , ^{131}I	Excellent
T ₃ resin	^{125}I , ^{131}I	Excellent
Parathyroid		
Imaging	^{75}Se -methionine	Poor
Radioimmunoassay	^{125}I	Not in regular use yet
Pancreas		
Imaging	^{75}Se -methionine	Poor
Function of islet cells (radioimmunoassay)	^{125}I , ^{131}I	Excellent
Adrenal gland		
Imaging	^{131}I -19-iodo-cholesterol	Excellent
Function	^{131}I -19-iodo-cholesterol	Excellent
Gonads	^{125}I radio-immunoassay of hormones	Excellent
Placenta	^{99m}Tc , HSA } Imaging	Excellent
	^{131}I HSA }	
	^{125}I radio-immunoassay of hormones	Excellent

Fig. 11 Left adrenal gland of patient No. 10: (a) Venogram showing suggestive areas of tumors; a 6-mm area, medial aspect near apex; a 10-mm area, midlateral aspect; a 6- to 8-mm area midportion. "Probable tumor within left adrenal." (b) Scan showing increased uptake in left adrenal gland, the site of two primary aldosterone tumors found surgically. The percent uptake was 0.21 on the left and 0.15 on the right.

Dr. Odell's paper on Diagnosis of Endocrine Disorders by Radioisotopic Methods and Dr. Sisson's paper on Diagnosis of Thyroid Disease emphasize one of the most important changing relations between conventional radiographic and isotopic methods in the diagnosis of disease today; namely, as radiographic methods become more and more specialized, time-consuming, and fraught with morbidity, isotopic methods are more and more adaptable as screening methods that require little time, have essentially no morbidity, and are becoming more precise in evaluation, particularly of endocrine function.

The competitive protein-binding techniques of the Murphy-Pattee T_4 and the T_3 resin test used together have almost displaced the radioiodine uptake test and the serum protein-bound iodine (PBI) in our Nuclear Medicine Clinic. Comparison of the utilization of these tests in the last 2 years in the Nuclear Medicine Clinic at the University of Michigan shows that the radioiodine uptake method total utilization fell from 774 to 691 while the T_3 resin tests totaled 1874 in 1969-1970 and 1674 in 1970-1971. During this time the Murphy-Pattee T_4 total utilization increased from 488 to 1756. A projection from our figures of the first month would give us a total of 3228 Murphy-Pattee tests for 1971-1972. This utilization is perhaps largely dependent on two factors.

First, the two tests (T_3 resin and Murphy-Pattee T_4) used together are the most reliable direct measures of active thyroxine today. For the first time the results are not put in question by iodides, organically bound iodine in any contrast media, estrogen-androgen effects, or drugs that alter binding affinity.

Second, the use of newer and more reliable do-it-yourself kits has made the techniques immediately available in all hospitals.

For 1971-1972 it seems evident that the most important development will be the widespread application of radioimmunoassay and competitive binding analysis techniques for a wide variety of hormones. Kits are proliferating in profusion. The techniques are more practical financially than almost any of the isotope techniques today because large numbers of patients can be studied in a short time with bloodletting being the only contact with the patient. As O'Dell says, "These types of assays had several advantages over all previous hormone measurement systems: Decreased cost and greater ease of performance, the ability to quantify hundreds of samples at one time, greater sensitivity than bioassays, and related to the last, the ability to quantify hormones in unextracted serum or plasma."

We note therefore that O'Dell has pointed out that use of these assays has resulted in a new set of problems. Formerly the clinician needed to know only the simplest physiology to permit interpretation of urinary hormone excretion data. Now he must be aware of the latest information on the control of the blood level of that hormone. The blood level of all these hormones fluctuates widely at different times of the day except T_3 and T_4 .

Thus we are beginning to see that the efficiency of accurate measurement of hormonal levels and the number of these determinations made daily are outstripping the physicians' ability to use these values in diagnosis.

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DISCUSSION: ENDOCRINES

Charkes: Perhaps I can take my prerogative as chairman of the session and start off by asking Dr. Odell a question concerning the cause of goiter. Many years ago Dr. Odell developed a beautiful radioimmunoassay of thyroid-stimulating hormone (TSH) which now has found widespread clinical use. This has been applied to several large groups of patients with acromegaly, finding normal TSH levels in most of them. I am curious, Dr. Odell, whether you have measured growth-hormone levels in patients with acromegaly. In animals studied perhaps with growth-hormone stimulation, have you correlated growth-hormone levels with thyroid enlargement? In other words, is the goiter in acromegaly in your opinion due to growth-hormone excess?

Odell: I think that is a very difficult question to answer objectively at present. If you want me to guess, off the record, I would say no it is not due to growth hormone. Growth hormone does not appear to produce a goiter as judged by animal studies and patients receiving growth-hormone treatment. I think that the problem is somewhat akin to our discussion of gonadotropins. In a few patients with goiter caused by inborn errors of metabolism but who were euthyroid, we have observed "normal TSH concentrations." Furthermore, in adult humans exposed to cold temperatures, we observe an increase in TSH, but *invariably* TSH remains "within normal limits." It appears that small changes in TSH, occurring within our defined "normal population limits," may have physiological importance. I would guess thus that mean TSH in acromegalic patients with goiter may be higher than mean TSH in normal subjects. No data exist to support such an hypothesis. We have looked at two or three patients with acromegaly and goiters and, in general, TSH concentrations were within the normal range.

I would like to comment on some of the other papers. First, a pinealoma was mentioned as cause of precocious puberty. This is a rare tumor, and we have had the opportunity to examine several patients with this disease. It is interesting that the patients we have seen had pineal teratomas and that these tumors produced tumor gonadotropin. Puberty was caused by increased gonadotropin production by the tumor and not by a "mass effect" within the hypothalamus.

Second, we have seen patients in whom we could diagnose the presence of the tumor because of tumor elaboration of a hormone but were unable to find the tumor using all kinds of radioisotopic methodology or with surgical exploration. Dr. Rudnick and I [P. Rudnick and W. D. Odell, In Search of a Cancer, *New Engl. J. Med.*, 284: 405-408 (1971)] published the most dramatic case a few months back. For 1 year every known investigative procedure failed to reveal the location of the tumor, and yet we could positively state that this young man had a neoplasm; blood gonadotropin concentration was outside physiologic range. The patient expired with widespread metastases, and the tumor was found to be a 3-mm teratocarcinoma in one of the testes. Previously the testes had been exposed and explored by a surgeon, but no tumor was seen.

Third, the diagnosis of acromegaly should not be made radiologically. I would like to suggest that we, as endocrinologists, teach that acromegaly not be diagnosed by radiologists anymore. That diagnosis at this stage is far too late. The disfigurement has already occurred, and, with a woman in particular, this is a psychologically destructive event. We must teach people to diagnose acromegaly on the basis of the early symptoms and then to confirm these with glucose-suppressive studies of growth hormones. These early symptoms are (1) increased perspiration, (2) fatigue, (3) subtle skin changes, and (4) subtle hair changes.

Fourth, concerning thyroid-function tests: we believe the present battery of thyroid-function tests which physicians should use always if they suspect any thyroid disease are the following: (1) measurement of T_4 by radioimmunoassay on unextracted serum (see Chopra et al., *J. Clin. Endocrinol. Metab.* (June 1972)); (2) radioimmunoassay measurement of T_3 ; (3) a radioimmunoassay of TBG [see R. P. Levy et al., Radioimmunoassay of Human Thyroxine-Binding Globulin (TBG), *J. Clin. Endocrinol. Metab.*, 32: 372-381 (1971)]; and (4) the radioimmunoassay of TSH. With that battery of tests, hopefully no repetition will be necessary, and we hope the ultimate cost will be decreased because patients will be evaluated accurately on initial evaluation.

Charkes: Why, other than theoretical interests, do we need a TSH determination if the T_3 and T_4 levels on radioimmunoassay are normal?

Odell: The TSH appears at present to be our most sensitive indicator of hypothyroidism.

Charkes: It is that borderline situation where it is definitely clinically useful. Dr. Baltaxe, do you have any response to make to these direct statements?

Baltaxe: Well, I agree as far as acromegaly is concerned. We certainly showed you the late manifestations of this disease.

Can I make some other comments on Dr. Beierwaltes' remarks? First, as far as the pheochromocytoma is concerned, I draw your attention to that one case where it did not show on your scan. In addition to that your scan showed the kidney area only, and I think, as far as we are concerned, we have to make sure that we examine the entire body; when we have these patients come to us, we do angiograms from the thorax to the pelvis. I do not have a particular

case that demonstrates this very well, but I ask you, do you do total-body scanning in order to exclude or rule out malignancies?

We cannot distinguish primary aldosteronism from metastatic disease in patients with a history of carcinoma because we have avascular lesions that we cannot distinguish as benign or malignant. On the other hand, if a patient comes in with carcinoma and we are looking for metastases, any lesion seen is likely to be called a metastasis. So this is one criticism we can rule out. You showed a case of nodular hyperplasia. I am sure that your method would not allow you to demonstrate the nodules, not that it is very important that one demonstrate it so long as the diagnosis is being made.

As far as complications go, I preceded you in saying that we have complications. Personally, I have not had any. I wonder whether some of these complications are related to a gland that is already abnormal. This is my defense mechanism, I suppose, but we are aware of potential complications and we know that we must not use too much contrast material or too much pressure. The unfortunate thing is that all of us are in teaching hospitals and we cannot do these procedures ourselves, not that we are so magnificently talented, but we do have more experience. Most of the procedures are done by residents, and a lot of the complications are handled by people who are in training. Finally, I would like to say that we are not competitors, we are partners. Certainly, if a noninvasive technique is better than or as good as an invasive technique, again we must consider the one who is invaded.

Beierwaltes: I want to thank Dr. Baltaxe. Both of us have been in nuclear medicine a long time. We get so discouraged trying to match anything the radiologists are doing that if we get anything that looks promising we cannot help but talk about it. This is the way I feel about radioiodocholesterol scanning. I think it is such a breakthrough for the long struggle we have had. In 1942 radioiodine was developed for the treatment of hyperthyroidism. There has not been a radiolabeled pharmaceutical developed since then that goes positively where we want it. For example, brain scanning does not show a positive concentration in brain tumor. It is merely normal concentration in a tissue that normally shows no uptake. Most diagnostic applications of scanning in nuclear medicine today are based on cold-spot scanning. We are happy therefore to have achieved scanning that is comparable in some respects to radioiodine in the thyroid gland.

As far as the pheochromocytoma is concerned, I want to emphasize that iodocholesterol does not concentrate in adrenal medullary tissue. However, our greatest interest actually is in the adrenal medulla. We have shown in two previous publications that within 6 hr after administration ^{14}C -dopamine, of all agents tested in dogs, concentrated in the adrenal medulla by a factor of 60 greater than in liver tissue. Dr. Lieberman and I then published our studies on the neuroblastoma in the human, demonstrating a far higher concentration of ^{14}C -dopamine than in normal adrenal medullary tissue, hepatoma, and a neurilemmoma. This finding encouraged us to speculate that some day we might

develop a gamma-labeled analog that would go to the adrenal medulla. We could do a total-body scan to look for neuroblastoma metastases.

I also thought your angiograms of nodular hyperplasia were beautiful. That is a difficult diagnosis that we are not going to make unless we get down to imaging at 2 mm. Even then I would guess that at the present time our count rate is too low to really pick up such beautiful nodules as you showed.

Charkes: I think I can summarize the last few minutes by saying it appears that the human race has gotten to this stage of development because of the great resistance of patients to doctors.

Haynie: What is the availability of ^{131}I -iodocholesterol for adrenal scanning? Is this a procedure that can be performed in the average nuclear medicine laboratory with conventional equipment?

Has ^{131}I -iodocholesterol been employed in scanning other steroid-producing endocrine glands and tumors such as the ovary and testes?

Beierwaltes: Well, first of all I can tell you that radioiodocholesterol is not immediately available today. Second, we wish very much that it could be. The drug companies cannot help very much on new compounds. For example, one drug company showed me a compound they submitted in 1967 to the Food and Drug Administration (FDA). I thought it was a very good compound, not radioactive. They submitted 29 volumes of documentation. In 1971 they showed me that they had submitted a total of 50 volumes of documentation. This compound is still not approved by the FDA. The cost obviously is going to cut their profit margin. They cannot afford to help the investigator on new drugs. They want to improve the drugs that they have already. As a result, I think we are on our own. Of course, we cannot submit even an aliquot of batches of drugs without clearing everything with the FDA first and that is what we are trying to do. However, if you are interested, I would like you to submit a letter stating that you do want it, to our radiopharmacist, Dr. Rodney Ice, Nuclear Medicine, University Hospital, Ann Arbor, because this helps us in trying to plan for the future. We would hope that we could get out batches to others at least by September 1972. Whether we will or not probably only God knows.

For all practical purposes the only need for the computer for the percent uptake test is to differentiate pituitary ACTH excess as a cause of Cushing's syndrome from non-Cushing syndrome. You can do a great deal in determining adrenal function with just a rectilinear scanner. For example, if you have a functional adrenal adenoma on one side, it shuts off the adrenal on the other side.

The last question: tumors elsewhere. There are three places where cholesterol is stored in the normal individual: the adrenal cortex, interstitial cells of testes, and the corpora lutea of the ovaries.

The concentration of radioactivity in the ovaries in the dog is $\frac{1}{12}$ that in the adrenal, and in the testes it is $\frac{1}{20}$ that in the adrenal. To date we have not found a diagnostically helpful concentration of radioiodinated cholesterol either

in the testes or in the ovary. I am sure that you all know that one of the most common places where cholesterol is stored pathologically is in the atherosclerotic plaques of arteries. We have done a year's work on the rabbit now, studying atherosclerosis. I can summarize this work by saying that I do not think that it will be clinically helpful.

Wellman: I would like to mention the thyroid uptake test, at least for nostalgic reasons. It is ironic that this test, which is "the granddaddy of nuclear medicine tests," should be relegated to the "old folk's home," but I am not sure it is as close to death as the speakers designated. Indeed, I believe it is still a very valuable test.

A further comment on the recent reports of lowered thyroid uptakes due to dietary iodides: This may be an effect of changed uptake instrumentation which is more sophisticated and has differing counting characteristics.

The 20-min thyroid uptake of $\text{Na}^{99\text{m}}\text{TcO}_4$ has been shown to be a valuable test to determine whether patients being treated with thionamides are responding to therapy. This technique is used very widely in Europe.

A brief question to Dr. Baltaxe: Do you use a thyroid scan in conjunction with arteriography for parathyroid adenomas to rule out tumor blushes due to multinodular goiters?

Baltaxe: If I understand you correctly, you are saying that you have difficulty distinguishing what nodule is thyroid and what is parathyroid?

Wellman: Yes, it is very difficult to tell whether these nodules are parathyroid adenomas.

Baltaxe: We have the same problem. The only thing you can do is to go by the clinical presentation of the patient. If you suspect hyperparathyroidism and you see a blush, why it is a parathyroid adenoma. I do not have any other way of distinguishing one from the other. Obviously, both receive their blood supply from the inferior thyroid artery; it could be one or the other. That is all I can tell you.

Eckhardt: Dr. Baltaxe, please comment on the prior report of Segal et al. regarding significance of calcification of the thyroid and its relation to associated follicular carcinoma. Dr. Sisson, how long after therapy of (a) hyperthyroidism (low dose) and (b) thyroid carcinoma (high dose) will the immunoassay tests that depend on ^{125}I be influenced?

Baltaxe: There is no problem in applying a soft-tissue technique. One may use tomography for calcifications. To my knowledge the presence of calcium can occur in either a benign or a malignant process. I do not think you can distinguish one from the other.

Charkes: In view of what Dr. Odell pointed out about the state of our knowledge a few years ago, it now appears that the psammoma bodies in the thyroid are actively involved in the synthesis of thyroid hormone, and, as you know, psammoma bodies are the areas that calcify, not to mention the fact that there is much calcium in the thyroid gland normally. Other than that perhaps Dr. Sisson would like to answer the second part of the question.

Sisson: There are two ways that ^{131}I therapy may influence the in vitro tests that employ radioactivity. One problem is the therapeutic radioiodine in the plasma being added to the radioiodine used in the tests. If one is using ^{125}I in the in vitro procedures, presumably pulse-height analysis would distinguish ^{131}I and permit appropriate corrections. On the other hand, there are many tests performed with ^{131}I , and one cannot say how long after the administration of a large therapeutic dose the blood level of radioiodine is elevated such that it affects T_3 resin uptake tests or the binding type of T_4 tests. The effect should last only a few days since these in vitro tests employ levels of radioactivity (10,000 to 20,000 counts/min) which would be unlikely to persist in a milliliter of blood.

The second problem is the time it takes for the therapy to alter the hormonal status of the patient. In hyperthyroidism one does not see a great deal of clinical response from radioiodine for 4, 5, or 6 weeks. I doubt if there will be much change in the T_4 and T_3 resin test values for a couple of weeks at least. Most patients we treat for carcinoma are hypothyroid already, and therapy would not alter the hypothyroid status. On the other hand, if a patient with cancer is not hypothyroid, again there is not much clinical change for several weeks.

May I say one thing about the radioiodine uptake? I would agree that the radioiodine uptake test is not dead. I would also agree that things other than iodine in bread are altering the normal values of this procedure. On the other hand, the diagnosis of hyper- and hypothyroidism is usually made clinically and confirmed with in vitro tests, and the radioiodine uptake is not necessary. The radioiodine uptake test was never very accurate in the diagnosis of hypothyroidism. Uptakes are of value, however, for confirming the presence of hyperthyroidism in difficult diagnostic problems, for suppression and stimulation tests, and as a guide to the therapeutic dose of ^{131}I in hyperthyroidism.

Charkes: At this point I would like to ask Bill Beierwaltes a question about ACTH testing of adrenal glands for Cushing's syndrome. One might make an analogy with the thyroid gland where, in the presence of an autonomous nodule, the administration of TSH makes the diagnosis not by measuring the overall uptake but by getting the sequential scan of the thyroid gland and demonstrating that there has been stimulated or suppressed extranodular tissue. Now going to the adrenal gland, have you done any stimulation or suppression studies on patients with adrenocortical disease, either on aldosteronomas, cortical adenomas, or carcinomas, and have you observed the response of the scan to ACTH or to metapyrone? Or is it not possible to do this because of the long biological half-life of the material in the adrenal gland which makes sequential scanning difficult?

Beierwaltes: We have some information on the subject but not very much. Our first dog work was published this year [R. J. Blair et al., Radiolabeled Cholesterol as an Adrenal Scanning Agent, *J. Nucl. Med.*, 12: 176-182 (1971)]. We were interested to find that the total-body biological half-life of

^{14}C -cholesterol was 65 days in dogs and 72 days in humans. With the ^{125}I -19-iodocholesterol, the total-body biological half-life was 6 days without ACTH and 3 days with ACTH due to the rapid clearance of iodocholesterol from organs other than the adrenal. We wondered then if the ACTH had something to do with the short biological half-life of the iodocholesterol or whether it was the steroid produced by the adrenal after ACTH stimulation. It was natural, therefore, that when we started to work with Dr. Conn on primary aldosterone tumors, he was interested to try dexamethasone suppression. These results are very preliminary, but we appear to be able to suppress adrenal tissue but not the primary aldosterone tumor. I agree with you in general, Henry, that the 24-hr urinary excretion of stable iodine does not conclusively correlate with the lowered values of thyroidal ^{131}I uptake.

In my opinion we do use the radioiodine uptake commonly, but it is used more commonly in patients where the T_4 and T_3 resin are borderline. We may then do a T_3 suppression test. We measure the radioiodine uptake and T_4 before and after T_3 suppression. If they fail to suppress, this is strong evidence that the patient has the metabolic defect of Graves' disease. If the thyroid gland suppresses beautifully, this tends to rule out Graves' disease. Similarly, we use TSH stimulation of radioiodine uptake and T_4 serum concentration. If these respond normally, this finding helps us rule out hypothyroidism in the borderline case.

Wellman: Dr. Beierwaltes' slide showing data on thyroid weights was taken from Mortensen's work wherein thyroids were taken at autopsy in a routine method. In a personal communication Mortensen has indicated that no attempt was made to exclude excessively large goiters or to meticulously dissect the thyroid glands obtained at autopsy. Thus these data skew the mean thyroid weight to the high side. We reported a mean normal thyroid weight of about 16 g at the last Oak Ridge Symposium in December 1969; our weight was less than that found by Mortensen.

Charkes: Did Mortensen collect these data in Rochester, Minnesota, a common, known goiter-belt area?

Wellman: Yes, I think this is where he was a pathology resident.

Oxley: I wish Dr. Sisson would comment on the clinical utility of the direct measurement of serum-free thyroxine since (1) a technique is available and (2) the amount of this constituent is that sought in most of the "combined tests" (e.g., T_4 and T_3 resin uptake).

Sisson: The measurement of free thyroxine, at least in theory, would be one of the best measures of thyroid hormone effects. In practice, however, free thyroxine determinations are difficult to perform; they are not as precise as one would wish. Second, in patients who are acutely ill and in those who have had recent injuries or operations, the free thyroxine increases in concentration in the serum. This change is unrelated to any change in metabolic status; these patients are not hyperthyroid. Rather, this is a normal response to injury or illness. Unfortunately, it is with the sick patient that the physician needs some

confirmatory help from the laboratory. However, in these patients the value of the free thyroxine is limited. There is one valuable clue to be obtained from the free thyroxine level. Following injury or acute illness, the free thyroxine value does not rise above twice the normal mean in contrast to hyperthyroid levels which frequently exceed this height. If one has a clinical problem that is terribly complex, many factors may act on the total serum-thyroxine concentration. In this instance the free-thyroxine determination is valuable in differentiating euthyroidism from hyperthyroidism. If the free-thyroxine value is more than twice the normal mean, it strongly suggests the presence of hyperthyroidism.

Eckhardt: I would like to ask Dr. Sisson about his comments, which were extremely negative, on free thyroxine as a single determination. At a recent Endocrine Society Postgraduate Assembly, this discrimination of thyroid-function tests in relation to the true clinical status of patients was reviewed by a number of clinicians. The general opinion was that more tests are required, and it is becoming exceedingly difficult to determine, based on any one particular study, if a patient is euthyroid, hypothyroid, or hyperthyroid. You can make great regression equations, tables, etc., and correlate them with clinical status, but obviously there is no one thyroid-function test. But then also the T_4 and T_3 index, or any one of these other numbers of studies, approximates what you are trying to measure in free thyroxine studies per se. If it were not so technically difficult, nobody would be doing T_3 or T_4 studies. I am afraid you negated, or at least I assume you negated, single free-thyroxine determinations, but maybe this was not an accurate representation of your comment.

Sisson: It is true that we would do more free-thyroxine studies if the test were not so difficult. Perhaps I should raise the question as to what data constitute a diagnosis. If we put it another way, a diagnosis is only as good as the help it gives the clinician in managing the patient. What data will direct you to take this action or that action on the patient? These are the data, laboratory or otherwise, to be sought in a "diagnosis."

Charkes: Some of these tests are reasonably simple. I would like to ask Dr. Odell a question but he is not here so I will ask Dr. Shapiro to answer this one. Approximately how long does it take to do a TSH radioimmunoassay?

Shapiro: In actual hours it is only a few hours, but, if you consider the time needed for incubation, it is about 8 days.

Moderator:
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KIDNEY

RENAL ANGIOGRAPHY WITH EMPHASIS ON THE DIAGNOSIS OF RENOVASCULAR HYPERTENSION

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ABSTRACT

The practical clinical application of renal angiography is concerned with the detection and differentiation of mass lesions of the kidneys, study of patients suspected of renovascular hypertension, evaluation of kidneys in patients subjected to renal trauma, and study of the kidneys of patients having undergone renal homotransplantation. In patients suspected of having renovascular hypertension, angiography provides anatomic information which, when correlated with the type of lesion and other clinical factors, provides important information in selecting the type of treatment and prognosis. In a group of patients who have had both renal angiography and radiorenography, a low degree of correlation was found in atherosclerotic lesions, but a very high degree of correlation was found between abnormal renograms and the angiogram in patients with the fibrotic lesions. Postoperative radiorenograms provide prognostic information about the surgical result and relief of hypertension.

Since the introduction of renal angiography by the translumbar technique by dos Santos¹ in 1929, there have been many technical changes which have resulted in improved angiographic study of the kidney in virtually all diseases that affect it or its vasculature. Selective renal angiography coupled with improvements in contrast materials and new developments in radiographic equipment now make possible visualization of vascular structures within the kidney as small as glomeruli.

Although virtually all disorders of the kidney have been studied by selective renal angiography with the newer techniques, the practical clinical application of renal angiography falls into four general areas: (1) the detection and differentiation of mass lesions of the kidney, (2) the study of patients suspected of having renovascular hypertension, (3) evaluation of the kidneys in patients who have been subjected to renal trauma, and (4) study of the kidneys of patients who have undergone renal homotransplantation.

Renal angiography in mass lesions of the kidney, renal homotransplantation, and renal trauma will be briefly summarized, with a pertinent bibliography. Renovascular hypertension will be considered in more detail.

MASS LESIONS OF THE KIDNEY

Selective renal angiography is considered generally an integral portion of the evaluation of patients suspected of mass lesions of the kidney. Just a few years ago, during the era of aortographic study of the kidneys, angiography in this category of patients fell into disrepute. Aortographic techniques for renal angiography achieved limited vascular detail, primarily due to dilution of contrast material by aortic blood and overlap of the kidneys by extrarenal vasculature. Because there were many false-negative renal angiograms performed by the aortographic technique in patients who had renal masses, it was felt that all patients with mass lesions of the kidney should be subjected to surgical exploration without previous angiography. However, angiography carried out by the selective technique and technical radiographic developments have demonstrated a high level of accuracy in diagnosis, making renal angiography an integral part of the management of patients with mass lesions of the kidney.² Rigid criteria for interpretation of angiographic findings have further lessened the possibility of the most serious diagnostic error, interpreting a renal-cell carcinoma as a cyst.³

RENAL TRAUMA

Severe contusions and fractures of the kidney may result from blunt trauma to the flank. Fractures are diagnosed by linear disruption of the arterial vasculature and extraluminal leakage of contrast material within the renal parenchyma or outside the kidney. Later, as healing occurs, a nonanatomical scar forms which is different from the segmental or lobar scarring from infarction or pyelonephritis.⁴ Contusion to the kidney may show less dramatic angiographic changes, such as localized arterial spasm, altered flow patterns, and localized abnormalities in the nephrographic (capillary) phase.

RENAL TRANSPLANTATION

Information for the diagnosis of cortical necrosis, rejection, and vascular anastomotic problems may be obtained from an angiographic study of the transplanted kidney.

Marked delay in the arterial clearance of contrast material is characteristic of acute or hyperacute rejection.⁵ In chronic rejection there is a lesser delay in clearance and focal loss of small branches due to thrombosis.

RENOVASCULAR HYPERTENSION

The diagnosis of renovascular hypertension is essentially retrospective. In a hypertensive patient in whom an operative procedure of nephrectomy or reconstructive arterial surgery results in relief of hypertension, identification of an arterial or renal parenchymal lesion is the only certain method of establishing the diagnosis of renovascular hypertension.

In patients with suspected renovascular hypertension, information derived from renal angiography is primarily morphologic and to a much lesser extent, physiologic. The cause and effect relation between a demonstrated angiographic lesion and the patient's hypertension is not established by angiography; although, empirically, a high probability of such a causal relation can be deduced in certain circumstances. These include the determination of the type of arterial disease, a knowledge of the natural history of each of these diseases, an estimated degree of stenosis, the relative size of the kidneys, and the status of the opposite kidney.

CLASSIFICATION OF RENAL ARTERIAL DISEASE

In general, renal arterial disease may be divided into two primary categories: atherosclerotic lesions and fibrous or fibromuscular dysplasias. A further

TABLE I
FIBROUS AND FIBROMUSCULAR DYSPLASIAS

Predominant site of involvement	Lesion
Intima	Intimal fibroplasia
Media	Medial dissection
	Medial fibroplasia
	Medial hyperplasia
	Perimedial fibroplasia
Adventitia	Periarterial fibroplasia

subdivision of the fibrous and fibromuscular dysplasias is possible on both pathologic and angiographic grounds. The classification of McCormack et al.⁶ and the more recent combined classification of Harrison and McCormack⁷ is based on the primary location of the disease in the arterial wall, i.e., intima, media, and adventitia (Table 1). In each the pathologic diagnosis can usually be predicted from a study of the angiographic characteristics of the lesion.^{6,7}

Experience with the clinical management of hypertensive patients with renal arterial disease and study of the natural history of these lesions⁸ permits certain conclusions:

1. Atherosclerotic disease of the renal artery is unpredictable in its natural history. The angiographic characteristics of the lesions are of no value in predicting whether the lesion will remain stable or progress.

2. The operative treatment of renovascular hypertension is less likely to result in relief of hypertension in patients with atherosclerotic disease than in patients with lesions of fibrous or fibromuscular dysplasias. Our experience indicates that the expected "cure" rate in atherosclerosis approximates 40% as compared with 60 to 75% in patients with fibrous or fibromuscular dysplasias.

3. Subdividing the fibrous and fibromuscular dysplasias, there are distinct differences in their natural histories.⁸ Medial fibroplasia, the most common nonatherosclerotic disease,⁹ shows little tendency for progression after the age of 40, whereas the other fibrous diseases commonly progress or new disease is likely to develop in the same or opposite kidney.

4. The age and sex distribution in patients and the predominant site of involvement differ among the fibrous and fibromuscular dysplasias. Eighty percent of the patients diagnosed with medial fibroplasia are women who are usually in the fifth decade of life. Almost half the lesions are bilateral; an equal number have unilateral lesions on the right side with only about 10% of the lesions occurring unilaterally on the left. Perimedial fibroplasia, on the other hand, is a disease primarily of young women, most under the age of 30, who usually have the disease in the right side. Intimal fibroplasia and medial dissection are not dominant in either sex, nor do they tend to occur on a particular side; these diseases do occur primarily in patients under the age of 35.

DEGREE OF STENOSIS

The estimation of the degree of luminal compromise produced by an arterial lesion is essential to establish a causal relation between the lesion and the patient's hypertension. The two-dimensional radiograph of an arterial lesion is most accurate in those lesions seen in profile, but even in this instance the lack of the third dimension reduces accuracy. Estimation of the severity of stenosis of lesions seen en face must be judged by variation in the density of the column of contrast material, a most difficult estimation. Nevertheless, the following conclusions can be drawn from experience:

1. Estimation of the degree of stenosis in focal lesions such as atherosclerosis, intimal fibroplasia, medial hyperplasia, and in some patients with perimedial fibroplasia correlates well with pathologic findings.

2. A significant part of the lesion of medial fibroplasia is always viewed en face so that the lesion is usually more stenotic than judged from the arteriogram.

3. There is an excellent correlation between causal relation of the dissecting aneurysm seen in medial dissection and resultant relief of hypertension by surgical intervention.

4. The presence of collateral circulation is important in the assessment of the severity of stenosis. However, in medial fibroplasia the presence of collaterals is rarely observed in this type of patient who commonly responds to revascularization surgery.

The question of what percentage of luminal stenosis is "significant" often arises. Empirically, lesions judged to narrow the lumen less than 25% are unlikely to produce renovascular hypertension. Narrowing of more than 75% carries a strong probability of a causal relation between the lesion and the patient's hypertension. The evaluation of lesions in the patients between these extremes must depend more heavily on other parameters, both clinical and angiographic.

RENAL SIZE

Variations in the length of the kidneys of more than 1.0 to 1.5 cm are generally considered an important clue to the presence of a renal arterial lesion. This should be placed in perspective and the following points considered:

1. A decrease in renal size from a stenosis is caused by the death of nephrons; renin release frequently occurs in kidneys with no loss in volume.
2. A unilateral decrease in renal size is only rarely observed in medial fibroplasia.
3. A small kidney is the rule in patients with perimedial fibroplasia.
4. A difference in renal size may not be observed in patients with bilateral lesions.
5. Branch stenoses may not produce generalized or segmental decrease in size, and in children and young adults complete branch occlusion is often present without any size or contour abnormality because of rich collateral circulation.

CORRELATION OF RENAL ANGIOGRAPHY AND RADIORENOGRAPHY

There is extensive literature dealing with the accuracy of the ^{131}I -Hippuran radiorenogram. It is important to emphasize that the radiorenogram is a measure of renal tubular function and not of the activity of the renal pressor system. Although it is true that renal tubular function may be impaired by a lesion that also has activated the renal pressor system, lesions without radiorenographic abnormalities may be responsible for hypertension, and, obviously, many abnormalities of the renogram are not due to renal-artery stenoses.

Recently we have correlated the radiorenogram in patients whose renal arterial lesion has been classified using the criteria set forth by McCormack et al.⁶ and by Harrison and McCormack.⁷

The details of the method for evaluation of the radiorenograms are briefly: 420 consecutive radiorenograms were carried out in hypertensive patients who also underwent renal angiography. Details of the radiorenograms can be only summarized in this presentation. The patients were first injected with ^{197}Hg to localize the kidneys and then 30 μCi of ^{131}I -Hippuran was administered intravenously. Radiorenograms were evaluated using both subjective and objective criteria. Table 2 shows the almost random changes in patients with

TABLE 2
RENAL-ARTERY ARTERIOSCLEROSIS

Arteriogram	Renogram			
	Right kidney		Left kidney	
	Normal	Abnormal	Normal	Abnormal
Arteriosclerotic obliterans				
Right renal-artery stenosis (32 cases)	7	25	25	7
Left renal-artery stenosis (21 cases)	15	6	3	18
Bilateral stenosis (37 cases)	8	29	6	31
Minimal nonstenotic (26 cases)	16	10	17	9

atherosclerotic lesions as might be predicted on the basis of coexisting arteriolar nephrosclerosis. Furthermore, there was a rather high percentage of false-positive renograms in the patients who had minimal, nonstenotic atherosclerotic disease.

In contrast, the accuracy of radiorenography in locating lesions of medial fibroplasia and intimal and perimedial fibroplasia was quite high (Tables 3 and 4).

Of particular interest was the correlation of the radiorenograms in operated patients with bilateral medial fibroplasia (Table 5). These five operated patients all had abnormal radiorenograms on the right, and, following operation and relief of the hypertension, four of these became normal (Figs. 1 to 3). This small number of cases does not allow a significant conclusion to be drawn from the data which indicate that two of the patients with abnormal radiorenograms on the left side returned to normal after operations on the right side.

The practical application of these data in correlation with renal angiography appears to be that the radiorenogram is an exceedingly useful and simple way to evaluate the operative results in patients with fibrous or fibromuscular dysplasia and with medial fibroplasia in particular (Figs. 4 and 5).

TABLE 3
RENAL-ARTERY MEDIAL FIBROPLASIA

Arteriogram	Renogram			
	Right kidney		Left kidney	
	Normal	Abnormal	Normal	Abnormal
Medial fibroplasia				
Involving right renal artery (17 cases)	1	16	17	
Involving left renal artery (4 cases)	4			4
Bilateral involvement (16 cases)	2	14	2	14
Minimal nonstenotic (30 cases)	26	4	26	4

TABLE 4
RENAL-ARTERY INTIMAL AND PERIMEDIAL FIBROPLASIA

Arteriogram	Renogram			
	Right kidney		Left kidney	
	Normal	Abnormal	Normal	Abnormal
Perimedial fibroplasia				
Involving left renal artery (3 cases)	2	1		3
Involving right renal artery (7 cases)		7	6	1
Intimal fibroplasia				
Involving right renal artery (4 cases)		4	4	
Bilateral (1 case)		1		1

TABLE 5
BILATERAL MEDIAL FIBROPLASIA
(NORMOTENSIVE PATIENTS AFTER OPERATION)

Renogram preoperative				Renogram postoperative					
Normal		Abnormal		Normal		Improved		Abnormal	
Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
	1	1		1	1				
		1	1	1					1
		1	1	1					1
		1	1	1	1				
1		1			1	1

Fig. 1 Aortogram showing lesions of medial fibroplasia bilaterally. On the left disease involves the distal main artery and primary bifurcation.

Fig. 2 Selective right renal arteriogram of the same patient demonstrating the extensive "beading" of medial fibroplasia throughout the main renal artery.

Fig. 3 Preoperative (a) and postoperative (b) radiorenograms on the patient in Fig. 1. The preoperative renogram reveals bilaterally abnormal curves. Following repair of the right renal artery, the right-side radiorenogram returned to normal while the left remained abnormal. The patient has been normotensive since operation.

Fig. 4 Aortogram showing medial fibroplasia involving the right renal artery and a normal left renal artery.

Fig. 5 Radiorenogram showing an abnormal right curve preoperatively (a). Following operation, the patient's blood pressure did not return to normal, and the normal right renogram curve persisted (b).

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STUDY OF RENAL DISORDERS WITH RADIONUCLIDES

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ABSTRACT

The application of radionuclides in nephrology has not yet achieved its full potential. An increasing number of useful procedures have been described each year, but their clinical application lags. Radionuclides for performing clearance procedures provide a rapid, simple way of assessing renal function. Measurements of renal blood flow may be obtained qualitatively with camera imaging devices, and quantitative values can be derived from the radioactive xenon washout procedure. Renal imaging is of proven value in assessing renal functional integrity and in estimating renal size in the presence of advanced azotemia. With minimal patient radiation, radionuclides provide a sensitive means for the detection of vesicoureteral reflux. Radiorenography, although of dubious value in the screening of patients with suspected renovascular hypertension, is an exquisitely sensitive means of detecting and following the obstruction of the urinary outflow tract. Radioisotope procedures obviate the need for catheterization of the urinary tract to measure residual urine and evaluate lower urinary-tract obstruction. In addition to these uses, radionuclides at times provide a sole means of safely evaluating the urinary tract in a patient with known or suspected allergy to contrast materials.

A great many physicians consider the available renal studies with radionuclides to consist only of radiorenography and perhaps some renal scanning with ^{197}Hg . Although it certainly is true that the application of radionuclides in nephrology received its greatest single stimulus from the conception and development of the radiorenogram,¹ this is, at the same time, unfortunate. Renography initially offered many attractive features: easy performance, no known side effects, and, perhaps the most important of all, the potential for evaluation of individual renal function without the need for instrumentation of the patient. Only individuals gifted with the greatest foresight could predict the tremendous impact that radionuclides would ultimately have on the clinical practice of nephrology and the great reluctance of the medical community to accept this invaluable tool. This paradoxical statement, unfortunately, is quite true. There

are two major obstacles to the general acceptance of the application of radionuclides to the study of the urinary tract. Each is easily resolved by open discussion. First, the nuclear medicine specialist frequently is very insecure about the evaluation of renal function. He generally has had only limited contact with nephrology and has given little thought to the complex functions performed by the kidney. Second, the nephrologist is loath to accept any procedure that is not based on the renal physiologist's classic conception of functional evaluation of the kidney, although some of these concepts are more than 25 years old.² Neither of these objections to using radionuclides in nephrology is any longer valid. Old concepts of the evaluation of renal function with classic clearance methods are generally not clinically practical since they require procedures that are usually expensive and time-consuming.

This review will attempt to place in proper perspective for the internist, radiologist, and nuclear medicine specialist the relations and uses of radionuclide and radiologic tests in the clinical evaluation of renal function.

The use of renal clearance as an approach to the clinical evaluation of renal function and disease generally has failed. The concept that only substances measurable in the urine may be used with complete reliability for evaluation of renal function is certainly correct, but it is of little help to the busy internist confronted with the need to care for several patients per hour and not with several hours per patient. These tests generally hinder the clinician. Even the simplest, the creatinine clearance, is beset by the frequent inability of the ward nurse to get a reliable, accurate collection of voided urine over a 24-hr period. Such problems result from a lack of personnel or poor patient cooperation. Serum creatinine concentration and measurements of the concentration of blood-urea nitrogen are at best crude and relatively inaccurate methods for the estimation of renal function. The determination of serum creatinine concentration is especially inaccurate at low plasma concentrations, and the blood-urea nitrogen is influenced by many extrarenal factors of production. In addition, the hyperbolic relation between clearance and plasma concentration makes these tests insensitive to wide changes in renal function.

The areas in which the radiologist functions best are intravenous urography, retrograde pyelography, voiding cystourethrography, and renal arteriography. Each technic is of great and indisputable clinical value. Ease of performance, low morbidity, and excellent anatomic resolution and accuracy are their chief features. Because of its clinical utility, the specialized equipment needed for these tests is available in most medical centers. However, each of these radiologic procedures is complemented by a variety of radionuclide technics. The major accomplishment of radionuclide procedures in nephrology is the total absence of patient morbidity, lack of expense, and, in a great many instances, a yield of information otherwise unobtainable. We will enumerate the wide variety of radionuclide procedures applicable to nephrology and some of the specific advantages and drawbacks. The reader is referred to the individual references for

detailed explanations of methodology. This review is only to put these tools in perspective, not to explain the methodology.

CLEARANCE TECHNIQS

Clearance methods may be readily divided into three categories for ease of discussion: classic clearance methods that utilize measurement of urinary excretion; single-injection technics that estimate renal function from the rate of disappearance of an injected tracer that is excreted only by the kidney; and technics that simplify the use of the single-injection technic.

Classic Clearance Methods

The classic clearance method² referred to earlier requires the continuous intravenous infusion of test material to maintain constant plasma levels and collect urine. We calculate clearance by:

$$C = \frac{UV}{P}$$

where C = clearance (ml/min)

U = urine concentration (mg/ml)

V = urine volume (ml/min)

P = plasma concentration (mg/ml)

The only advantage of radionuclides in this setting is their ease of measurement at extremely low concentrations. It is quite simple to determine accurately very low levels of test substances in the plasma if they are labeled suitably with a radionuclide. This advantage is offset by the disadvantage of frequent contamination of commercially available test substances with free radionuclide,³ which is excreted at a different rate than the labeled compound. Most commercial manufacturers do not provide pure material. It is inherent in the infusion technic that a steady accumulation of the contaminant will appear in the bloodstream. In addition, the patient is burdened with a completely avoidable dose of radiation, which, no matter how small, is unnecessary. Most of the chemical analyses used are reasonably easy and rapid to conduct and compete favorably.

We must conclude that there is little or no place for the continuous infusion of radionuclides in measuring clearance in the armamentarium of clinical nuclear medicine. If the continuous-infusion clearance is to be used, it should be done with nonradioactive materials.

Single-Injection Technics and Technics that Simplify Their Use

The single-injection clearance procedure is entirely different from the method discussed earlier. The dose required is small, the technic obviates the need for urine collection, and it has the further advantage that imaging of the kidney or radiorenography may be done simultaneously. These qualities create a significant place for such technics in clinical medicine. The method requires rapid intravenous injection of a bolus of ^{131}I -orthoiodohippurate or another suitable indicator, after which six to eight plasma samples are obtained during 1 hr. The concentration of radioactivity in the plasma is plotted as counts per minute per milliliter vs. time on semilogarithmic graph paper.⁴ This disappearance curve can usually be resolved into two components, and the clearance is calculated from the intercepts and slopes of the two components (Fig. 1). Close correlations have been shown to exist between standard para-aminohippurate clearances for measuring renal plasma flow and results simultaneously obtained by this method. Similar results are obtained with measurements of agents excreted solely by glomerular filtration.⁵ If only a measure of the glomerular filtration rate is sought, the information can be obtained with a single injection of inulin as the indicator, avoiding the unnecessary administration of radioactivity. If simultaneous imaging is indicated, then, of course, a radiopharmaceutical should be used.

The clinical settings in which these tests are valuable are many and varied. Single-injection clearances and various simplified adaptations⁶ of the technics have been used extensively for studying renal-transplant function and for providing a rapidly obtained, clinical indicator of rejection and concurrent loss of renal function.

In children the collection of voided urine and the continuous infusion of an appropriate pharmaceutical for measuring renal function pose special problems. In individuals in whom an accurate assessment of the level of renal function may be a necessary guide to therapy and prognosis, the single-injection clearance tests are useful. Similarly, in adults, either in the hospital or as outpatients, the accurate measurement of the glomerular filtration rate and the effective renal plasma flow may be more easily obtained by these methods.

Single-injection clearance is not useful in rapidly changing physiologic states; in any setting it is a meticulous technic. Common sources of error are the presence of free radioiodide, infiltration or improper measurement of dose, absence of a steady state, and the use of an improper indicator.

RENAL BLOOD FLOW

Imaging Studies

The accurate measurement of renal blood flow is not easily performed in most clinical circumstances. Some qualitative assessment of the renal blood

Fig. 1 The plasma concentration of ^{131}I -orthoiodohippurate (Hippuran) is shown during the first 90 min after a single intravenous injection of $75\text{ }\mu\text{Ci}$. The concentration (counts/min/ml) is plotted as the logarithm of the count rate vs. time. After about 40 min the values obtained approach an exponential function and can be fitted with a straight line with a $t_{1/2}$ of 37 min. After subtracting all the values of this first extrapolation from the experimental data, a second group of values is obtained (open circles). These values also may be fitted with a straight line, suggesting that the experimental data may be described mathematically as the sum of two exponential functions. The renal clearance (C) of Hippuran may be calculated from the expression C is equal to $\text{Dose}/(A b_2 + B b_1)$, where the dose is the amount of radiohippuran injected (counts/min) and A and B are the intercepts of the extrapolated lines with slopes b_1 and b_2 , respectively. The slope is equal to $0.693/t_{1/2}$.

flow^{7,8} can be obtained with rapid-sequence scintiphotos obtained immediately after the rapid, intravenous injection of a small-volume bolus containing a large amount of radioactivity (Fig. 2). This type of study may be performed easily with a camera imaging device. Such methods are purely qualitative, and no quantitative data are presently derived from them.

Fig. 2 Four scintiphotos obtained after the rapid intravenous injection of 10 mCi of ^{99m}Tc -pertechnetate. The upper left scintiphoto shows the appearance of radioactivity in the abdominal aorta after traversing the heart and lungs. At the lower right, the scintiphoto next obtained shows persistent visualization of the aorta, and the renal perfusion can be evaluated by the appearance of the kidneys at a time when the pertechnetate is still confined to the vasculature. The final film in the series at the lower left reveals the renal scan obtained when the ^{99m}Tc has been taken up by the kidney and is now present in renal tissue and urine. The upper right scintiphoto is a ^{201}Hg -chlormerodrin study which was performed prior to the ^{99m}Tc study in order to delineate kidney size, shape, and position. This is a normal study.

Perfusion studies may have some role in the assessment of renal mass lesions. The rapid-sequence scintiphotos will reveal whether a renal mass is perfused (tumor) or not perfused (cyst) with about 80% accuracy. The test clearly has a place in the evaluation of renal-transplant perfusion, renal effects of trauma, and the assessment of possible vascular accidents involving the kidney. In these situations quantitative information is not really necessary.

The Xenon Washout

The xenon washout⁹⁻¹² is at present the most easily applied radionuclide method for quantitative assessment of renal blood flow (Fig. 3). However, its

Fig. 3 A xenon washout study obtained after the injection of 1 mCi of ^{133}Xe into the renal artery. The logarithm of the counting rate is plotted against time. A series of subtractions are performed in a manner similar to the peeling of the curve shown in Fig. 1, only in this case three or four components are usually obtained. Component IV is derived from the terminal component of the curve, which is not shown. Components III, II, and I are then serially derived. Component I is thought to be a function of the distribution of the renal blood flow to the outer cortex. Note the scintiphotos in the inset. The scan obtained during 24 to 48 sec after the injection of the xenon reveals clearing of the outer edge of the kidney (white line). This supports the relation of component I to cortical blood flow since this clearing of the cortex occurs when component I has been largely dissipated. The fraction of the renal blood flow reaching the cortex can be estimated from the intercept of component I, and the blood flow to the cortex can be calculated from the slope as milliliters per minute per gram of cortex. [From M. D. Blafox, A. Fromowitz, A. Gruskin, C. H. Meng, and M. Elkin, Validation of Use of Xenon 133 to Measure the Intrarenal Distribution of Blood Flow, *Amer. J. Physiol.*, 219: 442 (1970).]

clinical efficacy has not yet been evaluated adequately, and it must still be considered an investigative technic. Even if fully accepted, it would suffer from the disadvantage that the test requires catheterization of the renal arteries. Therefore it will probably never be more than an adjunctive procedure that can be performed at the time of renal arteriography. It complements the qualitative interpretation of the angiographer by providing an additional quantitative measurement.

So far the method has provided a considerable amount of physiologic information. Changes in the intrarenal distribution of the renal blood flow in man have been reported in states of salt deprivation, acute renal failure, hepatorenal syndrome, malignant hypertension, and essential hypertension. The elucidation of these physiologic and pathologic alterations would not have been possible without the availability of a noninvasive technic such as the xenon washout. Unfortunately, renovascular hypertension, a condition in which alterations of renal blood flow may be primary, has not been shown to have any characteristic pattern of changes.

RENAL IMAGING

Renal imaging cannot possibly compete with urography as an all-purpose diagnostic procedure. It lacks both the resolution and the anatomic specificity so well provided by urography. However, renal imaging does yield information that may complement the urogram because of its close relation to renal-function testing. In this sense renal imaging and radiorenography are complementary tests, both of which provide important insight into renal function. This combined application will be discussed later. Two strictly anatomic uses of imaging do exist which provide useful information in spite of the limitations of resolution.

Azotemia

The busy consultant is confronted frequently with problems of severely azotemic individuals whom he has never seen. Little or nothing may be known about the history of such patients. Retrograde pyelography is often used to resolve the possibility of urinary-tract obstruction and the question of whether the severe renal insufficiency is a result of chronic vs. acute renal disease. However, it is completely feasible to image the kidney with radiohippurate (Fig. 4) even in the presence of severe azotemia.^{13,14} This imaging potential permits an accurate assessment of renal size, allowing for reasonably certain detection of renal atrophy, which, if present, would suggest chronicity. It also determines if the patient has one or two kidneys. The chance of anuria or severe oliguria resulting from bilateral obstruction of the urinary outflow tract is extremely small. Imaging of the kidneys in uremia may eventually be refined to permit differentiation of various types of obstructive disease from chronic parenchymal disease. If the number and size of the kidneys are established, the physician can choose objectively the proper sequence of diagnostic procedures.

Vesicoureteral Reflux

The use of voiding cystourethrography is well established in the detection of vesicoureteral reflux. Several radionuclide methods have evolved which provide

Fig. 4 Rectilinear scan of the kidneys obtained in a patient with moderate azotemia after the intravenous injection of 300 μCi of ^{131}I -orthoiodohippurate. This study was performed at a time when the urogram did not adequately visualize and a ^{197}Hg -chlormerodrin scan was uninterpretable. The orthoiodohippurate scan is useful even in the presence of severe azotemia.

information about the urinary outflow tract.^{15,16} These studies complement the roentgenograms. No radionuclide method is useful for evaluation of the bladder, vesical neck, or lower ureter. In this region the X-ray study alone suffices. Small quantities of reflux of urine may be detected in the renal pelvis after the instillation of ^{99m}Tc -pertechnetate into the urinary bladder (Fig. 5). In 12 patients whom we have studied with proven reflux, 2 cases were detected by the isotope study but not by X ray. The radiation dose from the ^{99m}Tc procedure is quite small, being confined mostly to the urinary tract with probably less than 5 mrad exposure to the gonads. Such a low radiation dose makes this procedure especially suitable for follow-up studies in children with proven reflux. The full potential of this technic has yet to be reached. Theoretical possibilities include studies after intravenous injection of a suitable radionuclide which would circumvent the need for urethral catheterization.

RADIORENOGRAPHY

The renogram first caused great interest because of its potential as an atraumatic screening test in the detection of renovascular hypertension.¹ This

Fig. 5 The bladder in this child was filled with 500 μ Ci of ^{99m}Tc -pertechnetate. It can be seen at the bottom of the figure as the larger accumulation of radioactivity. Low-pressure reflux occurred to the left renal pelvis. The reflux is easily recognized by the accumulation of radioactivity at the upper left. This examination results in minimal radiation to the patient and detection of small volumes of reflux.

may really be a secondary application since the test is of much greater value in the study of urinary-tract obstruction. Its great potential in evaluating urinary-tract obstruction has not yet been realized by the urologist and internist.

Renovascular Hypertension

In seeking renovascular lesions, the renogram is completely nonspecific. It will detect any unilateral reduction or asymmetry of renal function regardless of cause. Because of this it has a high "false-positive," case-finding rate which in some active centers is reported to be as much as 20%. The usual reported accuracy of the test will permit the detection of a renovascular lesion in 80% of

all patients with this disease.¹⁷ This is approximately the same sensitivity that has been reported for intravenous urography. However, there is not complete overlap between the two procedures since lesions in about 90% of afflicted patients will be detected if both tests are performed.

In our institution we find the test simple to perform and interpret. There is no morbidity. Under these circumstances we find it of value in screening hypertensive patients, keeping in mind the high incidence of false positives. The number of false positives can be minimized with conservative interpretation without greatly affecting the sensitivity of the test.

Urinary-Tract Obstruction

The area of diagnosis in which the renogram is of great value and in which it is not used frequently enough is upper urinary-tract obstruction. The intravenous urogram is, of course, essential in all cases of urinary-tract obstruction, but once precise anatomic information is obtained, the renogram becomes of great value. During early phases of urinary-tract obstruction associated with normal renal function, the initial portion of the renogram curve remains normal. However, instead of reaching a peak at 3 to 5 min and then falling, there is a continued accumulation of radioactivity that depends on the severity of the obstruction.¹⁸ The initial, rapidly rising, second segment of the renogram curve will permit the early detection of changes in function secondary to the obstruction. The renogram has the distinct advantage that it has no effect on urine flow rate or on urine osmolality. It permits a study of the integrity of the outflow tract under completely normal physiologic circumstances. This is a great advantage over the urogram, which induces a profound osmotic diuresis and will result in a urinary specific gravity of 1.040 or greater.

Recent developments in imaging equipment may permit the specialist to refine the renogram further and to enhance its practical significance. An important criticism of the test has been the great influence of variability in renal position and the contribution of nonrenal background radioactivity to the shape of the curve¹⁹ (Fig. 6). It is now possible to sequentially image the kidneys with ¹³¹I-orthoiodohippurate for a visual, qualitative assessment of the kidney and its function. If an abnormality is suspected, the renogram curve can be generated from a selected area of interest encompassing the kidney region alone.²⁰ If a segmental abnormality is present, this region alone may be chosen for evaluation. If dysfunction of the collecting system is the problem, a curve may be generated from the renal pelvis and another curve from the area of the renal cortex alone (Fig. 6). This potential ability to selectively generate renogram curves creates the further possibility that chronic, parenchymal, renal disease may be differentiated from obstructive disease with this test. Once severe, irreversible, parenchymal disease has intervened, the renogram tracing will probably be abnormal throughout the kidney. In obstruction prior to total loss of the integrity of the renal parenchyma, it may be possible to generate normal

Fig. 6 Series of scintiphotos obtained 5 min after the administration of radiohippurate. In the figure at the top right, the region of interest chosen included the entire renal area (black box). The data were replayed from this area only to generate two renograms as shown at the top left. The upper curve is the typical delayed excretory pattern seen in urinary-tract obstruction and represents the time-course of orthoiodohippurate in the left kidney. The lower curve is a normal renogram. In an effort to delineate the site of obstruction, the cortex of the kidney was marked out (middle right) and the set of curves in the middle left figure was generated. Some improvement in the obstructive pattern resulted. It was then appreciated that the area of interest included part of the upper ureter and the lower portion of the renal pelvis. A new area of interest was chosen omitting part of the lower pole (lower right). The resultant renogram at lower left appears normal, confirming the impression that the renal cortex is relatively intact and the abnormality of the renogram was a result of an abnormality of the renal pelvis. Such an approach appears to be a promising method of differentiating renal parenchymal from obstructive disease in situations where the renograms are similar.

curves in selected areas. This is one of the most exciting recent developments in renal imaging.

RESIDUAL URINE

The renogram may easily be followed by a determination of residual urine volume.^{21,22} It is a simple matter after most of the orthiodohippurate has been excreted to count over the bladder and count again after the patient voids. The residual urine is:

$$\frac{\text{Final count over bladder}}{\text{Initial count—final count}} \times \text{voided volume}$$

In addition, the urine flow rate also can be determined. It should be categorically stated that catheterization of the urinary bladder to determine the residual urine volume is totally unnecessary in any institution equipped for routine nuclear medicine procedures. The risk of infection of the urinary tract following urethral catheterization far outweighs the risk of somatic effects of the radiation. Catheterization of the urinary bladder should be abandoned and substituted with isotope studies whenever the procedure is meant to be diagnostic rather than therapeutic. The use of diagnostic X ray for such tests cannot compete on any level with the great accuracy of the procedure when performed with radionuclides. This accuracy may be appreciated by inspection of Table 1, which shows the results of a previously reported study.

ALLERGY

One final category of patient remains to be considered: the individual with drug sensitivity to contrast media, who, in the past, was usually subjected to retrograde pyelography when urinary-tract disease was suspected. Now, with all the procedures described above, in most instances the needed information can be obtained with radionuclide studies, in which no allergic reaction has ever been reported.

CONCLUSIONS

Radionuclides have commanded an increasing place in nephrology. In our institution, clinical, renal rounds are constantly supplemented by information derived from radionuclide tests. We have just begun to tax the imagination. As better detection equipment and renal specific agents with a high-photon yield are developed, these tests will gain universal acceptance and widespread application.

TABLE 1
RESIDUAL URINE

Patient	Calculated residual,* ml	Measured residual,† ml	Patient	Calculated residual,* ml	Measured residual,† ml
1	34	40	11	22	25
2	57	46	12	27	30
3	68	92	13	65	58
4	64	60	14	22	30
5	27	24	15	16	24
6	190	250	16	83	90
7	196	180	17	25	32
8	187	180	18	27	25
9	18	12	19	62	70
10	50	50	20	290	280
			Mean	77	80

*Residual urine calculated from radionuclide procedure described in text.

†Residual urine measured by catheterization of the bladder immediately after completion of isotope procedure.

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EDITORS' NOTE

Apparently the reader can assume, from its failure to be mentioned here, that the radiochlormerodrin uptake or accumulation test is not useful in screening hypertensive patients for unilateral renal disease. This test [R. C. Reba, J. G. McAfee, and H. N. Wagner, Jr., Radiomercury-Labeled Chlormerodrin for In Vivo Uptake Studies and Scintillation Scanning of Unilateral Renal Lesions Associated with Hypertension, Medicine, 42: 269-296 (1963)] compared the counting rates at time t , usually $\frac{1}{2}$ to 1 hr after injection, to the counting rate 5 min after injection. This counting-rate ratio of C_t/C_5 over the right kidney divided by the ratio of counting rates over the left kidney was nearly identical for normal persons and patients with essential hypertension. The normal mean ± 2 SD was 0.95 ± 0.1 . Larger differences were found in patients with renovascular hypertension and in other unilateral abnormalities. The test was not of value in patients with moderate or severe uremia, and often too much

radiochlormerodrin concentrated in the liver, making interpretation of renal disease difficult.

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EVALUATION OF KIDNEY STRUCTURE AND FUNCTION BY RADIOISOTOPE IMAGING

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ABSTRACT

In the decade since McAfee and Wagner introduced radioisotope imaging of static distribution of ^{203}Hg -chlormerodrin in the kidney, renal imaging procedures have been developed to evaluate dynamic distributions of radiopharmaceuticals. These dynamic studies allow evaluation of kidney function and of the intrarenal distribution of kidney blood flow. Examination with several radiopharmaceuticals in a single test allows comparison of structure and function of small areas of kidney tissue. Similarly, mass lesions can be evaluated for vascularity and for any influence on kidney function. Many authors have reported highly accurate identification of kidney mass lesions, and evaluation by combinations of static and dynamic procedures has been shown to be accurate in determining whether such lesions are vascular or avascular. Our experience confirms this, showing that all of 22 neoplastic lesions of the kidney had the characteristics usually attributed to neoplastic mass lesions, whereas all of 10 cysts were seen to be avascular defects in the kidney images. Radioisotope imaging procedures have also been shown to be useful for identifying functional renal ischemia causing hypertension, for evaluating renal trauma, and for identifying and studying poorly functioning kidney tissue; these procedures are also useful for pediatric urology, for following the transplanted or postsurgical kidney, and for evaluation of patients sensitive to radiographic dyes. Radioisotope imaging can be expected to assume an increasing role in evaluating kidney structure and function.

In 1960 McAfee and Wagner¹ suggested the value of kidney scanning with ^{203}Hg -chlormerodrin for diagnosis of mass lesions. In the decade that followed, a profusion of radioisotope imaging instruments and radiopharmaceuticals provided for evaluation of the kidney by a variety of procedures. These techniques have had to compete with several well-established radiographic methods, but they have been well accepted for several specific diagnostic problems. There is reason to believe that a much wider application can be justified.

The value and limitations of both static and dynamic imaging procedures should be considered. Comparing static and dynamic images of the distributions

of several types of radiopharmaceuticals offers a possible increase in diagnostic accuracy and versatility. After proposing kidney evaluation by serial use of three radiopharmaceuticals and the scintillation camera^{2,3} in 1965, I have performed approximately 360 triple-isotope renal studies and 200 double-isotope studies. This experience supports the value of comparing kidney structure and function by imaging more than one radiopharmaceutical distribution in a single examination.

This paper reviews the diagnostic accuracy of these procedures. After a survey of the published information, our own experience with the triple-isotope examination will be reviewed, and comments will be made about additional information that it can yield.

We do the examination in a manner similar to that originally proposed. The patient is examined prone with the abdomen compressed by a polyurethane wedge. The scintillation-camera detector is positioned above the patient to provide a posterior view. With these conditions the interrenal distance is reduced, and most kidneys fit within the field of view of a 10-in.-diameter, parallel-hole, multichannel collimator. The flat surface of each kidney is presented parallel to the plane of the scintillation-camera detector; thus spatial resolution is optimal for any defect in the renal cortex. If the patient cannot maintain this position for a 40-min study, the examination can be conducted with him supine; the kidneys can then be viewed through a hole in the examination table or through a radiolucent surface. The patient should be instructed to empty his bladder before the study to avoid functional disturbance.⁴

Serial localization of the three isotopes is photographed without any change of the patient's position so as to allow precise comparisons of the localization of each radiopharmaceutical. The original radiopharmaceuticals proposed are still the most readily available and generally used for these purposes. The sequence is ²⁰³Hg—chlormerodrin, ¹³¹I—hippurate, and ^{99m}Tc—pertechnetate. Doses administered, timing of photography, and radiation dosimetry are summarized in Table 1.

Static images with chlormerodrin are used to evaluate kidney structure. The amount of chlormerodrin accumulated in the kidney is a function of renal blood flow.⁵ Chlormerodrin uptake by the kidney is not associated with any specific renal function but has been shown to be specifically localized by the proximal renal tubular cells. Excretion⁶ occurs as a two-phase curve with half-times of 5¼ hr and 7 days; 75% is lost during the first phase and the remaining 25% during the second. Thus, during the first few hours after intravenous administration of chlormerodrin, we see a rather homogeneously labeled renal image due to labeled urine in the calyces and pelvis. Later, the intrarenal urine collecting and draining structures will appear as negative defects. Any decrease in the rate of renal accumulation of chlormerodrin allows proportionately greater deposition in the liver and spleen, causing readily recognizable images of these organs to appear above the kidneys. Even with normal renal function, sufficient

TABLE 1
RADIOPHARMACEUTICALS USED FOR THE TRIPLE-ISOTOPE EXAMINATION

Radiopharmaceuticals (in order of use)	Details of scintiphotography			Absorbed radiation doses,* mrad	
	Dose (I. V.)	Start photography	Photo exposure time	Total body	Principal organ
Chlormerodrin- ¹⁹⁷ Hg or Chlormerodrin- ²⁰³ Hg† Hippurate- ¹³¹ I	150 µCi	>30 min	10 to 15 min	15	1050 (kidney)
	100 µCi	>30 min	10 to 15 min	100 to 200	7000 (kidney)
	200 µCi	Stat	2 min ‡ (serial x 15)	6 to 40	20 to 200 (kidney)
Pertechnetate- ^{99m} Tc	12 mCi	Stat	4 sec § (serial x 8)	120 to 240	480 to 2400 (stomach)

*Adapted from G. J. Hine and R. E. Johnston, Absorbed Dose from Radionuclides, *J. Nucl. Med.*, **11**: 468-469 (1970).

†Preferred for scintiphotography in adults (see text).

‡If renal function is reduced, use longer exposure times (4 or 8 min).

§ Requires rapid I. V. injection of a bolus, augmented venous return.

labeling of the liver occurs to allow estimation of any kidney displacement from the liver by an unlabeled mass. Kidney neoplasms ordinarily do not accumulate radiomercury, although accumulation in a renal tubular adenoma has been reported.⁷

The use of ^{203}Hg -chlormerodrin has been criticized because of the radiation exposure encountered, and the use of ^{197}Hg -chlormerodrin has been recommended.⁸ However, the use of ^{197}Hg -chlormerodrin has also been criticized because the degree of internal absorption of its gamma radiation makes it necessary to use a larger dose and because it delivers its absorbed radiation dose more rapidly than the ^{203}Hg , thereby causing a greater biologic effect.⁹ With the scintillation camera, ^{203}Hg -chlormerodrin is preferred because of the perceptibly higher spatial resolution that its 280-keV gamma photon provides even when the scintillation camera is equipped with alkali multiplier phototubes, which have a high photon efficiency. The ^{203}Hg -chlormerodrin is the material of choice for adults despite its causing as much as a 10-fold greater absorbed dose to the kidneys. Hopefully, one or more of the new static renal-imaging agents^{10,11} that have been proposed will prove to be satisfactory substitutes for chlormerodrin. Other technetium-labeled agents^{12,13} have been proposed for static renal imaging but have disadvantages of relatively high background counting and limited usefulness in uremia.

Hippurate labeled with ^{131}I is in general use for evaluation of renal function and for isotopic pyelograms. In uremia the slow transit time of hippurate across the kidney cortex allows its use for static imaging.¹⁴ The resulting images are so superior to chlormerodrin images in uremics that the initial imaging with chlormerodrin is usually omitted. Accumulation and excretion of hippurate depend on a variety of factors. Accumulation in the renal cortex depends on effective renal plasma flow and is the result of clearance by glomerular filtration and tubular excretion.^{15,16} Transit from the renal cortex to the renal pelvis requires water clearance. In renal ischemia, as well as in several other types of renal diseases, increased water reabsorption from the tubules causes prolongation of hippurate transit time through the cortex.¹⁷ What distinguishes the ischemic kidney with some reliability is the finding of a prolonged hippurate transit time in the presence of a normal one in the other kidney (or, with segmental disease, in another part of the same kidney).¹⁸ The pyelographic phase of the ^{131}I -hippurate imaging study can be used as a substitute for retrograde pyelography in patients with hypersensitivity to radiographic contrast agents and in other situations where conventional studies are difficult.

The third part of the triple-radiopharmaceutical evaluation is the use of $^{99\text{m}}\text{Tc}$ -pertechnetate to evaluate vascular filling of the kidney parenchyma. Pertechnetate is given as a rapid intravenous injection with provision for increased venous return so that after an ideal injection there will be delivery of a discrete bolus of radioactivity to the kidneys. Since renal blood flow is approximately 20% of cardiac output and the kidney mass is less than 0.5% of body mass, an image of renal vascular filling can be readily distinguished from

less well perfused tissues around the kidneys. Initial arterial filling provides a fair image of the aorta and its bifurcation, followed by images of the kidneys and then the spleen. The renal arteries are not seen. If a longer exposure photograph is obtained immediately after the rapid-flow study, one obtains a higher resolution image of kidney vascular filling patterns sufficient for the evaluation of vascularity in a mass lesion. This photograph is obtained before significant loss of pertechnetate from the vascular compartment. Technetium-labeled albumin would permit an even more deliberate high-resolution photograph of this type. It is essential that a careful comparison of the blood-flow study be made with all preceding studies, particularly the chlormerodrin study, so that any space-occupying lesion can be identified and its vascularity assessed.

The simultaneous use of these three radiopharmaceuticals in a single study is possible since the gamma energy of ^{131}I -hippurate, which is given second, is well above the gamma energies of either ^{203}Hg or ^{197}Hg , one of which is given first. The third part of the study does use a gamma energy below the others, and some Compton scatter radiation will be recorded with the discriminator window set for ^{99m}Tc ; but the dose of pertechnetate is 12 mCi as compared to 100 μCi of ^{203}Hg -chlormerodrin and 200 μCi of ^{131}I -hippurate. The ratio of ^{99m}Tc photons to scatter radiation from the previous isotopes is so large that a clear ^{99m}Tc image is obtained.

The serial use of these three radiopharmaceuticals is not always required. As previously mentioned, chlormerodrin is omitted if there is moderate uremia since the structural information in the chlormerodrin study is better provided by hippurate in this situation.⁴ The blood-flow study with pertechnetate is obtained only when it is thought that this will provide additional useful information after evaluation of the chlormerodrin and hippurate images.

A number of new radiopharmaceuticals have been proposed for dynamic renal imaging in addition to the new ones for static imaging that I have already mentioned. This other group of agents consists largely of chelated substances, which are excreted by glomerular filtration. Therefore, if radioactivity doses similar to those used for the ^{99m}Tc -pertechnetate flow study are administered, blood-flow distribution information can be obtained by rapid serial imaging followed by longer exposure scintiphotographs that show first the renal cortex and later the renal drainage structures. These agents provide better spatial resolution than does ^{131}I -hippurate owing to the large number of available counts that are recorded. Among the more promising of these new agents are chelates of ^{99m}Tc (Ref. 19), ^{113m}In , and ^{169}Yb (Ref. 20). Glomerular filtration clears them slowly compared to hippurate. The slower clearance presents high body backgrounds at a time when the kidney cortex is best labeled. Prolonged cortical transit time is not as readily identified with glomerular agents, as judged from our initial observations with ^{99m}Tc -DTPA. The use of ^{123}I -hippurate (Ref. 21) instead of ^{131}I -hippurate promises a major advance in kidney-function studies since it will provide increased spatial resolution in images through an ideal gamma energy for scintiphotography and,

with the short half-life allowing larger doses, much higher counting rates are available than with ^{131}I .

The information content of each part of the triple-radiopharmaceutical examination of the kidney is outlined in Table 2. This table also identifies the special applications of hippurate for evaluation of the uremic kidney and for identification of poorly functioning ectopic kidney tissue in patients who are

TABLE 2
INFORMATION PROVIDED BY EACH RADIOPHARMACEUTICAL
IN A TRIPLE-ISOTOPE EXAMINATION OF THE KIDNEY

	Chlormer.*	Hippur.*	Pertech.*
Anatomic information about whole kidney			
Size	N	U	N, U
Shape	N	U	N, U
Position	N	U	
Masses interposed between kidney and liver or spleen	N		
Kidney-structure information			
Cortex replacement or displacement	N	U	N, U
Vascular filling and transit			N, U
Calyceal and pelvic function		N, U	
Kidney-function information			
Effective renal plasma flow (isotope localization)	N	N, U	
Free water clearance (relative excretion function)		N, U	
Serial function comparisons		N, U	
Drainage-system evaluation			
Renal calyceal and pelvis volumes		N, U	
Ureteral function		N, U	
(Bladder structure and function)		N, U	

*N, normal or nearly normal renal function; U, uremics. Blank space indicates no important application or contribution.

not uremic. Table 3 summarizes the major applications of the triple-isotope studies. Earlier published studies have described the use of more than one radiopharmaceutical in a single test, but they give little information on the diagnostic advantages of a double- or triple-isotope examination over examination with a single isotope. Table 4 summarizes the general advantages of kidney-imaging procedures with radiopharmaceuticals compared to radiographic techniques.

To formulate a statement of the current status of renal imaging techniques, I will summarize the reported findings in several diagnostic applications. Al-

TABLE 3

APPLICATIONS OF KIDNEY IMAGING BY RADIOPHARMACEUTICALS

A. Disease-oriented applications

1. Evaluation for mass lesions.
2. Identification of regions of renal ischemia causing hypertension.
3. Evaluation of the kidney in uremia.
4. Determination of the location of poorly functioning ectopic kidney tissue in the absence of uremia.
5. Determination of the amount of function in a poorly functioning kidney.
6. Serial evaluation of kidney structure and function
 - a. Posttrauma.
 - b. Postsurgery.
 - c. Obstructive uropathy.
 - d. Acute tubular necrosis.
 - e. Kidney transplantation.

B. Applications in special situations

1. To avoid retrograde urography, especially in male pediatric patients.
 2. In patients with radiographic-dye sensitivity.
 3. For patients with difficult-to-interpret pyelographic examinations owing to
 - a. Bowel gas or contents.
 - b. Obesity.
 4. Kidney localization for percutaneous biopsy.
-

TABLE 4

**GENERAL ADVANTAGES OF KIDNEY IMAGING WITH
RADIOPHARMACEUTICALS COMPARED TO RADIOGRAPHIC TECHNIQUES**

1. No preparation of patient.
 2. No hypersensitivity to agent used.
 3. Noninvasive (no instrumentation of patient).
 4. Provides for quantification of radiopharmaceutical localization.
 5. Useful despite poor renal function.
 6. Direct comparison of several mechanisms of radiopharmaceutical localization gives added information.
 7. Good definition of renal cortex without need for tomography, continuous infusion, or other special techniques.
-

though the major diagnostic areas are covered, applications in less common special situations are not completely described but should not be overlooked since radioisotope imaging techniques often provide adequate information where conventional urographic techniques cannot be used.

EVALUATION FOR MASS LESIONS

There are relatively few published reports concerning diagnostic accuracy of radioisotope imaging for identifying mass lesions of the kidney. Limited

utilization of the scintigraphic method may reflect the profusion of radiographic means of kidney evaluation: intravenous pyelography, infusion pyelography, nephrotomography, retrograde urography, and selective renal arteriography. However, a number of authors have suggested that the scintigraphic methods should receive strong consideration as primary diagnostic methods to be used in evaluating the renal cortex for mass lesions. Table 5 summarizes the diagnostic accuracy described for several of the larger published studies. These papers are predominantly descriptions of rectilinear scanning with ^{203}Hg -chlormerodrin without simultaneous examination by other radiopharmaceuticals. Histopathologic confirmation of the diagnosis was lacking in some of the cases. The diagnostic accuracy suggested by this compilation is excellent, and the nature of the false negative scans suggests an even better correlation than the large number of confirmed positive scans. For example, the one false negative scan in Morris's experience²⁵ showed a generalized decrease of renal accumulation of chlormerodrin on the side harboring the neoplasm, and there was a displacement of the long axis of the kidney. The two false negative cases noted by MacEwan²⁴ were both occult carcinomas adjacent to cysts that were recognized as abnormalities in the scans. Thus there was definite abnormality in each of these kidneys that were among the few false negatives in renal carcinoma. MacEwan commented that in five instances of involvement of the kidney by metastatic neoplasm or by lymphoma, there was only one positive scan. However, both Morris²⁵ and Hennig²⁶ observed focal abnormalities regularly with renal malignancies other than renal-cell carcinoma. The renal scan appears to demonstrate abnormality in the presence of renal cysts about as effectively as in the presence of renal neoplasms. Both MacEwan²⁴ and Morris²⁵ commented on finding extra cysts in the scan image which were not discovered by pyelography.

Several aspects of the chlormerodrin image can be used to distinguish between neoplasms and cysts. Certainly, both carcinomas and cysts can produce defects with smooth curvilinear margins that are indistinguishable in some patients.²⁸ Generally speaking, however, it is the benign cysts that produce perfectly spherical defects with characteristic smooth margins.²⁶ Carcinomas tend to invade the kidney, whereas cysts tend to protrude from it. The finding of several lesions typical of cysts is an even stronger indication of cystic disease.²⁴ Morris et al.²⁵ emphasized that renal carcinomas are often associated with diminished chlormerodrin accumulation adjacent to the focal defect caused by the actual neoplasm. The adjacent renal cortex or even the entire remaining cortex of the affected kidney may show diminished chlormerodrin as a result of obstructive uropathy, venous stasis, lymphatic obstruction, interference with arterial blood supply by obstruction or diversion to the tumor, or direct toxic effects of the neoplasm. Obstructive uropathy and renal-vein obstruction are probably the more common mechanisms. To these might be added the direct pressure effect of the tumor on adjacent tissues.

The major reason for using multiple pharmaceutical agents in examining the kidney is to increase the specificity of the examination. Particularly, when

blood-flow-imaging studies are performed with pertechnetate and compared with those made with chlormerodrin, the degree of vascularity in a mass can be clearly distinguished (Figs. 1 and 2). Several publications have described this way of differentiating between cysts and renal neoplasms. After Powell^{2,3} described this method, Black²⁹ reported the study of 15 cases in which there was one lesion missed both by arteriography and by scintiphotography, a 1.5-cm benign adenoma. He also reported that in one case of a kidney studied for a suspected cyst, which was confirmed by the scintiphotographic examination, a renal-cell carcinoma was revealed in another part of the kidney. Rosenthal³⁰ described evaluations of 51 cysts and 35 primary malignant neoplasms plus 14 other lesions, including 3 renal pelvic tumors and 8 instances of focal infections. These evaluations involved only one misdiagnosis, a cyst that, owing to the overlying spleen, appeared to have vascularity. Three renal pelvic carcinomas were found to have no demonstrable vascular blush, but no photograph was obtained to show the static distribution of pertechnetate immediately after the flow studies. Not all the vascular lesions visualized in the cortex were malignant since 2 hamartomas, an arteriovenous (AV) malformation, and focal pyelonephritis were all shown to have vascularity by this method. Focal infections generally appeared to be avascular, as did all but the one misinterpreted cyst.

Table 6 summarizes our experience in distinguishing renal cysts and neoplasms with the multiple-isotope (²⁰³Hg-chlormerodrin, ¹³¹I-hippurate, and ^{99m}Tc-pertechnetate) renal scintiphotographic technique. This experience is primarily with patients whose intravenous pyelography (IVP) or renal arteriography is inconclusive, leading to their referral for radioisotopic imaging studies. We have not done a sufficient prospective study to know the incidence of false negatives, but the technique appears to be highly accurate for detecting mass lesions of the kidney and for differentiating between vascularized neoplasms and cysts or other avascular lesions. Several observations can be made in addition to those already discussed. Vascular renal lesions quite often perfuse at a time different from the remainder of the adjacent cortex. Early perfusion is more frequent than late perfusion in renal-cell carcinomas. In all three transitional-cell carcinomas in our experience, there was a very slow perfusion and reduced labeling with pertechnetate during the rapid-sequence flow study (Fig. 3). This is followed by filling with a concentration of pertechnetate similar to that in the remainder of the kidney, as can be shown in a 500,000-count photograph obtained immediately after the rapid-sequence-flow study. This 500,000-count scintiphotograph is most useful in demonstrating the limited vascularity in these neoplasms and in others that are less well vascularized than the renal-cell carcinomas. In this manner two lipoangiomas of the peripheral cortex were demonstrated to be vascularized lesions. As might be expected from the common occurrence of vascular compromise by renal-cell carcinomas, the kidneys involved often show abnormalities of hippurate accumulation and excretion so that there is a prolongation of hippurate transit time in the cortex adjacent to the tumor or in the whole kidney. This abnormality is less frequently

TABLE 5
IDENTIFICATION OF KIDNEY MASS LESION BY RADIOISOTOPE IMAGING
WITH RADIOPHARMACEUTICALS THAT LOCALIZE IN THE CORTEX

Author	Renal-cell carcinoma*			Other kidney malignancies*			Renal cysts*		
	No.	Image+	Image—	No.	Image+	Image—	No.	Image+	Image—
Stewart ^{2,2}	7	6	1	1	1	0	5	3	2
Brooks ^{2,3}	4	4	0	0			11	9	2
MacEwan ^{2,4}	22	20	2	5	1	4	57	53	4
Morris ^{2,5}	24	23	1	3	3	0	11	11	0
Hennig ^{2,6}	34	34	0	6	6	0	21	21	0
Baker ^{2,7}	6	6	0	1	1	0			
Total	97	93 (96%)	4	16	12 (75%)	4	105	97 (92%)	8

*Image+ indicates regional abnormality in the radioisotope image consistent with the radiographic or anatomic findings. Image— indicates radioisotopic image abnormality absent in the region that would be suspected on the basis of other examinations. A high positive correlation of radioisotope image abnormalities and the actual position of lesions is demonstrated.

TABLE 6
SCINTIPHOTOGRAPHIC EVALUATION OF SUSPECTED MASS LESIONS BY MULTIPLE ISOTOPES

	No.	No. with triple study*	Tissue diagnosis	Agree†	Clinical diagnosis	Agree†	No. with IVP	Agree†	No. with arterio.	Agree†
Renal-cell carcinoma	8	7	6	6	2	2	8	4	8	7
Necrotic renal-cell carcinoma	3	3	3	3			3	1	3	2
Wilms' tumor	4	1	4	4			4	3	1	1
Transitional-cell carcinoma	3	3	3	3			3	2	1	0
Angiolipoma	2	2	2	2			2	1	2	2
Lymphoma, leukemia	4	2	4	4			4	2	2	2
Subtotal			22	22	2	2	24	13	17	14
				(100%)		(100%)		(54%)		(82%)
Cyst	13	12	6	6	7	6	12	12	8	7
Multicystic kidney	5	4	1	1	4	2	5	2	1	0
AV malformation	1	1	1	1			1	1	1	1
Other benign lesions	5	4	2	2	3	2	4	2	0	
Subtotal			10	10	14	10	22	17	10	8
				(100%)		(71%)		(77%)		(80%)
Total			32	32	16	12	46	30	27	22
				(100%)		(75%)		(65%)		(81%)

*Patients evaluated with ^{203}Hg -chlormerodrin, ^{131}I -hippurate, and $^{99\text{m}}\text{Tc}$ -pertechnetate.

†"Agree" indicates that the study was satisfactory for interpretation and that overall evaluation was consistent with final tissue diagnosis or with other studies and clinical diagnosis if no tissue examination was available.

KIDNEY STRUCTURE AND FUNCTION

^{203}Hg -CHLORMERODRIN

^{131}I -HIPPURATE

0-2 min

2-4 min

4-6 min

8-10 min

14-16 min

24-26 min

^{99m}Tc -PERTECHNETATE

8-12 sec

12-16 sec

16-20 sec

20-24 sec

24-28 sec

500 K

Fig. 2 Scintiphotograph of renal cyst. The typical renal cyst has a curvilinear margin, which is seen outlined by the remaining kidney tissue in the ^{203}Hg -chlormerodrin view. There is no interference with renal hemodynamics; so the remainder of the kidney appears to have normal accumulation of chlormerodrin. In a like manner, ^{131}I -hippurate accumulates at a rate similar to that in the other kidney, and there is no evidence of any late retention of hippurate except when the cyst has caused obstruction to drainage of labeled urine from the kidney. This seems to be the case in this example, which shows late retention of hippurate in an upper pole calyx of the left kidney. Often a cyst will protrude from the kidney and be largely extrarenal. A cyst of this sort on the kidney surface will cause *minimal* change in the outline of the static kidney images but may displace the kidney. This example shows a slight cortical retention of hippurate, which is a mild abnormality, but it appears to be symmetrical in each kidney and does not appear to reflect any regional effect of the mass lesion on renal hemodynamics in the left kidney. The ^{99m}Tc -pertechnetate blood-flow study confirms that the defect is avascular, both in the series of 4-sec exposures and in the 500,000-count higher resolution photograph obtained immediately after the flow study.

^{203}Hg -CHLORMERODRIN **^{131}I -HIPPURATE** **^{99m}Tc -PERTECHNETATE**

Fig. 3 Scintiphotograph of transitional cell carcinoma. This is the typical appearance of a triple-isotope scintiphotographic evaluation of a transitional cell carcinoma. The ^{203}Hg -chlormerodrin picture shows a defect of the upper pole of the right kidney which is not associated with diminished uptake of chlormerodrin in the remainder of the kidney. Hippurate is not excreted in the region of the upper pole of the kidney, but there is no interference with hippurate excretion function in the remainder of the kidney. The ^{99m}Tc -pertechnetate blood-flow study shows diminished early filling of the upper pole of the right kidney but a fairly normal late labeling in the region, confirming vascularity in the lesion. The relatively poor vascularity, late filling, and similar vascularity to the remainder of the kidney cortex in this kidney and the normal contralateral kidney seen in the picture obtained in the second minute after injection are all typical of a poorly vascularized renal neoplasm, such as transitional cell carcinoma.

seen in the presence of single cysts, but in polycystic disease generalized renal-function abnormality is common and often causes prolonged hippurate retention.

Undoubtedly, a prospective study of the diagnostic accuracy of renal imaging with triple radiopharmaceuticals would demonstrate that there is an appreciable incidence of minor areas of decreased chlormerodrin accumulation which have some decrease of function and perfusion in the hippurate and pertechnetate studies. This description fits kidneys affected by pyelonephritis, granulomatous disease, and other localized abnormalities that usually occur in several areas of one or both kidneys. Mass lesions are usually larger and have more discrete margins, which allows their identification. Rosenthal³⁰ described minor abnormalities in kidney images due to inflammatory and other changes and stated that these areas often appeared vascularized in blood-flow studies, but he did not comment on the frequency with which they might be confused with renal-cell carcinomas. Kidney carcinomas among our series of mass lesions were larger and were readily identified as discrete focal lesions.

Thus the combined examination by several radiopharmaceuticals appears to have a very high diagnostic accuracy for renal masses. As an accurate, completely safe, simple, and relatively inexpensive screening technique, it should be more widely used for evaluating renal mass lesions. Certainly the method is particularly valuable for elderly patients or others in whom angiography and other more hazardous procedures produce their highest morbidity. The advent of newer radiopharmaceuticals that produce increased spatial resolution in static images of the kidney cortex promises to improve the already impressive statistics concerning diagnostic accuracy of scintigraphic methods for the detection and characterization of masses in the kidney.

IDENTIFICATION OF RENAL ISCHEMIA CAUSING HYPERTENSION

The radioisotope renogram³¹ with ¹³¹I-orthoiodohippurate has long been used to screen for kidney disease among hypertensives. Maxwell's¹⁸ review of several authors' experience with renograms suggests an overall 85% positive correlation with significant renal-artery stenosis, but there are 15% false negatives.¹⁸ Control subjects with primary hypertension showed 19% false positives. This review described 423 controls and 377 patients with proven renal-artery stenosis but without any determination of the functional significance of the proven vascular lesions. The question of functional significance of a lesion remains central to the evaluation of any hypertensive patient: Is the renal ischemia etiologic for the hypertension?³² A number of tests have been proposed for identifying functionally significant lesions. The evaluation of urine contents and volume from each kidney, as originally proposed by Howard³³ and then further developed by Stamey,³⁴ has proved to be a helpful test of functional significance but has two important drawbacks. First, the Howard-Stamey test requires ureteral catheterization, and, second, the observations are

made on the mixed urine from an entire kidney, which may obscure findings relating to segmental disease within the kidney. More recently, renal-vein renin assays³⁵ have been helpful in predicting surgical results, but this method requires renal-vein catheterization. Kaufman³⁶ reviewed the diagnostic accuracy of various methods for evaluation of renovascular hypertension and indicated that with proven renal-artery stenosis, consideration of all parameters of intravenous urography will yield a 90% positive correlation. Function tests performed separately for each kidney will yield 80% positive correlation in main-stem lesions, 62% in bilateral lesions, and 29% in branch lesions, for an overall accuracy of 71%. Kaufman also indicated that plasma renin could be expected to be normal in one-third of patients with hypertension secondary to renal-artery stenosis. These data indicate a major need for means of identifying the site of renovascular ischemia and determining whether it is functionally significant.

Kidney scintiphotography with multiple radiopharmaceuticals offers both a means of identifying renal ischemia and a method for confirming its functional significance. Powell² presented scintiphotographic abnormalities in renal localization of all three radiopharmaceuticals in functionally significant renal ischemia. Burke¹⁷ described in considerable detail the renal-function information that can be obtained from a sequence of scintiphotographs showing the various phases of hippurate excretion. He did not study renovascular ischemia in his initial evaluation but commented that the photographs would allow direct correlation of various segments of the renogram curve with the intrarenal location of the hippurate in transit. He suggested that such a study could distinguish between abnormalities caused by obstruction, hydropenia, and renal-artery stenosis, all of which might give identical renograms. As discussed earlier, an area of kidney cortex with a prolonged hippurate transit time contrasted with normal cortical function in other areas is the finding in a triple-isotope study that can confirm functionally significant regional ischemia in hypertensives. Very little information is available on the diagnostic accuracy of such observations. As recently as 1970, Rosenthal³⁷ reviewed his experience with hippurate scintiphotography and commented that for renovascular ischemia the hippurate series did not add appreciably to information derived from the renogram.

DiOrio³⁸ reviewed his experience with chlormerodrin scanning of the kidneys for evaluation of hypertension and summarized the varying experience of others. Of the four papers he summarized, only MacEwan²⁴ had found a good correlation when he compared the results of urographic procedures with renal scanning and renography in the diagnosis of renovascular hypertension. Wagner,³⁹ McAfee,⁴⁰ and Meier⁴¹ all had considered renal scanning rather unsatisfactory, with false negatives of 10, 19, and 15%, respectively. DiOrio reported a somewhat more satisfactory experience with scanning, indicating that none of 20 patients with normal renal scans proved to have surgically correctable hypertension. In predicting surgical outcome, he found the scan to be more

consistent than excretory urography, aortography, renin levels, or split renal-function tests. The scan was correct in predicting the outcome of six of seven patients that were operated on. In the one inaccurate prediction, follow-up studies disclosed thrombosis of a renal-artery graft and a surgical failure. Although the aortogram showed a lesion in every patient operated on, aortograms showed bilateral lesions in one patient and a renal-arterial stenosis in another patient where there was no response to surgery and the scan had been normal.

Pertechnetate flow studies have been used to demonstrate renal ischemia, but this information only describes the ischemia and does not relate to its functional significance. Freeman⁴² reported the use of pertechnetate blood-flow studies to define major renovascular occlusions and reported excellent correlations.

TABLE 7

MULTIPLE-ISOTOPE EVALUATION OF KIDNEYS IN RENOVASCULAR
HYPERTENSION SHOWING GOOD OR EXCELLENT RESPONSE
TO UNILATERAL SURGERY

	²⁰³ Hg—chlormerodrin (including size evaluation)	¹³¹ I—hippurate (function aspects only)	^{99m} Tc—pertechnetate
Number	15	15	12
Number abnormal	11	15	10
Kidney operated on showed:			
Greater abnorm.	9	14	9
Equal abnorm.	1	1*	0
Less abnorm.	1†	0	1†
No abnorm.	4	0	2
Localized abnorm.	4	5	7

*Kidney operated on was small and had greater abnormalities of chlormerodrin labeling.

†Kidney operated on showed more abnormality of hippurate excretion than an atrophic kidney that had more striking abnormalities in the chlormerodrin studies.

In the absence of a reported description of the use of a triple-isotope examination to identify renovascular ischemia causing hypertension and correlation of the results with surgical success, we have reviewed our own experience (Table 7). This experience was highly selected since referrals were patients in whom there was doubt about the diagnosis of renovascular hypertension or about which side should be operated on (Fig. 4). Considering only cases that had either marked improvement or disappearance of hypertension after surgery, Table 8 describes the correlations of the findings by triple-isotope scintiphotography with those by intravenous pyelography or arteriography. For 7 patients

^{203}Hg -CHLORMERODRIN L R
36.5 K 21.4 K ^{131}I -HIPPURATE

0-2 min

2-4 min

4-6 min

8-10 min

14-16 min

28-30 min

 ^{99m}Tc -PERTECHNETATE

12-16 sec

16-20 sec

20-24 sec

24-28 sec

28-32 sec

500 K

Fig. 4 Scintiphotograph of renal ischemia causing hypertension. This patient posed a diagnostic problem with the finding of bilateral renal arterial lesions without a clear definition of which kidney might be predominantly involved. There was obviously a much smaller renal volume on the right. The ^{203}Hg -chlormerodrin study showed a normal-appearing image of the left kidney and a small right kidney that had diminished uptake of chlormerodrin, even allowing for its smaller volume. This is consistent with renal ischemia on the right. The ^{99m}Tc -pertechnetate blood-flow study confirmed that there was diminished filling of the right kidney compared to the left. A distinct image of the spleen filled at about the same time as the left kidney and can be seen above and lateral to the kidney. The functional significance of the right renal arterial lesion was confirmed in the ^{131}I -hippurate study, which demonstrated slowed accumulation of hippurate and prolonged retention in the cortex of the right kidney compared to the left. The prolonged hippurate transit time in the entire cortex of this kidney is typical for renal ischemia due to a lesion of the right renal artery. Right nephrectomy was followed by disappearance of hypertension. The lesion in the left renal artery was not operated on.

TABLE 8
COMPARISON OF SCINTIPHOTOGRAPHIC EVALUATIONS WITH
INTRAVENOUS PYELOGRAPHY AND ARTERIOGRAPHY IN
HYPERTENSION SHOWING GOOD OR EXCELLENT
RESPONSE TO UNILATERAL SURGERY

Localization of abnormality by preoperative test	Agreement of preoperative test with surgical findings*					
	Multiple- isotope study	Agree†	IVP	Agree†	Arterio.	Agree†
One kidney	7	7	8	8	10	10
Both kidneys, one predominating	8	8			4	4
Both kidneys, symmetrical abnorm.					1	0
No indication of localized abnorm.			6	0		

*All numbers are numbers of patients.

†"Agree" indicates predominant abnormality in kidney operated on with favorable response of hypertension.

the radiographic test did not give sufficient evidence to decide on a side for corrective surgery, and there were 4 patients with bilateral renal-vein renin abnormalities. Thus the scintiphotographic test was requested to obtain additional evidence upon which to make a surgical decision. Split-function studies were performed in only 2 of these 10 patients and in both showed abnormality in the side that was later operated on. Considering that these cases were referred for isotope examination predominantly because of diagnostic uncertainties after pyelographic and arteriographic evaluation (plus, in some patients, renal-vein renin assays or split-function studies), it is remarkable that the scintigraphic studies were able to identify the abnormal kidney with the accuracy demonstrated. A triple-isotope examination appears to identify both the kidney abnormality and its functional significance in causing renovascular hypertension. It is probable, therefore, that the scintiphotographic evaluation, or at least the hippurate part of it, should be used more widely both for screening hypertensives to detect possible renal etiology and for characterizing the functional significance of any ischemic area discovered in a hypertensive patient's kidney.

In our experience there are a number of cases not yet subjected to a detailed analysis where pyelography and renal arteriography were originally interpreted as normal but where there was clear abnormality on the triple-isotope scintiphotographic evaluation. In most instances this has led us to a reinterpretation of arteriographic findings as showing minimal abnormality. This situation

most often arises with regional renovascular disease which the scintiphotography has identified. At this time we do not have data on the incidence of false positives or false negatives. A prospective study would be required to provide these data.

Several general observations can be made about findings in renovascular hypertension. The abnormalities of hippurate transit time correlated best with favorable response to unilateral surgery. The patient in whom this was not true had bilateral minimal abnormalities of hippurate transit time but a more pronounced unilateral of chlormerodrin localization abnormality in the kidney that was successfully operated on. By contrast, in another patient the chlormerodrin and pertechnetate studies showed an atrophic kidney with striking reduction of blood flow, whereas the hippurate study showed that the opposite kidney was etiologic in the hypertension, as confirmed by successful surgery on this kidney. Similarly, there were several chlormerodrin and pertechnetate studies that showed no abnormality in patients who had distinct abnormalities of hippurate transit time. Therefore, in this small group of patients with good response to unilateral surgery, it appears that the hippurate evaluation was the part of the scintigraphic testing that best identified functionally significant ischemia. This is the part of the examination, then, that appears to have the most general usefulness as a screening technique, although the definition of cortical outlines with ^{203}Hg -chlormerodrin is often required to give further definition to cortical lesions and to differentiate cortical from pelvic retention.

SCINTIGRAPHIC EVALUATION OF THE KIDNEY WHEN INTRAVENOUS UROGRAPHY IS INADEQUATE

There are two situations in which scintigraphic kidney studies can provide diagnostic information when intravenous urography is inadequate. In each situation the problem is to evaluate poorly functioning renal tissue, either the kidneys in a uremic patient or poorly functioning ectopic renal tissue in a patient with normal kidney function. Rosenthal¹⁴ first emphasized the superiority of imaging with hippurate in renal failure compared to chlormerodrin imaging and intravenous pyelography. Other reports have followed,^{3,7,43} and our experience confirms this. Renal failure of various etiologies often occurs with a clinical situation that requires evaluation for ureteral or renovascular obstruction. The late hippurate images often show symmetrical function and urine drainage without obstruction. Symmetrical function is unlikely with a vascular etiology of failure, assuming that obstruction of the abdominal aorta or inferior vena cava is excluded. Thus the late hippurate image may contain enough information to exclude the major surgically correctable types of renal failure. Vascular perfusion can be assessed with a pertechnetate flow study. The scintigraphic technique often avoids more traumatic procedures, such as retrograde urography and renal angiography.

Similarly, the search for poorly functioning ectopic renal tissue by hippurate scintigraphy is often successful after failure of intravenous pyelography to identify the ectopic kidney. Again, late views at one-half to several hours are required to find the ectopic tissue. After sufficient time for slow accumulation of a small amount of hippurate and after decrease of blood background, there is an optimal chance to identify the ectopic tissue. Identification can be improved by photographic superimposition of several scintiphotos obtained without position change. This type of study was successful in defining the location of ectopic kidney structures in two of our pediatric patients in whom repeated pyelographic examinations had been unsuccessful. One was confirmed by arteriography; both were successfully operated on, with removal of the poorly functioning ectopic kidneys.

SERIAL EVALUATIONS OF KIDNEY STRUCTURE AND FUNCTION

Several other types of problems are also particularly suitable for scintiphographic evaluation because of their need for repeat or serial examinations. Numerical data in the simultaneously obtained renograms are susceptible to comparisons that cannot be performed on images alone. Thus renograms become an especially important part of these serial examinations. These problems (outlined earlier) are serial evaluation of kidney structure and function posttrauma, postsurgery, in obstructive uropathy, during acute tubular necrosis, and after kidney transplantation. Obviously some of these problems are interrelated, and, in addition, many involve evaluation during renal failure.

Scintigraphic evaluation is particularly efficient in kidney trauma.⁴⁴⁻⁴⁶ Kazmin, Swanson, and Cockett⁴⁵ found that ^{197}Hg -chlormerodrin scans distinguished kidney lacerations from simple contusions in all of 21 cases, whereas pyelography and renal arteriography were frequently unsatisfactory. They described the scan as an excellent preoperative confirmatory test, as judged from clinical experience, and considered the scan more reliable than aortography on the basis of work with animals. Their work with animals showed that minimal renal injury, such as contusion or subcapsular hemorrhage, usually does not cause scan abnormality. We followed a traumatized kidney using the original dose of chlormerodrin for structural evaluations over several days and repeat hippurate studies to assess function and urine extravasation (Fig. 5). Since many minor lacerations can be managed conservatively, serial scintiphographic evaluations should be particularly helpful in following these kidneys.

Perhaps the single most frequently reported use of serial imaging is in the evaluation of transplanted kidneys. Collins et al.⁴⁷ reported this use in 1963, and Figueroa et al.⁴⁸ in 1965 evaluated ^{203}Hg -chlormerodrin for this application. After necrosis of the kidney, the chlormerodrin studies showed a negative renal image in a positive background, and with oliguria after transplantation, there were varying degrees of uniform uptake of the labeled

^{203}Hg -CHLORMERODRIN

Fig. 5 Scintiphotograph of renal trauma. A kidney scintiphotographic examination after abdominal trauma showed inferior displacement of the left kidney associated with minimal decrease of labeling in the upper poles of both kidneys. Close inspection of the hippurate series demonstrates evidence of extravasation of hippurate above the upper pole of the left kidney. The ^{203}Hg -chlormerodrin image was considered evidence against a major renal laceration that would require surgical repair. The $^{99\text{m}}\text{Tc}$ -pertechnetate blood-flow study showed separation of the kidney image and the spleen, probably due to a large hematoma. All changes subsided in a repeat study performed after 2 weeks of conservative management.

 ^{131}I -HIPPURATE

0-2 min

2-4 min

6-8 min

12-14 min

18-20 min

24-26 min

 $^{99\text{m}}\text{Tc}$ -PERTECHNETATE

4-8 sec

8-12 sec

12-16 sec

16-20 sec

20-24 sec

24-28 sec

material. Irregular labeling was thought to represent regional vascular insufficiency. Iodine-131-hippurate and ^{99m}Tc -pertechnetate have since supplanted ^{203}Hg -chlormerodrin for transplant evaluations.^{49,50} Scintiphotography provides reliable evaluation for the function of the vascular and ureteral anastomoses but in our experience does not distinguish acute tubular necrosis from rejection.

Other uses of serial imaging procedures are less well documented. There were early reports of using renography to evaluate postoperative anuria,⁵¹ obstructive uropathy,⁵² toxemia of pregnancy,⁵³ and ureterovesicular reflux.⁵⁴ The addition of the information available in a radioisotope image greatly enhances the renographic study and by a multiple isotope examination can give direct information on distribution of renal blood flow. In our experience hippurate studies have correlated quite well with pyelographic information. Perhaps the best confirmation of the value of radioisotope imaging procedures in general urologic evaluations has been in pediatric work.^{55,56} Radwin and Novoselsky⁵⁵ suggested the pediatric use of the method in 1967, and the more recent work by Shuler, Meckstroth, and Maxfield⁵⁶ strongly supports the superiority of scintiphotography with ^{131}I -hippurate plus scintillation-camera renograms over intravenous pyelograms. Of 88 patients, there were 7 in whom the scintigraphic study obtained diagnostic information that was not obtained by intravenous pyelography, 2 in whom the pyelograms could not be done because of uremia, and 5 with known dye allergy; there was correlation between the radioisotopic and radiographic tests in the 74 remaining patients.

SUMMARY

Kidney scintiphotography appears to be an accurate procedure for distinguishing between avascular and vascularized tumors of the kidney, for identifying renal ischemia and estimating its functional significance in hypertension, and for assessing a variety of other renal diseases. This noninvasive, rapid, and widely applicable method can be used when urography cannot: in uremia, in patients with dye sensitivity, and for evaluation of poorly functioning kidney tissue in the absence of uremia. Kidney scintiphotography has amply demonstrated its usefulness to most physicians who have used the method. It is destined to become a major method for evaluating kidney structure and function.

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APPROPRIATE USE OF RADIOISOTOPIC TECHNIQUES IN EVALUATION OF RENAL DISEASE

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ABSTRACT

Laboratory nephrology—encompassing the associated disciplines of radiology, nuclear medicine, clinical chemistry, and microbiology—provides a broad array of anatomic and functional information to assist the clinical nephrologist in the diagnosis of renal, renovascular, and urinary-tract diseases, and in the management of patients afflicted with these. The tests available range from simple procedures to some of considerable complexity, and extensive investigation requires a considerable expenditure of time and money. We propose a rational sequence of employment to obtain the necessary results as easily and inexpensively as possible.

This principle is illustrated by the process of diagnostic evaluation and management in five representative cases. Radiography, supplying predominantly anatomic information, and nuclear medicine, supplying predominantly functional information, should be complementary rather than competitive; and the clinical need is served best when urologist, radiologist, and laboratory and clinical nephrologists cooperate fully and freely in selecting the tests and synthesizing their results.

Clinical concern with radiographic and radioisotopic diagnostic procedures centers logically around their direct value in assessment and management of patients. To nephrologists and urologists these two groups of diagnostic tests offer interesting points of corroboration and difference in their contributions to the diagnosis of a wide variety of functional and anatomic disorders of the renal and genitourinary systems.

TYPES OF PROCEDURES AND RATIONALE OF SELECTION

Laboratory evaluation of renal disease depends heavily on measurements of function, visualization of the kidney and its vascular system, and delineation of the urinary tract. Long and widespread usage has established the resultant information as essential. The most reliable estimates of renal function remain the

measurements of glomerular filtration rate and of effective renal plasma flow, derived from clearance techniques set forth in the early works of Smith and his many distinguished collaborators.¹ Well standardized also are the radiographic techniques of excretory urography, nephrotomography, and renal angiography.

More recent additions to the diagnostic armamentarium are the tests that use selected pharmaceutical agents bearing radioactive nuclides.² These include the isotope renogram, clearance procedures paralleling the classic inulin and *p*-aminohippuric acid (PAH) methods,³ scintiscans and scintiphotos employing *o*-iodohippuric acid (OIH) or mercury-labeled chlormerodrin or both, and radioimmunoassay of plasma renin activity in the peripheral and renal-vein blood.

Because current problems in diagnosis are so complex, we advocate consideration of all possible aids and judicious selection from this battery of test procedures for optimal assessment of clinical status, choice of therapy, and follow-up study. Radiography provides essential information that is predominantly anatomic or structural in character, and the details of this information are familiar to all in nephrology. Qualitative estimation of function may also be derived from these studies, and they may be followed by more definitive and quantitative measurements of function where these are considered necessary. Such quantitative data are best obtained with clearance techniques, employing either the classic agents or their radioactive counterparts. From radioisotopic renography and from imaging of the kidney with radioactive agents comes information predominantly functional in character, but with implications of anatomic status that often complement the information gained from radiography.

We believe it unwise to rely on single lines of study. However, the mounting expense of laboratory investigation necessitates realistic consideration of the multifaceted battery available and a rational selection of those tests likely to be of greatest value in the clinical assessment of the problem presented. It is too easy to place the newer applications of radioactive pharmaceuticals in a competitive relation to the accepted techniques of radiography and classic measurements of function. We judge it important to stress that these procedures are not in competition: they are complementary and of cumulative value in their potential for aiding the nephrologist or urologist in managing the clinical problem at hand.

Initial evaluation of the patient likely to have a renal or genitourinary disorder is based on appropriate specimen collection, urinalysis, and microscopic review of the urinary sediment. These, together with the measurement of the serum creatinine level and with gram staining and culture of urine, may suffice if the results are normal or negative and the patient is asymptomatic from the nephrologic standpoint. Where the history, physical findings, or initial laboratory observations indicate an abnormality, testing must be extended until all information necessary to the clinical objective has been obtained or all avenues

have been explored. For this the clinician must know the laboratory methods available to him and the contribution that each can make to the solution of his diagnostic problems.

It is equally necessary that the laboratory nephrologist and radiologist have available control values and normal limits for the procedures that are their responsibility; and most of these are well established. However, the principles underlying radioisotopic techniques are not yet applied uniformly, and many potentially useful tests remain in a development stage. Appropriate clinical application of established procedures requires continuing quality control, and the development of techniques by prospective investigation remains the responsibility of the radiologist and the laboratory nephrologist.

LABORATORY TECHNIQUES

Nuclide-Labeled Pharmaceuticals in Renal-Function Tests

Agents most commonly used include radioiodinated sodium iothalamate (IOT), radioiodinated OIH, and radiomercury-labeled chlormerodrin.

For practical purposes IOT is excreted entirely by glomerular filtration, and, for estimation of the glomerular filtration rate, the standard renal clearance of this agent does not differ significantly from that of inulin.⁴ The OIH is excreted by a combination of glomerular filtration and transport across the cells of proximal tubular epithelium as is PAH (Ref. 5). From an extensive investigation of this comparison, we are satisfied that in estimating effective renal plasma flow the standard renal clearance of OIH corrected by a factor of 1.255 does not differ materially from the renal clearance of PAH (Refs. 6 and 7). Chlormerodrin is thought to be bound intracellularly, especially in proximal tubular epithelium; and hence the renal uptake of this agent is a measure of the uniformity of tissue distribution and of functional integrity in the proximal renal tubules.

On these processes and relations are based renography, renal imaging, and clearance procedures for evaluation of renal function.

Radioisotope Renogram

The normal renogram in our laboratory has the form illustrated in Fig. 1. For this test we prefer to have the patient supine and moderately hydrated with a urinary flow rate of 3 to 5 ml/min. Use of the sitting or prone positions and varying degrees of dehydration may be of supplemental value in particular situations.⁸ After 30 μ Ci of OIH has been given intravenously, its passage through the kidney is indicated by the curve as an inflow phase that rises rapidly to the peak concentration and a succeeding outflow phase that combines disappearance from the plasma with urinary transport away from the kidney (and the field of the monitoring detector). Coincident with the concentration peak is the initial appearance of activity over the urinary bladder.

Abnormalities may be noted in the initial rate of uptake and the slope of ascent, in the height and time of the concentration peak, and in the delay of the outflow phase. Particularly noteworthy are any differences between the functional patterns of the two kidneys which may be of lateralizing import. Despite extensive investigation we have not yet made practical application of mathematical analyses of renogram curves.

Fig. 1 Normal renogram made after injection of 30 μ Ci of ^{131}I -*o*-iodohippurate. The patient was supine and hydrated. Clearances of inulin and of PAH were 124 and 700 ml/min, respectively, per 1.73 m^2 of body surface. (Original tracings have been reversed to show progression left to right.)

OIH Scintiscan—Scintiphoto

After the injection of ^{131}I -labeled OIH, radioactivity may be seen on the scintiphoto to spread diffusely and uniformly over the kidney, much as it does in the nephrographic phase of renal arteriography⁹ (Fig. 2). Labeled medium is then concentrated in tubular filtrate, and it disappears progressively from the parenchyma only to accumulate in the renal pelves and bladder. Abnormalities may be noted in the time and uniformity of initial distribution and in the progress of the agent from the parenchyma to the calyceal systems and urinary bladder.

Fig. 2 Sequential gamma-camera scintiphotos (posterior views) made after injection of 300 μ Ci of ^{131}I -OIH (in patient with recurrent infection, obstruction at right ureteropelvic junction, and hypertension). Early parenchymal distribution of activity over right kidney is followed by excretion of isotope label from renal cortex and collection in renal pelvis. Progression through right kidney is delayed by postrenal resistance; left kidney is atrophic.

Chlormerodrin Scintiscan

For scintiscanning we use 100 μ Ci of chlormerodrin labeled with ^{197}Hg and allow 1 hr or more after injection, depending on our preliminary estimate of renal function, before we begin the scanning. In a normal pattern of distribution, the parenchyma is a diffuse mass with areas of relative pallor approximately delineating the calyceal systems (Fig. 3).

We have used the chlormerodrin scintiscan in selected instances of renovascular disease to define suspected sites of renal ischemia or infarction and to supplement information gained from the excretory urogram and the renal arteriogram. Valuable information can be obtained from scintiscans where contrast radiography is not practicable. We have not made use of chlormerodrin uptake rates, but we recognize the technique as having potential value.

EVALUATION OF PATIENT IN THE NEPHROLOGY LABORATORY

Prospective Kidney Donor (Case 1)

A 34-year-old man was examined as a possible kidney donor to his sister, who was in advanced renal failure due to polycystic renal disease. Evaluation of a supposedly normal man for this purpose includes the need to establish the presence of two normal kidneys.

Except for moderate obesity the findings from his general examination were satisfactory. The specific gravity of the urine was 1.029, and the results of

Fig. 3 Scintiscan over normally functioning renal allograft after injection of $60 \mu\text{Ci}$ of ^{197}Hg -chlormerodrin. Distribution of activity is diffuse, and cystlike appearance over renal calyces is normal.

urinalysis were normal or negative. Gram staining of preparations from uncentrifuged urine was negative as were cultures prepared from midstream collection. Microscopic examination of the urinary sediment revealed microhematuria and cylindruria of low degree. The excretory urogram was interpreted as normal except for the reduction of renal mass: polar lengths were 12 and 13 cm for the right and left kidneys, respectively. The serum creatinine concentration was borderline at 1.2 mg/100 ml.

Clearances of inulin and of PAH were 72 and 321 ml/min, respectively, per 1.73 m^2 of body surface. These quantities are approximately 60% of our mean normal values and indicate a substantial reduction of renal reserve. The isotope renogram (Fig. 4) revealed a considerable reduction in the maximal values of the bilateral concentration peaks, indicating parenchymal disease that affected the two kidneys equally. A chlormerodrin scintiscan presented an irregular distribution of activity (Fig. 5), particularly evident over both poles of the right kidney and over the upper pole and lower lateral border of the left kidney.

Altogether, the results obtained from the examination of the urine, the renal clearances, the radioisotope renogram, and the scintiscan indicated the presence of bilateral parenchymal disease with reduced renal mass and function. When the excretory urogram (Fig. 6) was reviewed in the light of these findings, it was noted that, besides the bilateral reduction in renal mass, the left kidney showed evidence of caliectasis and a fanlike distribution of the contrast medium with filling of the collecting ducts. The right kidney was judged to be urographically normal save for the diminution of total mass.

Fig. 4 (case 1) Renogram demonstrating reduced function of each kidney. The patient was supine and hydrated. Clearances of inulin and of PAH were 72 and 131 ml/min, respectively, per 1.73 m^2 of body surface.

A diagnosis of bilateral interstitial renal disease was made, and the patient was considered unacceptable as a renal donor. Investigation for this purpose was terminated, but he remains under observation.

Suspected Renal or Renovascular Hypertension

If a patient has persistent diastolic hypertension and is thought physically acceptable for surgery, the diagnostic evaluation should provide a basis for rational choice of surgery, medical management, or combinations of these.^{2,6,10,11} For this purpose data based on structure and function are necessary to identify patients whose hypertension is secondary to renal or renovascular disease. We consider surgery the treatment of choice if it appears that the hypertension is a functional result of a stenosing renal arterial lesion and no contraindications are noted in the overall examination. In our investigation of the hypertensive patient, we adhere to an established sequence until a diagnosis is made or until it becomes evident that further testing will not be helpful.

1. Preliminary laboratory examination consists of urinalysis, microscopy of urinary sediment, gram staining and culture of the urine, and determination of the serum creatinine concentration. If the information from these tests and the physical examination does not suggest a specific cause for demonstrated hypertension, we try to obtain morphologic and functional data.

2. The presence and size of the kidneys are best demonstrated and their collecting systems best visualized by excretory urography, including tomographic exposures. We seek differences between the kidneys in timed appearance

Fig. 5 (case 1) Scintiscan made after injection of 100 μ Ci of ^{197}Hg -chlormerodrin. Kidneys appear small, and distribution of activity over them is irregular.

Fig. 6 (case 1) Excretory urogram revealing reduced size of each kidney and caliectasis of left kidney.

of medium and in concentration and excretion of medium; and, for aid in recognizing them, we use rapid multiple filming techniques.³

3. Renal function is measured by the classic procedures for renal clearance, using inulin or ^{125}I -labeled IOT to determine the glomerular filtration rate and PAH or ^{131}I -labeled OIH to determine the effective renal plasma flow.

Angiographic visualization of renal arterial stenosis does not establish a functional basis for coexisting hypertension; nevertheless, we consider the renal arteriogram to be essential early in the evaluation of any hypertensive patient for whom renal or renovascular surgical treatment is potentially desirable.¹¹ Demonstration of a parenchymal or renovascular lesion amenable to surgical correction warrants further functional study.¹²

4. The radioisotope renogram portrays functional patterns of the two kidneys, making possible a qualitative assessment of function, a comparison of patterns to normal ranges for the laboratory, and an estimation of the type and severity of any lateralizing differences in the functional patterns. Scintiscanning and scintigraphy are not usually considered worthwhile if excretory urography and renal arteriography have been successful. The imaging procedures are particularly appropriate where severe iodide sensitivity or another contraindication precludes excretory urography and arteriography. They serve to further the search for a suspected anatomic lesion when excretory urography and arteriography have failed to determine its presence or absence, especially if the lesion seems likely to be unilateral; and they can further the investigation of functional deficiency indicated by results of clearance studies that seem at variance with those of radiographic studies.

5. Measurement of renin-activity concentrations in renal-vein blood reveals the pressor kidney in most instances of hypertension having that cause. Preparation of the patient for this determination is of critical importance. For 30 days or longer, diuretics and ovulation-suppressing agents should be withheld and an unrestricted sodium diet should be followed. In the 3 days prior to sampling, acute volume depletion should be accomplished by restricting dietary sodium to 20 mEq per day and by daily administration of 1 g of chlorothiazide.¹³ Just prior to the performance of renal arteriography, ordinarily, samples of blood are taken from the renal veins and from the vena cava below the renal veins, and the renin-activity levels in these samples are measured by radioimmunoassay.

6. Differential renal-function studies have long served us as a yardstick in the selection of patients for surgical management of renal or renovascular hypertension.^{12,14-16} We no longer require the classic differential-function studies if the procedures described above provide adequate information on function and on lateralizing characteristics. They may be necessary when preceding studies have provided data whose implications conflict in regard to the desirability of surgery and the probability that surgical treatment would produce favorable results or when the renal blood flow is moderately to severely reduced and more

precise measurement of the function of the separate kidneys is definitely needed.

This account of laboratory aids to diagnosis of renal disease has progressed from simple but informative tests such as routine urinalysis to sophisticated radiologic, radioisotopic, and biochemical procedures. Judicious selection from this imposing but time-consuming and costly array must be the forte of the clinical nephrologist.

Atheromatous Stenosis of Renal Artery and Hypertension (Case 2)

A 65-year-old woman referred for evaluation had been proved normotensive 1 year earlier but for the last 6 months had had hypertension resistant to

Fig. 7 (case 2) Renal arteriogram revealing severe atheromatous stenosis in midportion of left renal artery and poststenotic dilatation.

medical management. Excretory urograms forwarded by her referring physician showed the polar lengths of the right and left kidneys to be 15 and 11.5 cm, respectively. These values suggested anatomic hypertrophy of the right kidney associated with diminution of the renal mass on the left. The urograms also suggested somewhat greater concentration of medium on the left side than on the right. The renal arteriogram supplied by the referring physician showed virtually complete atheromatous stenosis of the middle portion of the left renal artery (Fig. 7) with marked fusiform poststenotic dilatation. The distal circulation appeared to be normal, and a moderate degree of atheromatous

disease noted in the aorta seemed consistent with the patient's age. Renin activity in renal-vein blood (also measured by her home physicians) strongly indicated that the excessive pressor influence came from the left kidney. The patient's general health and her poor control of blood pressure had caused increasing concern to her physician, and he had referred her to us for evaluation of the desirability and feasibility of surgical correction in view of her age.

The urine had specific gravity of 1.017 with other findings normal or negative except for proteinuria of mild degree. Microscopy of the urinary sediment revealed low-grade microhematuria and cylindruria with an occasional granular cast. Gram staining of preparations from uncentrifuged urine was negative as were cultures of the urine. The serum creatinine was borderline at 0.95 mg/100 ml.

Renal clearances of inulin and of PAH were 84 and 326 ml/min, respectively, per 1.73 m^2 of body surface. The right renogram evidenced normal function, but the left showed delay in concentration, diminished maximal concentration, and delay in the outflow phase, strongly suggesting functionally significant renal-artery stenosis and confirming residual function of moderate degree in the left kidney (Fig. 8). On a chlormerodrin scintiscan, the right kidney appeared normal; but the left kidney was considerably reduced and the activity in it, though uniformly distributed, was low (Fig. 9).

The renal arteriogram indicated a surgically accessible lesion in the artery supplying the left kidney, which was salvageable. Renin activity values confirmed that the left kidney was functionally causative of the hypertension, and the clearances measured in conjunction with the renography gave assurance of a good level of total function. The renogram indicated that perfusion of the left kidney was severely diminished. The scintiscan was consistent with this and also with the evidence of severe cortical atrophy of the left kidney which had been noted on the arteriogram.

In our experience operation usually has confirmed findings like these. In this instance biopsy of the pressor kidney demonstrated moderate to severe ischemic tubular atrophy with slight to moderate interstitial fibrosis and little, if any, hilar arteriolar sclerosis. The findings supported prediction of a good surgical result. Surgical endarterectomy and transplantation of the left renal artery were accomplished uneventfully. Renal blood flow on that side was measured as 100 ml/min prior to repair and 225 afterward. Biopsy of the left kidney revealed no significant hypertensive nephrosclerosis. There was moderate, diffuse tubular atrophy and slight interstitial fibrosis, in good agreement with our prediction. Contraction of glomeruli and slight to moderate hypertrophy of juxtaglomerular structures were noted. Biopsy of the right kidney revealed moderate hilar arteriolar sclerosis, consistent with moderately severe hypertension of considerable duration. There was no other significant abnormality (Fig. 10).

The postoperative course was free of complications and the blood pressure and serum creatinine concentration were normal before dismissal. Although

Fig. 8 (case 2) Renogram: curve for right kidney is normal; curve for left shows delayed, reduced concentration phase and delayed outflow, suggesting arterial stenosis. The patient was supine and hydrated. Clearances of inulin and of PAH were 84 and 326 ml/min, respectively, per 1.73 m² of body surface.

Fig. 9 (case 2) Schintiscan made after injection of 100 μ Ci of ¹⁹⁷Hg-chlormerodrin. Distribution over right kidney is normal; distribution over left kidney confirms residual activity at much reduced level and indicates reduced renal mass.

Fig. 10 (case 2) Evidence from biopsy after correction of stenosis of left renal artery. A, Left kidney: moderate, diffuse tubular atrophy and slight interstitial fibrosis. B, Right kidney: moderate arteriolar nephrosclerosis but no other significant abnormality. (Hematoxylin and eosin stain; magnification, 64x.)

Fig. 11 (case 2) Postoperative renogram shows normal function on right (contralateral to correction of renal-artery stenosis) and persistent but mitigated abnormality on left. The patient was sitting and dehydrated. Serum creatinine was 1 mg/100 ml.

postoperative renography showed that the right kidney was normal, on the left there remained a moderate reduction of peak concentration and some delay in the outflow phase, indicating persistence of some reduction of function. Even so the pattern was remarkably improved from that of the preoperative renogram, and the later study did not suggest an ischemic state (Fig. 11). For 6 months after surgery the patient's blood pressure has remained normal without antihypertensive medication, and she has experienced a gratifying recovery of vitality and sense of well-being. From postoperative studies a slow but progressive recovery of renal reserve on the left is anticipated with expectation that its completion may require an additional 6 months or longer as in other varieties of ischemic tubular damage.¹⁷

Systemic Vasculitis and Renal Disease (Case 3)

A 32-year-old man was seen in October 1970 for evaluation of severe hypertension of approximately 1 year known duration. Two years earlier a

diagnosis of periarteritis nodosa had been established by biopsy of the epididymis, and a program of suppression with prednisone had been instituted. Excretory urography and renal angiography, done by his home physicians 1 year prior to referral, had revealed incomplete infarction of the lower pole of the right kidney but had not shown the arterial supply to that pole. Angiographically, the left kidney was anatomically hypertrophied and the solitary renal artery was normal (Fig. 12). Repeat renal angiography 3 months prior to referral had been less than satisfactory but had given similar findings. We sought to define the influence of the right kidney in the hypertensive process and to evaluate the probability that surgery would relieve the hypertension.

The urine had specific gravity of 1.029 and contained a moderate amount of protein. Microscopy of the urinary sediment revealed only occasional hyaline casts. The serum creatinine measured 1 mg/100 ml. Repeat excretory urography showed that the left kidney had a normal configuration, but the right kidney was smaller than the left (12.5 vs. 14 cm in polar length) and had diffuse cortical thinning over the right lower pole, consistent with incomplete infarction (Fig. 13).

The clearance of inulin was 91 and that of PAH 404 ml/min per 1.73 m^2 of body surface. Renographically, the left kidney was normal but the right showed a considerable reduction in the concentration phase, indicating a corresponding reduction in parenchymal renal function. Outflow phases were normal and not lateralizing (Fig. 14). The chlormerodrin scintiscan recorded an incomplete right renal outline and indicated functional loss of the lower half of the right kidney; the uptake of activity was markedly reduced in the upper pole of the left kidney also, indicating ischemia or incomplete infarction (Fig. 15). Scintiscans prepared with OIH demonstrated effective concentration of this agent by the remaining nephrons in each kidney (Fig. 16).

The differences noted between scintiscans made with chlormerodrin and those made with OIH reflect differences in the renal handling of these agents (previously described). The severely diminished uptake of chlormerodrin over the upper pole of the left kidney delineates the site of reduced tubular function. The uptake of OIH activity apparent over this area may well be due to concentration, by tubular reabsorption of water, of the amount of this agent that is excreted by glomerular filtration. As such it may indicate residual functional capability of the tubules there. Failure of the excretory urogram to delineate a filling defect in the upper left pole may stem from a similar cause since the diatrizoate used is excreted by glomerular filtration.

Renin-activity levels in renal-vein blood samples were strongly lateralizing, the concentration in the right renal vein being three times that in the left. These data indicated that the right kidney was indeed pressor. However, the excretory urogram, the renogram, and the scintiscans had produced evidence of bilateral parenchymal disease. The possibility of multiple intrarenal aneurysms compli-

Fig. 12 (case 3) Renal arteriogram, nephrographic phase (made 1 year prior to referral), demonstrating incomplete infarction of lower pole of right kidney.

Fig. 13 (case 3) Excretory urogram, tomographic view, showing cortical thinning of lower pole of right kidney and normal configuration of left.

Fig. 14 (case 3) Renogram demonstrating normal function of left kidney, reduced function (indicating reduced nephron population) of right, but no other lateralizing features. The patient was supine and hydrated. Clearances of inulin and of PAH were 91 and 404 ml/min, respectively, per 1.73 m^2 of body surface.

cated by rupture and bilateral parenchymal loss was not confirmed by the angiogram made elsewhere 3 months prior to his admission.¹³

Repeat arteriography with selective injections was considered desirable, but instead of that a decision was made to try medical antihypertensive therapy.

Parenchymal Renal Disease and Hypertension (Case 4)

A 60-year-old woman returned to this clinic for more complete evaluation of known hypertension and left renal abnormality. Examination had been initiated some 8 months previously because of urinary-tract infection that had been recurrent over a period of 20 years or more and hypertension of uncertain etiology that had persisted 12 years or longer. Excretory urography 2 years earlier had revealed partial infarction of the left kidney. Investigation had not been completed at that time and subsequent treatment had been intermittent and not consistently effective.

When she returned, the specific gravity of the urine was 1.007 and the results of urinalysis and microscopic examination of the urine were normal or negative. Gram staining of a preparation from uncentrifuged urine and cultures of the urine were negative. The serum creatinine concentration was above normal, being 1.05 mg/100 ml. Repeat excretory urography revealed anatomic hyper-

Fig. 15 (case 3) Mercury-197—chlormerodrin scintiscan showing functional loss of lower half of right kidney and incompleteness of renal outline, indicating severe ischemia or infarction of upper pole of left kidney.

Fig. 16 (case 3) Iodine-131—OIH scintiscan revealing residual function of remaining nephrons. Note concentration of this agent by parenchyma of upper pole of left kidney.

trophy of the right kidney, which had a polar length of 15 cm (Fig. 17). The left kidney measured 11 cm from pole to pole and showed multiple infarcts with virtually complete loss of lower-pole tissue and no significant change from the urogram of 2 years earlier. A cinecystourethrogram gave no evidence of reflux. Renal arteriography demonstrated that the left kidney was atrophic and partially infarcted, with cortical scarring in its upper and lower polar regions. There were two left renal arteries, and atheromatous stenosis (estimated as less than 50%) was at the aortic orifice of the upper one. Two renal arteries also supplied the hypertrophic right kidney. The lower of these passed over the upper ureter near the ureteropelvic junction, and the pelvis on that side was dilated (Fig. 18).

Clearances of inulin and PAH were 87 and 498 ml/min, respectively, per 1.73 m^2 of body surface. The right renographic pattern was normal except for early delay in the outflow phase, conceivably related to the dilatation of the right renal pelvis and the aberrant renal artery that crossed the right ureter to the pelvis. The left renographic tracing paralleled that of the right kidney at a lower level of concentration, demonstrating diminished function of the left kidney. The outflow phases were not lateralizing and did not support an impression of functionally significant renal-artery stenosis (Fig. 19). The functional manifestations in a chlormerodrin scintiscan were in agreement with the anatomic observations from the urogram and the renal arteriogram. Renin-activity levels in samples of renal-vein blood were not lateralizing.

The diagnosis was pyelonephritis, atrophy, and infarction of the left kidney with coincident atheromatous disease of a left renal artery and hypertension. Left nephrectomy was advised because of chronic recurrent infection of the urinary tract. Since the evidence then available did not identify the left kidney as the source of an abnormal pressor influence, it could not be argued that the recommended nephrectomy would ameliorate the hypertension. The question might have been resolved by differential renal-function studies; however, the patient preferred a continuation of medical therapy for the urinary-tract infection and coincident hypertension.

Renal Arteriovenous Fistula (Case 5)

A 46-year-old woman sought evaluation, principally because of chest pain and fatigue that had been present for approximately 1 year. Abnormal findings on physical examination included minimal blood-pressure elevation at 160/100 mm Hg and a loud, continuous bruit that seemed to be maximal in the left upper anterior region of the abdomen. These findings gave an initial impression of hypertension with a renovascular basis, which was what the referring physician had suggested.

The specific gravity of the urine was 1.024, and the results of urinalysis were negative except for low-grade proteinuria. Microscopic examination of the urinary sediment disclosed only microhematuria. The serum creatinine concentration was 0.9 mg/100 ml. The electrocardiogram signified left ventricular

Fig. 17 (case 4) Excretory urogram: Right kidney measured 15 cm in polar length and left kidney 11 cm. Left kidney also shows multiple infarcts and loss of lower pole.

Fig. 18 (case 4) Renal arteriogram. Left kidney is atrophic and partially infarcted, and there is atherosclerotic stenosis at orifice of upper of two left renal arteries. Right kidney also is supplied by two arteries and is hypertrophied but otherwise normal.

hypertrophy, and the exercise electrocardiogram revealed no further abnormalities.

On the excretory urogram the polar length of the right kidney was 14 cm. The left kidney measured 12 cm and showed cortical irregularity. Appearance times and concentrations of medium were equal bilaterally. Renal arteriography revealed marked enlargement of the left renal artery and a rapid communication

Fig. 19 (case 4) Renogram demonstrating normal function of right kidney with minimal delay in early outflow phase and reduced parenchymal function of left kidney. Outflow phases are normal and not lateralizing. The patient was supine and hydrated. Clearances of inulin and of PAH were 87 and 498 ml/min, respectively, per 1.73 m^2 of body surface.

to the renal venous circulation, which was tortuous and dilated and had ovarian collaterals (Fig. 20). The precise location of the fistula could not be identified angiographically. There was evidence of multifocal fibromuscular dysplasia of the midportion of the right renal artery. The cardiac output was 8 liters/min with a cardiac index of 5 liters/min/ m^2 .

Clearances of inulin and of PAH were 96 and 427 ml/min, respectively, per 1.73 m^2 of body surface. The right renogram showed normal function; the left was normal in contour but low in the concentration phase and in maximum concentration, indicating reduced perfusion. Outflow phases were normal and not lateralizing (Fig. 21). The chlormerodrin scintiscan recorded reduced activity over the upper pole of the left kidney, consistent with ischemia or infarction. Renin activity in samples of renal-vein blood was not lateralizing.

Fig. 20 (case 5) Transfemoral retrograde aortorenal angiogram. Left main renal artery is enlarged, and arteriovenous fistula in its distal portion communicates with renal vein. Renal vein and associated ovarian vein are enlarged also. Large saclike structures are dilated intrarenal and extrarenal portions of renal venous circulation.

Diagnostic evaluation of this patient was hindered by the diversion of arterial blood through the fistula, which made visualization of the arterial supply to the left kidney inadequate. Values for renin activity in renal-vein blood samples may have been invalid for diagnostic purposes because of unavoidable dilution on the left by arterial blood. The principal reason for recommending surgery was the need to correct a marked hemodynamic abnormality.

The operation disclosed a fistula measuring nearly 10 mm in a large aneurysm extending from a primary branch artery to the left kidney and lying adjacent to the renal vein. A second aneurysm was identified within the kidney. The renal blood flow on the left measured 3 liters/min. There appeared to be a thinning of the left upper pole of the kidney, suggesting atrophy due to infarction. The location of the fistula, the presence of the distal aneurysm, and the appearance of the upper pole of the left kidney deterred the surgeon from attempting repair, and left nephrectomy was performed. Examination of the kidney confirmed the presence of ischemic atrophy in the upper pole as noted on the scintiscan. Now, some 3 months after operation, the patient is asymptomatic and normotensive.

Fig. 21 (case 5) Renogram demonstrates that function of right kidney is normal. Curve for left is of normal contour, with reduced concentration phase and peak indicating reduced perfusion. Outflow phases are normal and not lateralizing. The patient was supine and hydrated. Clearances of inulin and PAH were 96 and 427 ml/min, respectively, per 1.73 m² of body surface.

COMMENTS

Renal and renovascular diseases afford complex problems in many cases, and their solution and management depend ultimately on the skill and experience of the physicians responsible for the patients. Of the wide array of laboratory procedures available to develop facts for use in the crucial decisions, not every one is needed in some instances, whereas in others the sum of data gained from all leaves grounds for differences of opinion.

The nephrologist usually regards excretory urography and renal angiography as generally safe procedures that are essential for providing visualization of the renal parenchyma, collecting systems, and renal vasculature. Additional information may be gained from renal-clearance studies, isotope renography, and renal

scintiscans and, on occasion, by determination of renin activity in renal-vein blood samples or by differential renal-function studies or both. The extent to which these studies are required varies with the nature of the problem, the findings obtained as investigation progresses, and the extent of information which the individual clinician considers necessary for diagnosis and management.

Values of this approach are well illustrated by our evaluation of the donor candidate for the renal transplant (case 1) and of the woman with hypertension secondary to renal-artery stenosis (case 2). In the former, nephrectomy to provide for transplantation was judged undesirable and was not done; in the latter, surgical management resulted in apparently lasting relief of hypertension with improved renal function. Our experience indicates that in such situations urography, standard renal-clearance studies, renal arteriography, isotope renography, scintiscanning, and, where appropriate, determinations of renin activity afford the information necessary for the decision regarding surgery.

SUMMARY AND CONCLUSIONS

To support the clinical nephrologist there is available a broad array of laboratory procedures, including some derived from nuclear medicine, for the evaluation of renal disease.

These tests are complementary rather than competitive. Especially in diagnosis and in choice of management, it is important to integrate the predominantly functional data from the radioisotopic tests with the predominantly anatomic information derived from excretory urography and renal angiography. When selecting a program of laboratory investigation, however, physicians must consider both the value of each test to the patient and the financial and personal exactions of its use.

An adequate background of normal values is essential as a standard for evaluating every laboratory report. Prospective studies in the application of new procedures will facilitate their acceptance by the clinical nephrologist.

We believe that evaluation of the renal patient is best accomplished by close association and free participation of the clinical nephrologist, the urologist, the radiologist, and the laboratory nephrologist in selecting tests, in comparing and interpreting results, and in considering their therapeutic implications.

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DISCUSSION: KIDNEY

Buonocore: Since many people believe chemical function tests correlate poorly with the definition of renal vascular hypertension, I would like to ask Dr. Powell if he feels that isotope scanning can be any better. Do you disagree with Dr. Meaney that only surgery will decide which patients have hypertension secondary to renal vascular disease?

Powell: I do believe the scintigraphic evaluation of kidney structure, function, and perfusion can add important information to the evaluation of renal vascular hypertension. The limited scintigraphic data presented here indicates that the method deserves careful evaluation to determine its diagnostic accuracy for detection of renal ischemia and for determination of the possible etiologic significance of that ischemia in causing hypertension.

Blaufox: I find it unfortunate that so much of this discussion is directed toward the diagnosis of renal vascular hypertension. Although radionuclides are certainly of value in renal vascular hypertension, this represents only a small aspect of their total overall potential. I would like to emphasize that in our medical center radionuclides are used extensively in nephrology and that the diagnosis of renal vascular hypertension is only a very small part of their application. Nuclides may be used to study reflux, residual urine, patients with severe azotemia, clearances, and the urinary outflow tract as I have discussed in my paper. These many other applications are of great importance, and, yet, people continue to fail to apply them in these areas. Part of this perhaps may be the disappointment at the results obtained in patients with renal vascular hypertension. If nothing else is accomplished, I would like to think that the people here will at least go away with a reasonable perspective of the relative merits of the applications of radionuclides in various renal diseases and will begin to think of the uses of radioisotopes here as a multiple-purpose procedure which can be applied in many, many areas and of which renal vascular hypertension is only one in a relatively unimportant aspect, although possibly the most glamorous. I do not refer many of these patients to surgery because personally I do not feel surgical treatment is that effective, nor does it really offer that much more by way of treatment than can be accomplished medically.

Buonocore: Maybe the surgeons in Cleveland feel differently about this problem and are more concerned about this disease since they feel surgery may be more effective in treatment of renal vascular hypertension? Dr. Meaney, would you comment please on the patients receiving surgical therapy for renal vascular lesions?

Meaney: In the last few years, there has been a decrease in the number of patients undergoing nephrectomy or renal vascular reconstructive surgery because of the improvement in medical therapy of the patient's hypertension. In general, surgical therapy is carried out in patients who do not respond to medical therapy or who, for personal reasons, do not or will not maintain themselves on the prescribed treatment. In addition, surgical therapy is likely to be carried out in patients in whom there is a threat to loss of renal parenchyma by virtue of the stenotic lesion.

Buonocore: Would you comment on the usefulness of angiography compared with the dynamic renal-function studies using a scintillation camera for evaluation of renal blood flow?

Meaney: Angiography to evaluate renal blood flow is a coarse and gross method and is inferior to methods using radionuclides. I would like to emphasize, however, the questionable importance of knowing renal blood flow in patients suspected of renal vascular hypertension. Liberation of renin by the affected kidney may not be the result of a decrease in blood flow but may well be due to reduction in renal perfusion pressure. As a consequence a patient may have renal vascular hypertension without any abnormality in blood flow.

Buonocore: Should we ever take a direct approach to early needling of renal masses detected on urograms without the aid of diagnostic studies such as angiography or renal scan? Dr. Blaufox, would you care to comment on using such a direct, rapid approach?

Blaufox: We would first do the triple radioisotopic study similar to what Dr. Powell described, but we would use ^{197}Hg -chlormerodrin instead of ^{203}Hg -chlormerodrin. In patients suspected of having renal tumors who are too debilitated or for some reason we cannot get on the angiography schedule, we do find a diagnostic accuracy in our radioisotopic work-ups very similar to Dr. Powell's results. In general, a patient should have both angiography and the renal scans, but, unless there is some contraindication or complication preventing these studies, we would not take a direct approach to immediate renal biopsy.

Buonocore: Do you ever not do a urogram or an arteriogram because of a history of allergy to the radiocontrast media? Do you think scans should be carried out as a screening method in patients who are allergic to contrast material?

Meaney: The subject of so-called allergy to contrast material is a very complicated one. It should be noted that reactions to contrast material may not be allergic; in fact, no antibodies to contrast material have ever been

demonstrated in so-called allergic patients. Moreover, the reactions to contrast material do not follow the pattern of other allergies. A patient with no previous exposure to contrast material may have a reaction, and a patient who has had previous reaction may not have one on a second exposure to the contrast material. As a result, we do not consider a previous reaction to contrast material as a contraindication to intravenous urography or angiography unless that reaction has been of the anaphylactic type with bonafide cardiovascular collapse. Even in patients with such a history, if good management of the patient would dictate an angiogram, it may well be carried out with supportive measures immediately available should the patient have a reaction.

Buonocore: Dr. Maxfield would like to comment on the uses of radioisotopic studies in the evaluation of renal disease in children.

Maxfield: It is true that intravenous pyelography (IVP) has been the routine screening test for the detection of urologic pathology for many years. This well-recognized procedure using currently available media such as diatrizoate sodium (Hypaque 50%) has a reported reaction rate of 10 to 14% and a mortality rate of 1 per 100,000. In addition, there is frequently the problem of the technical quality of the IVP study due to a degree of dehydration or gas, fecal material, and contrast media in the gastrointestinal tract. Adequate identification of the kidneys is especially a problem in infants and newborns. Our search for a safe, accurate test for urologic pathology was initiated by the death of a 5-year-old child from reaction to contrast media during IVP. As Dr. Powell has already stated in his presentation, we feel that the camera renogram, which consists of serial scintiphotos of the kidneys with simultaneous renogram curves obtained after the intravenous injection of ^{131}I -iodohippurate, should be the test of choice for initial evaluation of renal disease in newborns and infants.

The dose schedule used for the camera renogram was 3 μCi per kilogram of body weight with a minimum dose of 20 to 30 μCi and a maximum dose of 250 μCi . The radiation dose of the kidney is about 100 to 150 mR, assuming a $T_{1/2}$ effect of half-life of 20 min in the kidneys for the tracer material. The camera renograms were performed in a normal state of hydration or in a moderately hydrated state depending on the age of the child. After the intravenous injection of the tracer, serial scintiphotos at 0 to 1, 2 to 3, 3 to 4, 4 to 5, 9 to 10, 14 to 15, and 19 to 20 min were obtained. Simultaneous renogram curves for each kidney were obtained by use of the split-crystal mode with the curves being recorded through dual rate meters and strip-chart recorder (Nuclear-Chicago Pho/Gamma Mk III). Intravenous pyelograms were obtained in the routine manner, usually with an infusion technique, films being obtained at 1, 5, 10, and 15 min. The radiation dose for the camera renogram is about the same as the radiation exposure from one film of the abdomen and would be significantly less than that for a complete intravenous pyelogram study.

The conclusion from our preliminary study of 118 pediatric patients is that the camera renogram does not replace IVP because the anatomical detail

provided by the intravenous pyelogram exceeds that of the camera renogram. However, when the indication for evaluation of the urological tract was reflux, obstruction, or congenital anomaly, the camera renogram in this series was more accurate than the intravenous pyelogram in detecting abnormalities.

Considering the risk of complication with the intravenous pyelogram, it seems that we should now question the routine use of IVP as a test of choice for

TABLE 1
CONDITIONS EVALUATED BY CAMERA RENOGAM AND
INTRAVENOUS PYELOGRAM

Conditions	No. of cases	Intravenous pyelogram		Camera renogram	
		Normal	Abnormal	Normal	Abnormal
Urinary-tract infection	48	20	28	12	36
Vesicoureteral reflux	23	12	11	6	17
Atrophic or chronic pyelonephritis	15	0	15	0	15
Obstructive lesions					
Ureteropelvic junction obstruction	10	9	1	0	10
Calculi	3	0	2*	0	3
Vesicoureteral obstruction	2	0	1*	0	2
Glomerulonephritis	14	8*	0	8	6
Solitary kidney					
Ureteropelvic junction obstruction	5	0	5	0	5
Azotemia	2	0	2	0	2
Normal	1	1	0	1	0
Duplication of collecting system	6	1	5	0	6
Renal-transplant status	5	0*	0	0	5
Acute renal failure	3	3†	0	0	3
Renal hypoplasia	2	0	2	0	2
Polycystic kidneys	2	0	2	0	2
Renal tubular acidosis	2	2‡	0	2‡	0

*Intravenous pyelogram not done in all cases.

†Intravenous pyelogram normal on follow-up study.

‡KUB (kidney, ureter, bladder) shows nephrocalcinosis; pyelogram otherwise normal.

renal evaluation of renal disease in the pediatric age group. The risk associated with the intravenous pyelogram was previously accepted because there were no other methods for evaluation. Our comparative study of the camera renogram and the intravenous pyelogram indicates, however, that the camera renogram provides a safe, accurate alternative screening procedure for detecting urologic pathology in the pediatric age group (Table 1).

As I mentioned before, the technical quality of the camera renogram surpassed that of the intravenous pyelogram since the main problem with the infusion intravenous pyelogram was interference by gas shadows within the gastrointestinal tract. The camera renogram does not suffer from this technical problem and in most cases shows the parenchyma of the kidneys. In the newborn group the infusion intravenous pyelogram frequently failed to show the calyceal pattern and did not permit evaluation of the renal parenchyma (Fig. 1). Table 2 compares the accuracy of the intravenous pyelogram and camera renogram. The camera renogram can show the parenchyma and has the advantage of being a more satisfactory study technically and one that does not have to be repeated (Table 3).

TABLE 2
DIAGNOSTIC ACCURACY OF INTRAVENOUS
PYELOGRAM AND CAMERA RENOGAM IN
NEWBORNS WITH CONGENITAL ANOMALIES

Both studies normal	8
Both studies abnormal	3
Intravenous pyelogram normal, camera renogram abnormal	3
Intravenous pyelogram abnormal, camera renogram normal	0

TABLE 3
COMPARISON OF TECHNICAL QUALITY IN
14 NEWBORNS OF INTRAVENOUS PYELOGRAM
AND CAMERA RENOGAM

	Good	Fair	Poor	Repeats
Intravenous pyelogram	6	4	4	3
Camera renogram	10	3	1	1

Since the 1930's and 1940's, the intravenous pyelogram has been used to initially evaluate the urinary tract. When the intravenous pyelogram first became available, it was the best means of visualization of the kidneys and ureters. Now the techniques of nuclear medicine provide a safer, more accurate alternative. I wonder if physicians when asked the question as to the status of the kidneys should not be satisfied with the answer that the intravenous pyelogram was normal. I would rather have the answer come back that the camera renogram is normal.

Blafox: Our experience with the use of radionuclides in studying children has been similar to that of Dr. Maxfield. We have not compared the radionuclide

Fig.1 Newborn who has extrophy of the bladder. Infusion intravenous pyelogram gave poor visualization of the kidneys, especially on the right (a). Camera renogram showed normal function for both kidneys (b).

tests to the urogram, and I cannot comment on this aspect; however, the radionuclides have been extremely informative. They have the advantage that in follow-up studies the radiation dose received by the child is quite small. One area in which radionuclides have been useful in pediatrics and which was not mentioned by Dr. Maxfield is the evaluation of the presence of an extremely poorly functioning kidney. On several occasions we have been able to show with Hippuran that an extremely poorly functioning kidney was present in a child in whom it was thought that only one kidney was functioning. In order to do this, it is necessary to obtain late scintiphotos, and I recommend that, in studying children with severe impairment of renal function on one or both sides, scintiphotos should be obtained as late as 6 or 24 hr after the initial study. Also it has been useful to obtain scintiphotos and then infuse mannitol and obtain another set of scintiphotos which have permitted us to elucidate borderline obstructions of the urinary outflow tract because, when challenged with an osmotic diuresis, these become readily apparent.

Wellman: We have had experience with two cases of renal vascular hypertension using ^{99m}Tc -DTPA (diethylenetriaminepentaacetic acid) with the finding of a marked localization and prolonged uptake in the cortex of the kidney. Dr. Powell, is this similar to what you find in some studies of renovascular hypertension using hippurate? Also, would one of the speakers discuss the role of renal-vein renins in their work-up of the hypertensive patient?

Powell: We have had only limited experience with ^{99m}Tc -DTPA in our laboratory since we delayed its introduction until a complete chelation could be accomplished. We now have nearly 100% ^{99m}Tc binding after a reduction by stannous ion using Powell Richards' method. In a few cases we have studied to date with ^{99m}Tc -DTPA, there has been no example of hypertension due to renal ischemia. However, I expect late cortical retention of ^{99m}Tc -DTPA would be observed in the presence of functionally significant renal ischemia.

I expect also that it would be more difficult to distinguish late retention of DTPA than of hippurate because of the lower ratio of radioactivity between the renal cortex and surrounding tissues in DTPA studies. Hippurate will probably prove a better agent to distinguish prolonged cortical transit times; this should be particularly true for regional renal ischemia. I look forward to using ^{123}I -hippurate with our camera studies as a means of obtaining better data density in images showing prolongation of cortical transit times.

Moderator:
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LUNG

RADIOISOTOPIC STUDIES EVALUATING LUNG FUNCTION

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ABSTRACT

Regional pulmonary-function indexes were obtained for 23 healthy young adults and several patients with lung disease. Injected and inspired ^{133}Xe gas was used in conjunction with an Anger camera and a 1600-word memory store. For each individual, some 36 lung zones were subsequently computer analyzed to determine regional ventilation (V_1/V_2), perfusion (Q/V_2), and ventilation/perfusion ratios (V_1/Q). The washout of xenon from each lung zone was mathematically fitted in terms of an exponential plus linear model. In young normals a linear correlation was observed between the normalized ventilation index and the normalized exponential rate constant. No corresponding relation occurred between the rate constant based on wash-out half-time and V_1/V_2 , however. This discrepancy was particularly marked near the lung apexes and bases, i.e., regions having large tissue/lung ratios.

The young subjects exhibited V_1/V_2 and Q/V_2 indexes that increased with distance from lung apex. Tentative data on elderly normal men are in agreement with these results. The two gradients appear to reverse in typical chronic obstructive pulmonary disease (COPD) patients. A patient with diagnosed pulmonary emboli had essentially normal ventilation but greatly reduced perfusion indexes.

A variety of techniques using radioisotopes have been developed for the study of lung function. These techniques include the intravenous administration of labeled aggregates or microspheres of albumin, the inhalation of radioactive aerosols, and the administration of radioactive gases by intravenous injection or inhalation. This paper will be limited to one of the radioactive gases, ^{133}Xe , used with a scintillation (Anger) camera and computer processing of data for the study of pulmonary function. Considerations will be given to the acquisition of data on distribution of pulmonary blood flow and ventilation in normal subjects and in patients with pulmonary disease.

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Pioneer work with ^{133}Xe was carried out by Knipping and associates.¹ Modification and improvement of procedures have been made by many investigators working primarily in England and Canada.²⁻⁶ These investigators are credited with originating the concept of the ventilation and perfusion indexes and the ventilation/perfusion ratio. This ratio has important physiological significance because it relates ventilation to blood flow, which must balance to permit adequate gas exchange. Regions of the lung that are adequately ventilated but poorly perfused will have an inadequate gas exchange just as will other areas that are poorly ventilated but normally perfused.

Pulmonary disorders studied by this technique include pulmonary embolism, obstructive lung disease (cystic fibrosis, bronchiectasis, emphysema, and asthma), and primary or metastatic malignancy. These studies are also being used in the preoperative and postoperative evaluation of patients with either congenital or acquired heart diseases that cause alterations in pulmonary perfusion or ventilation or both. Examples of data obtained from several patients with obstructive lung disease and from one with pulmonary emboli will be included here.

MATERIALS AND METHODS

A survey of all radioactive gases that might be used for these studies⁷ has shown ^{133}Xe to be the only generally available gas with suitable characteristics. This radionuclide has a physical half-life of 5.27 days and emits an 81-keV photon in approximately 39% of its disintegrations.⁸ The photon energy is slightly below the optimal energy for use with a scintillation camera. Currently there is a concerted effort to obtain ^{127}Xe , which has more favorable physical characteristics (36-day half-life with the emission of 203-keV photons in 65% and 172-keV photons in 22% of its disintegrations). Techniques for handling 1-Ci glass ampules of xenon gas and placing this gas into sterile saline solution have been reported in detail elsewhere.⁹⁻¹¹ Likewise, considerations of the radiation dosimetry for ^{133}Xe have been published.¹¹

A scintillation (Anger) camera fitted with a diverging collimator has been used for these studies. This collimator has a lower sensitivity and a lesser resolution than can be obtained with an optimal parallel-hole collimator, but it was chosen for these studies because both lungs may be viewed in their entirety even for relatively large patients. A 35-mm camera was used to obtain sequential scintiphotograms during each study. Dual rate meters and strip-chart recorders attached directly to the camera were used initially to obtain a graphical presentation of radioactivity in each lung. For a more complete evaluation of regional pulmonary function, a computer has been used. There are a variety of ways to present camera data to the computer. The technique employed for the most part at our institution uses dual analog-to-digital converters, a 1600-word memory for storage, and sequential transmission of data to high-speed digital

magnetic tape. The magnetic tape is then hand-carried to the Biomedical Computer Center and processed by a Control Data 3300 computer through the use of programs written in FORTRAN IV language.^{1,2-14} Pulmonary-function studies are normally carried out with the patient seated and the scintillation camera placed against the posterior thorax. The technique for performing the study is illustrated in the case of a 40-year-old woman with mildly obstructive lung disease who was suspected to have pulmonary emboli. Routine pulmonary-function tests showed a measured vital capacity of 2400 ml and a 1-sec forced expiratory volume, which was well below normal. Figure 1* shows a plot and Fig. 2 selected scintiphotograms of the xenon activity in both lungs during various phases of this study, where (Q) represents the period of breath holding after the intravenous administration of 30 mCi of xenon in saline. Data recorded at this time determined regional perfusion indexes. The subject then exhaled the radioactive gas into a spirometer and rebreathed to equilibrium. A subsequent deep breath was held to determine lung volume (V_2). After the subject returned to normal tidal breathing, washout of the xenon gas was begun. After the xenon had cleared to background level, the patient took a final, single, maximum inspiration (V_1) from the spirometer containing ^{133}Xe . This provided data for the determination of ventilation indexes (V_1/V_2) in the various regions of both lungs. Similarly, the perfusion indexes are given by Q/V_2 .

A computer obtained the plot for Fig. 1. The collection of data in computer format enables subsequent processing to provide quantitative information on the distribution of pulmonary blood flow and ventilation for any area of lung. At present our technique calls for the division of each lung into 18 parts. The computer programs permit ventilation indexes, perfusion indexes, ventilation/perfusion ratios (V_1/Q), and clearance times to be printed out along with contour plots of xenon distribution in the lungs during various phases of each study. Figure 3 shows two computerized contour plots obtained in the study of this patient.

The plot during perfusion reveals an asymmetry in the distribution blood flow which was not apparent on the corresponding scintiphotogram. In this patient washout was somewhat irregular bilaterally (scintiphotogram number 3, Fig. 2), indicating obstructive lung disease. The plots of ventilation and perfusion indexes and ventilation/perfusion ratios (Fig. 4)* were essentially normal for the right lung, as evidenced by the gradual increase in perfusion and ventilation from the lung apex to base. This gradient is normally more

*Figures 1 to 3 are from M. K. Loken, Camera Studies of Lung Ventilation and Perfusion, *Seminars Nucl. Med.*, 1: 230, 231 (1971) and M. K. Loken, G. S. Kush, and C. F. Anderson, The Use of Computers for Processing Pulmonary Function Data Obtained with a Scintillation (Anger) Camera, in *Computers in Radiology*, R. DeHaene and A. Wambersie (Eds.), pp. 562, 563, 564, Karger, Basel, 1970.

*Figures 4, 11, 12, and 13 are from M. K. Loken, Camera Studies of Lung Ventilation and Perfusion, *Seminars Nucl. Med.*, 1: 231, 235, 236 (1971), by permission.

Fig. 1 Computer plots of ^{133}Xe activity in lungs of patient number 7965 with moderate obstructive lung disease during various phases of a pulmonary-function study. (See text footnote for credit.)

pronounced for perfusion than for ventilation. Because of this relation, the ventilation/perfusion ratio has an inverse slope from that of the ventilation and perfusion indexes. Indexes and ratios for the left lung were moderately abnormal, as seen from a comparison with the curves obtained for the right lung.

Fig. 2 Selected scintiphotograms of xenon activity obtained during study of patient number 7965. (See text footnote for credit.)

RESULTS AND DISCUSSION

Calculations of Ventilation Index from Single-Breath and Washout Data

Following the work of West,^{2,3} the ventilation index in our studies has been determined by having the subject take a single deep breath of radioactive gas and then comparing the ratio of gas entering a particular region of lung to that entering the total lung. The physiological significance of a single maximal breath as an indication of minute volume ventilation has been questioned.^{1,5} Also, this technique does not include a specific time factor as does the classical ventilation index (cm^3 of air/ cm^3 of lung/min). For these reasons we have investigated the single-breath approach for measurement of ventilation. We compared these data to those obtained from the regional lung clearance during tidal breathing. In the following text we consider an analysis of the washout curve $C(t)$ based on a two-component model.^{1,2}

$$C(t) = C(0) [we^{-Kt} + (1 - w)(1 - St)] \quad (1)$$

where $C(t)$ is the xenon activity in a given region, w is the weight of the exponential and $1 - w$ is the weight of the linear term. The rate constants are K and S , respectively. This equation was individually fitted to each of 36 lung regions for everyone studied.

Fig. 3 Computerized contour plots showing the distribution of xenon during the perfusion (top) and the ventilation (bottom) portions of study of patient number 7965. (See text footnote for credit.)

Fig. 4 Computerized plots of ventilation and perfusion indexes and ventilation/perfusion ratios from study of patient number 7965. Q, perfusion index (Q/V_2). V, ventilation index (V_1/V_2). R, ventilation/perfusion ratio (V_1/Q). (See text footnote for credit.)

We took two approaches to the analysis of washout data. The first was to obtain a rate constant (R) based on the half-time of the total washout curve. The second was the rate constant (K) of the exponential component of the washout curve. Plots of these clearance rates for healthy young subjects (normalized to an average value of one) are shown in Fig. 5. In this and subsequent figures, laterally adjacent areas in both lungs were combined to give nine regions from apex to base. Figure 5 also contains the ventilation index (V_1/V_2) obtained from the single-breath technique. It is apparent that the clearance rate constant (K) based on the exponential term of controlled ventilatory clearance compares

very favorably with the single-breath ventilation (V_1/V_2). The clearance constant (R) based on the entire washout curve shows poor agreement, with large discrepancies appearing at the apexes and bases. These discrepancies likely relate to slower clearance of xenon from extrapulmonary tissues (thoracic wall, diaphragm, etc.) included in the camera field. The mass of these tissues relative to lung is greater at or near the lung bases and apexes. It is likely, however, that the linear term of the model, and therefore the clearance constant R , contains a significant contribution from the lung in patients with chronic obstructive lung disease. A comparison of these clearance rates with the single-breath ventilation

Fig. 5 Comparison of ventilation indexes in 23 young normals calculated from single-breath and washout data.

in a patient with obstructive lung disease is shown in Fig. 6. Once again an excellent correlation between the exponential rate constant (K) and single-breath ventilation (V_1/V_2) is evident, whereas the clearance constant (R) based on the total washout curve correlates rather poorly, particularly at the lung bases. An electrical RC circuit model of the lung essentially predicts that the single-breath ventilation index should be linearly related to the exponential rate constant rather than to the total clearance constant. In the analogy the ventilated region of the lung appears as the capacitance. This topic and the effect of chest-wall and diaphragm radioactivity on clearance curves will be the subject of further communication.

Fig. 6 Comparisons of ventilation indexes in patient with chronic obstructive pulmonary disease.

Effect of COPD on Regional Lung Indexes

Earlier workers^{15,16} have shown that in normal adults ventilation and perfusion increase with distance from the lung apices. Our results for the distribution of ventilation, perfusion, and the ventilation/perfusion ratio for young normals are given in Fig. 7. The expected gradients of V_1/V_2 and Q/V_2 occurred for young adults, although the standard deviations of the perfusion distribution appeared somewhat larger throughout. Tentative data for elderly normals appear to demonstrate the same lung functional index distributions.

Selected scintiphotograms from an elderly patient with chronic obstructive pulmonary disease (COPD) are shown in Fig. 8. It is evident that the involvement was confined primarily to the left lung, which showed considerable retention of xenon after 1 min of washout. The clearance half-times derived from the computer are listed in Fig. 9. The functional indexes and V_1/Q ratio for the left lung are plotted in Fig. 10. The clearance half-times for the left lung were markedly prolonged, and the ventilation indexes for this lung were correspondingly diminished. This was consistent with the earlier data on another patient with COPD (Fig. 4) and was in sharp contrast with the young normals discussed earlier.

Pulmonary Function Evaluation in a Patient with Pulmonary Emboli

Figure 11 shows representative scintiphotograms from a patient with the clinical diagnosis of pulmonary emboli. The scintiphotogram labeled "Perfusion (Q)" shows a rather marked diminution in blood flow to the left lung, which is compatible with the presence of pulmonary embolism. The scintiphotograms

Fig. 7 Averages of ventilation (V_1/V_2) and perfusion (Q/V_2) indexes and ventilation/perfusion (V_1/Q) ratios in 23 young normals.

Fig. 8 Selected scintiphotograms obtained during pulmonary function evaluation of patient number 8342 with recurrent bronchitis.

Fig. 9 Clearance half-times (in seconds) obtained in regional evaluation of patient number 8342.

Fig. 10 Computerized plots of indexes of pulmonary-function evaluation of patient number 8342. Q, perfusion index (Q/V_2). V, ventilation index (V_1/V_2). R, ventilation/perfusion ratio (V_1/Q).

labeled " V_2 " and " V_1 " indicate that ventilation, although not entirely uniform, was nonetheless reasonably good in the left lung. It can also be seen that there was essentially no delay in washout bilaterally. Figures 12(a) and (b) are representative contour plots obtained from the perfusion and ventilation portions of the study, respectively. The count rate was significantly higher during the perfusion portion; so the statistics are better and the contours are more uniform than those obtained during ventilation. The maximum blood flow to the left lung was approximately one-sixth that to the right lung. The contour

Fig. 11 Selected scintiphotograms obtained during a pulmonary-function study of patient number 9459 with pulmonary emboli. (See text footnote for credit.)

plot obtained during ventilation [Fig. 12(a)] confirms the slight disparity in ventilation of the two lungs. The activity in the left lung at the time of single-breath ventilation was approximately two-thirds that in the right lung. Figure 13 is a computer plot tabulating ventilation/perfusion ratios and clearance half-times (in seconds) from selected areas of the right and left lung of this patient. The ventilation/perfusion ratios throughout the left lung were abnormally high because of the marked depression in perfusion. Regional clearance half-times in the left lung were slightly greater than those in the corresponding areas of the right lung but were not as prolonged as they are in obstructive lung disease (see Fig. 9).

Fig. 12 Computerized contour plots obtained during perfusion (a) and ventilation (b) portions of study of patient number 9459. (See text footnote for credit.)

SUMMARY AND CONCLUSIONS

We evaluated regional pulmonary ventilation and blood flow with ^{133}Xe and a scintillation camera with computer processing of data. Although ^{133}Xe does not have ideal properties for use in these studies, it is the only gas now generally available. Hopefully, ^{127}Xe , which has considerably better physical properties, may become available in the near future.

We have applied the technique described to the study of more than 400 patients, approximately one-fourth of whom were found to have normal pulmonary function. A summary of some of our recent data related to young normal subjects has been presented along with examples of patients with obstructive lung disease and one with pulmonary emboli. The examples shown indicate wide variations from normal values in patients with COPD.

The choice of 18 areas for evaluation of indexes in each lung was quite arbitrary. We have not observed any statistically significant differences in lung function in moving between two laterally adjacent regions in the same lung. Thus we are presently considering a decrease in the number of areas to 9, or even 6, per lung. Such a reduced number would be more amenable to analysis by a small computer directly coupled to the gamma camera.

In young normal subjects, our data revealed that a linear correlation exists between the normalized exponential rate constant (K) of Eq. 1 and the normalized single-breath ventilation index (V_1/V_2). No such obvious correspondence appeared for the mean clearance rate constant determined by the half-time of washout. In fact, large discrepancies between the latter index and V_1/V_2 occurred in the very regions of the thorax wherein large tissue/lung ratios were expected. For patients with chronic obstructive lung disease, however, much of the lung may be composed of compartments with linear (very slow) washout, and these will appear as tissue components in our model.

For healthy young persons, a monotonic increase of both V_1/V_2 and Q/V_2 with distance from lung apex was observed. These gradients were often found to reverse in patients with COPD. A typical emphysema victim would be expected to have significantly reduced ventilation and perfusion near the lung bases. Several examples of this effect are given in the text. By way of contrast, the patient with pulmonary emboli exhibited nominal ventilation but decreased regional perfusion. Diagnostic differentiation on the basis of these lung index differences was indicated.

Studies evaluating regional lung function in elderly normal men are now in progress. Preliminary results indicate age has no effect on the distribution of lung ventilation and perfusion.

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Fig. 13. Computerized tabulation of ventilation/perfusion ratios and clearance half-times from selected regions of lungs of patient number 9459. (See text footnote for credit.)

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ANGIOGRAPHIC STUDIES OF THE LUNG IN RELATION TO UROKINASE THERAPY

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ABSTRACT

One hundred sixty patients with angiographically proven pulmonary embolism were studied in the first phase of the National Cooperative Urokinase Pulmonary Embolism Trial. Base-line studies included pulmonary angiography, isotope perfusion studies, hemodynamic measurements, and hematologic determinations. After randomization patients were treated either with an infusion of heparin or an infusion of urokinase. Approximately 24 hr after the base-line studies (2 to 6 hr after completion of the infusion), the patients were restudied using the same diagnostic modalities as on the base-line evaluations. Angiograms were analyzed independently by three observers. Subjective and objective methods of analysis were performed. The observers had no knowledge of treatment.

After the studies on 64 patients had been analyzed, a significant advantage of urokinase over heparin in the angiographic evaluation of the pretreatment and posttreatment studies became apparent. This significance increased throughout the remainder of the study. It was apparent in both the subjective and objective methods of angiographic analysis.

The results of angiographic analysis are compared with other modalities.

The complete paper has not been released for publication. After review of the final phase of the Urokinase Pulmonary Embolism Trial by its Policy Committee, the information will be published elsewhere.

LUNG SCANNING IN PULMONARY THROMBOEMBOLISM

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ABSTRACT

Lung scanning is gradually achieving a significant role in the diagnosis of pulmonary embolic disease, in the documentation of the natural history of the disease, and in the evaluation of therapy. Lung scanning after the administration of radioactive particles or microspheres tells us the fractional distribution of pulmonary arterial blood flow. This knowledge is combined with chest radiography and an understanding of the clinical information about the patient to permit a more precise diagnosis. An important finding in lung scanning is that the vascular defects can often be correlated with specific segments of the lungs. For this to be done, it is helpful to have scans with multiple views, usually anterior, posterior, and both laterals. The finding of segmental defects together with either a normal chest radiograph or changes suggestive of pulmonary embolism greatly increases the probability of this diagnosis. The radiographic changes are elevation of hemidiaphragm, linear densities suggestive of atelectasis, small pleural effusions, and peripheral hemispherical defects, attributable to infarction. Advantages of lung scanning are that it is simple, causes little discomfort to the patient, is easily quantified, and can be carried out repeatedly in the same individual. As the result of an increased use of lung scanning and pulmonary arteriography, we have learned much about the natural history of pulmonary embolism and have obtained objective data about the efficacy of therapy.

First introduced into clinical medicine in 1963, lung scanning has rapidly achieved widespread clinical usefulness¹ (Table 1). As with other techniques that use radioactive tracers, it is helpful to ask what body function is being measured when we perform a lung scan. The procedure is used to delineate the regional distribution of pulmonary arterial blood flow and, indirectly, regional pulmonary function. It is based on the distribution within the lungs of particles or microspheres after intravenous injection.²

The validity of the method³⁻⁵ for measuring the distribution of pulmonary arterial blood flow is based on the assumptions that (1) after intravenous injection the particles or microspheres are uniformly mixed in blood by the time they reach the main pulmonary artery; (2) hemodynamic and gravitational

forces affect the distribution of particles in a manner similar to that of red blood cells; (3) the particles are completely extracted from the circulation in a single passage through the lungs; (4) in the small quantities administered, the particles themselves do not alter the distribution of blood flow; (5) the particles are not metabolized so rapidly that the initial distribution is significantly altered before their delineation by scanning or other imaging methods; and (6) proper

TABLE 1
CLINICAL USEFULNESS OF LUNG SCANNING

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1. Differential diagnosis of pulmonary embolism.
 2. Evaluation of the size, natural course, and effect of therapy in pulmonary embolism.
 3. Quantification of the degree of regional impairment of lung function in infectious, neoplastic, embolic, and obstructive lung disease.
 4. Pre- and postoperative quantification of regional function in patients with neoplasms, chronic infection, or bullous emphysema.
 5. Differential diagnosis of congenital heart disease, such as hypoplastic pulmonary arteries.
 6. Detection and quantification of pulmonary venous hypertension.
 7. Detection and quantification of right-to-left intracardiac shunts.
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calibration can be made to correct for variations in chest-wall thickness, lung volume, and other geometric factors affecting the quantification of radioactivity by external radiation detectors. The particle-distribution method meets these requirements.

The first agents used for lung scanning⁶ were macroaggregated human serum albumin labeled with either ^{131}I or ^{51}Cr . Subsequently the short-lived radionuclides $^{113\text{m}}\text{In}$ (Ref. 7) and $^{99\text{m}}\text{Tc}$ were used, either incorporated in inorganic salts, such as iron hydroxide, or bound to microspheres made of human serum albumin. The latter have the following advantages: (1) uniform size, (2) radioactive labeling immediately before use, and (3) extensive quality control.

When these agents are injected intravenously, in the absence of a right-to-left intracardiac shunt, they are completely removed from the circulation by the first capillary bed that they encounter, in this case the pulmonary capillary bed. The microspheres average 25 μm in diameter, about four times the size of red blood cells and about twice the mean diameter in the pulmonary capillaries. In most cases about 100,000 microspheres are injected. This amount is reduced to 30,000 in patients suspected of having anatomic right-to-left intracardiac shunts. These numbers of microspheres have no hemodynamic effect, presumably because of the great numbers of pulmonary capillaries (estimated by Weibel to number about 280 billion). Only when doses several thousand times larger than the usual dose are given is a significant hemodynamic effect detectable in experimental animals. To date, experience in thousands of patients has documented the safety of the procedure.

One of the main consequences of the use of short-lived tracers, such as ^{99m}Tc or ^{113m}In , is that millicurie doses can be given, which increases the number of available photons by a factor of about 10 when compared to the microcurie doses of radioactive iodine. This has facilitated the performance of multiple views; thus in many hospitals both lateral and anterior and posterior views are routine. This has had two consequences: first, the entire pulmonary vasculature is examined; and, second, the regions supplied by segmental pulmonary arteries can be readily identified. (On the anterior and posterior views, the segments overlap to a large degree.)

One point that scanning has taught us is that all diseases of the lungs result in a decrease in pulmonary arterial blood flow to the involved regions. This does not mean that the lesions are poorly supplied with blood since the blood supply from the bronchial circulation remains intact or in some cases is increased. The decrease in pulmonary arterial blood flow results in a decrease in the number of particles or microspheres reaching the lungs since in the absence of a right-to-left intracardiac shunt no particles reach the systemic circulation from which the bronchial circulation is derived.⁸

The finding of a general decrease in pulmonary arterial blood flow is of importance not only in our understanding of lung function during disease processes but also in the interpretation of lung scans in clinical medicine. When lung scans were introduced, we noted a relatively high incidence (72%) of concave perfusion defects at the periphery of the lungs.⁹ These were less common, occurring about 30% of the time, in patients with chronic obstructive lung disease. The finding of this type of perfusion defect, either in a patient with a normal chest radiograph or one that had the radiographic changes sometimes seen in pulmonary embolism (high diaphragm, linear densities of the type described initially by Hampton and Castleman), made it possible to diagnose pulmonary embolism with a moderate degree of certainty.

With the introduction of improved radiopharmaceuticals, labeled with short-lived radionuclides, such as ^{99m}Tc or ^{113m}In , and improved instruments, such as the dual 5-in. rectilinear scanners, laboratories could do routinely lung scans of four views (both laterals and anterior and posterior views). The lateral views showed us the nature of the peripheral concave defects. The frontal or posterior projections showed the avascular pulmonary segments, i.e., the regions supplied by segmental arteries. In the lateral views the territories supplied by segmental arteries do not overlap as much as they do in the anterior or posterior projections; so the specific segments can often be identified. In most patients with pulmonary thromboembolism, one or more segmental perfusion defects can often be identified, increasing the specificity of diagnosis.^{10,11} Infections or chronic obstructive lung disease often result in nonsegmental defects, i.e., lesions that cut across the boundaries between lung segments.

Specificity of diagnosis is increased in the following ways: (1) relating the perfusion defects to a chest radiograph taken at the same time as the scan;¹² (2) obtaining a history of the presence or absence of chronic obstructive lung

TABLE 2
ADVANTAGES AND DISADVANTAGES OF LUNG
SCANNING AND ANGIOGRAPHY

Lung scanning	Angiography
Advantages	
1. Simple to perform.	1. Specific because filling defects within the arteries can be seen.
2. Readily repeated.	2. High-resolution images.
3. Readily quantified.	
4. Safe.	
5. Little discomfort.	
6. Sensitive.	
Disadvantages	
1. Does not detect lesions less than 2 cm.	1. More difficult to perform.
2. Requires about 30 min to perform.	2. More discomfort for patient.
3. Relatively nonspecific.	3. Occasional serious complications.
	4. Difficult to repeat study frequently.
	5. Difficult to quantify.

disease (or other diseases, such as pulmonary infection); (3) understanding the appearance in the scans of the distributions of the segmental arteries of the lung;¹³ (4) performing simple tests for obstructive lung disease, such as the vital capacity and forced expiratory volume at 1 sec, the so-called FEV₁, which can be performed in every nuclear medicine department; (5) using radioactive ¹³³Xe in selected patients to look for regional ventilation defects,¹⁴ which are uncommon in acute pulmonary embolism; and (6) being cautious in the diagnosis of pulmonary thromboembolism if the patient has chronic obstructive lung disease.^{15,16} The latter circumstance, in my experience, is the most frequent indication for the performance of a pulmonary arteriogram.¹⁷⁻¹⁹

Since the introduction of both procedures, the relative advantages and disadvantages of lung scanning and pulmonary arteriography have been clarified. These are listed in Table 2.

The steps that we follow in the diagnosis of pulmonary embolism are listed in Table 3.

Finally, I want to mention the results of our experience with lung scanning in the diagnosis of pulmonary embolism. One hundred and twenty-one patients clinically suspected of having pulmonary emboli had lung scans followed by pulmonary angiograms. The time between studies was 1 day for each of 66 patients, 2 for 16, and 3 for 19. Twenty cases were eliminated because the interval was greater than 3 days.

The lung scans with the aid of chest roentgenograms were interpreted independently by two of the researchers without knowledge of the angiographic findings. Each lung-scan defect was categorized according to the type of perfusion abnormality and its location within the lung. The lung-scan defects

DIAGNOSIS OF PULMONARY EMBOLISM

Step 1 Clinical Suspicion

1. Postoperative state.	8. Cough.	15. Hypotension.
2. Postpartum state.	9. Hemoptysis.	16. Worsening of heart failure.
3. Prolonged immobilization.	10. Syncope.	17. Worsening of chronic obstructive lung disease.
4. Thrombophlebitis.	11. Sweating.	
5. Dyspnea.	12. Cyanosis.	
6. Tachypnea.	13. Palpitations.	
7. Pleurisy.	14. Anxiety.	

Step 2 Chest Radiograph and Lung Scan

1. Scan normal—greatly decreases probability of pulmonary embolism.
2. Scan abnormal:
 - a. Subsegmental, segmental, or lobar defects increase probability of pulmonary embolism.
 - b. Diffuse or patchy areas of decreased perfusion probably not due to embolism.
3. Radiograph normal with segmental defects on scan—increases probability of pulmonary embolism.
4. Radiograph shows atelectasis, elevated diaphragm, pleural effusion, or peripheral hemispheric defects—increases probability of embolism.
5. Radiograph shows parenchymal defects, i.e., patchy infiltrates, consolidation or lesions suggesting tumor—lowers probability of embolism.

Step 3 Angiography

1. Filling defects in contrast media—makes diagnosis of embolism a virtual certainty.
2. Amputation of segmental or lobar arteries—increases probability of embolism.
3. Tapering or delayed filling of vessels may or may not be due to embolism.

were divided into two groups, focal and diffuse. A focal anatomic defect was any well-defined decrease or absence of perfusion which corresponded to a lung, lobe, segment, or subsegment. If a well-defined decrease in perfusion did not conform to an anatomic division of the lung, it was described as a focal nonsegmental defect. A diffuse defect was any poorly localized diffuse or patchy reduction in perfusion. According to our premise a patient with a focal perfusion abnormality corresponding to an anatomic division of the lung was judged as having a high probability of pulmonary embolism. Any other perfusion abnormality was judged as having low probability, and a normal scan was judged as no probability.

Pulmonary angiography was interpreted without knowledge of the lung-scan findings. To facilitate correlation with the lung scan, we assessed the angiographic appearance of each lobe. Categorization of the findings was based on the criteria of Stein et al.¹⁹ First, there are abnormalities specific for a pulmonary embolus consisting of an intraluminal filling defect, abrupt vessel cutoff, and vessel pruning; second, there are nonspecific abnormalities consisting of slow flow and oligemia; and, third, we can have normal findings.

Of the 53 patients judged as having a high probability of pulmonary embolism, 77% (41 patients) had embolism angiographically. Three other patients were shown by angiography to have pulmonary embolism but were in our low-probability group.

There were 99 emboli (shown angiographically) in 44 patients, and these emboli correlated with the scan defects in the following manner: 91 corresponded to focal anatomic defects, 8 corresponded to focal nonsegmental defects, 1 corresponded to a diffuse defect, and 2 had no corresponding scan abnormality. The patients with pulmonary embolism whose scans showed absent perfusion of one lung had focal segmental defects in the opposite lung, whereas four patients who did not have embolism but had absent perfusion of a lung had normal opposite lungs.

Fifty-seven additional patients who did not have pulmonary embolism demonstrated angiographically and the 44 patients with pulmonary embolism had the following scan defects that correlated with the presence or absence of emboli. Of 129 focal anatomic scan defects, 71% correlated with emboli (lobar, 85%; and segmental, 64%), focal nonsegmental in 18%, and diffuse in one case.

All 44 patients with pulmonary embolism (as diagnosed angiographically) had abnormal lung scans. In these patients only 2 of the 99 emboli shown angiographically did not have an associated lung-scan defect. None of the 21 patients who had normal scans had emboli demonstrated angiographically. The chance of detecting an embolus angiographically in a patient with a normal lung scan must be very low. One possibility is a saddle embolus equally impeding flow to both pulmonary arteries.

Our premise that pulmonary emboli cause focal lung-, lobar-, or segmental-scan defects has been confirmed since 91 of 99 separate emboli produced this type of defect. The specificity of the focal anatomic lung-scan defect is 71%, whereas nonanatomic defects rarely correlate with emboli.

The focal lobar-scan defect has the best correlation with the presence of an embolus as shown angiographically. The poorer correlation of focal segmental-scan defects is probably due to the insensitivity of routine pulmonary angiograms to detect segmental or subsegmental arterial occlusions, and selective segmental angiograms should be used. Thus the specificity of the perfusion lung scan becomes 77% if the defect is focal and conforms to the segmental or lobar anatomy instead of 55% if the criteria is any perfusion defect. The use of the angiogram, which is not perfect as the standard for comparison, means that the scan may be even more specific than we have been able to determine.

The perfusion lung scan and the pulmonary angiogram are complementary procedures. In the clinical setting of a patient with chest pain who is in shock, the separation of pulmonary embolism from myocardial infarction, pleurisy, and dissecting aortic pulmonary embolism is necessary. If the scan has well-defined focal segmental or lobar defects, then pulmonary embolism is highly probable. However, some of these patients may have corresponding roentgenologic changes, such as opacities (homogenous or inhomogenous) or oligemia in

segmental distribution, and will require angiography in nonsegmental defects as did 27 of our patients, 3 of whom had embolism. These are the patients who need pulmonary angiography to detect their emboli. Angiography should also be used to confirm the scan diagnosis of embolism in patients who are to have embolectomies, inferior vena caval interruption, or thrombolytic chemotherapy. Selective segmental angiograms should be performed using the scan defects as a guide in choosing arteries to catheterize.

In summary, all 44 patients with pulmonary embolism shown by angiography had abnormal scans. None of the 21 patients with normal lung scans had emboli demonstrated angiographically. There is a good correlation of emboli with focal lobar-scan defects (85%) and focal segmental-scan defects (64%). Of 53 patients judged as having a high probability of pulmonary embolism, 77% had angiographically demonstrated emboli. The lung scan should be the initial screening procedure for pulmonary embolism, and, if the scan results are inconclusive (lack of graphic abnormality), then angiography should be performed. Angiography should also be used to confirm the scan diagnosis prior to pulmonary embolectomy, inferior vena caval interruption, or thrombolytic therapy.

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PULMONARY RADIOISOTOPIC AND RADIOGRAPHIC TECHNIQUES: WHAT THEY SHOW, DO NOT SHOW, AND WHY

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ABSTRACT

Pulmonary perfusion scintiphotography and pulmonary angiography are complementary, not competitive, procedures. Scintiphotography reflects the distribution of pulmonary blood flow; angiography displays pulmonary vascular anatomy. Therefore inference of anatomy from the scan and blood-flow distribution from the angiogram are both subject to substantial error. A variety of physiologic and pathophysiologic influences other than pulmonary thromboembolism can alter the distribution of pulmonary blood flow. All these mechanisms must be considered if interpretive errors are to be avoided. Proper interpretation also requires attention to the details of technic and the natural history of the disease process being studied by scintiphotography or angiography. The use of ventilation scintiphotography further enhances the ability of the scintiphotographer to determine the significance of perfusion defects. Developments in radiographic and radioisotopic techniques—including magnification angiography, videodensitometry, tantalum bronchography, and computerization of scintiphotographic information—should further extend our abilities to define the basis of alterations in pulmonary ventilation and perfusion.

I should like to pose a simple question at the outset: "If you were going to search for something, would you rather have a pair of binoculars, a horse, a microscope, or a helicopter?" I doubt that the question would lead you to promptly respond "horse!" or "microscope!" Rather, you would be likely to say, "That's a ridiculous question. I can't answer it until you tell me what you are asking me to search for!" That would be a rational response to a stupid question. But I submit to you that, in the case of pulmonary scintiphotography and angiography, the response of the medical community has been somewhat less rational. Many physicians have been shouting "binoculars!" or "helicopter!"—actually "scan!" or "angio!"—without stopping to ask first what they are searching for with these diagnostic tools.

It has been quite clear from the outset that perfusion scintiphotography and angiography provide different types of information. The pulmonary angiogram

displays the anatomy of the pulmonary vascular bed. It cannot provide quantitative data regarding blood flow; therefore any functional conclusions must be drawn from angiography with great caution. Perfusion scintiphotography, on the other hand, provides both qualitative and quantitative data regarding the distribution of pulmonary blood flow. It does not provide anatomic information and can be used for such a purpose only with substantial reservation.

These facts often have been overlooked. A peculiar syndrome has developed in which the technics themselves have assumed an independent diagnostic life, divorced from the anatomic and pathophysiologic realities that condition the results. This syndrome provokes diagnostic error and confusion because scan or angiographic patterns per se rarely have specific meaning. They simply mirror the underlying anatomic and physiologic situation. Therefore, unless the interpreter has a solid foundation in cardiopulmonary structure and function, valid diagnostic conclusions are rarely possible.

The interpretive confusion induced by neglect of this principle has been particularly dramatic for perfusion scintiphotography. Somehow, somewhere in its development scintiphotography came to be regarded chiefly as a diagnostic test for pulmonary embolism. This basic misconception then spawned several corollary misconceptions. For example, if the perfusion scan is considered to be a diagnostic test for embolism, then all conditions other than embolism which produce perfusion defects are regarded as "false positives," and all instances in which embolism fails to cause a defect are called "false negatives." Such an approach at best reflects a narrow way of looking at things; at worst it leads to serious diagnostic error and inhibits learning. Accepting the scan as a "test for embolism" and measuring its value on the basis of this single criterion is like stating that the chest X ray is exclusively a diagnostic test for tuberculosis. Thus all chest X rays that display an infiltrate that is nontuberculous would become false positives. Chest X rays without a visible lesion in a patient with tuberculosis would be false negatives. Obviously such an approach to chest roentgenography would be unacceptable; active or arrested tuberculosis can exist without a readily visible infiltrate by chest X ray, and many diseases other than tuberculosis can cause pulmonary infiltrates.

The chest X ray, however, long has been recognized as a diagnostic tool that never—almost never—establishes or denies a specific diagnosis. The shadows cast by too many diseases look alike, and too many disorders affect the lungs without creating visible shadows. The pulmonary perfusion scan shares these characteristics. Abnormalities in the distribution of pulmonary blood flow, like radiographic shadows, are inherently nonspecific. Therefore the perfusion scan never has been nor ever will be a diagnostic test for pulmonary embolism. Many cardiopulmonary conditions can alter the distribution of pulmonary blood flow; many others, even embolism, can exist without significantly altering this distribution.

The pulmonary angiogram also is subject to misinterpretation if the mechanisms that alter pulmonary blood flow are not considered carefully. Therefore I should like to review briefly what we know about these mechanisms.

In normal man pulmonary blood flow is not distributed uniformly throughout the lungs because it is gravity dependent.¹⁻⁴ Therefore in erect man there is diminished blood flow to the apical regions of the lung and an increased amount of perfusion to the lung bases (Fig. 1). If a normal subject lies supine, this apex-to-base gradient of blood flow disappears and is replaced by a sternum-to-spine gradient. If the subject lies on his side, a gradient again exists so that the dependent lung receives more blood flow than the superior lung.

These fundamental relations have a direct bearing on both angiography and perfusion scintiphotography. Normal patients who have perfusion studies in which the radionuclide is injected while they are in the upright position will have bilateral apical defects. Obviously these zones of decreased radioactivity do not reflect disease. If the radionuclide is injected with the patient supine, then distribution appears uniform in the anteroposterior (AP) and posterolateral (PA) views; but lateral views will show a gradient of flow favoring the dependent posterior zones and so on. Therefore care must be taken to ensure that these normal, gravity-dependent changes in flow distribution are either eliminated by the technic of injection or are interpreted properly.⁵

These same comments are applicable to pulmonary angiography. However, most angiograms are performed with the patient supine, and only PA or AP views are obtained. Thus no gradient of perfusion is noted in the capillary phase. Furthermore, most angiograms are analyzed primarily for large-vessel configuration rather than for details of the capillary phase. If, however, a lateral view of the supine patient is taken, a gradient will be seen in the capillary phase.

These gravity-dependent effects actually reflect the relations between pulmonary artery pressure, alveolar pressure, and pulmonary venous pressure (Fig. 2).³ Any physiologic or pathophysiologic event that alters one of these three pressures can alter the distribution of blood flow within the lung. For example, during exercise the pressure in the pulmonary artery rises. This rise tends to make the distribution of blood flow more uniform throughout the lung. Distribution of flow also varies somewhat at different lung volumes (e.g., at total lung capacity vs. functional residual capacity vs. residual volume) and is altered by performing either Valsalva's or Müller's maneuver.⁶⁻⁸ All these physiologic influences must be carefully excluded before a given scan or angiogram finding is interpreted as being indicative of disease. If this has been done, one must next have available an intellectual catalog of the pathophysiologic mechanisms that can influence blood-flow distribution. There are only three such mechanisms: luminal obstruction, vessel destruction, and vessel constriction.

When an angiogram demonstrates nonfilling of a vessel or a scan reveals a perfusion defect, luminal obstruction usually is the first cause to pop into our minds. Such obstruction can result from material within the lumen, such as a

Fig. 1 Distribution of blood flow in the lungs is gravity dependent. Therefore, in the erect position (left) there is increased basilar and decreased apical flow; in the supine patient (right) flow is increased in the dependent lung zones.

Fig. 2 Distribution of pulmonary blood flow depends on the relation between pulmonary arterial pressure (P_a), alveolar pressure (P_A), and pulmonary venous pressure (P_V).

thromboembolus; from extrinsic compression of the vessel by such processes as tumor growth; or from congenital anomalies which have an equivalent effect on blood flow. Total obstruction of the larger pulmonary arteries is easy to detect by scan or angiogram. It is not widely appreciated, however, that the presence of incomplete occlusion can readily escape detection. If it is to be reflected by scan, an obstruction must be of sufficient degree to elevate resistance to flow. Unfortunately the relation between extent of luminal obstruction and elevation of resistance is not linear. Several studies have shown that reduction of the lumen of a vessel by as much as 50% causes no significant increase in flow

resistance.^{9,10} Resistance does rise between 50 and 80% occlusion; but only beyond 80% occlusion is flow resistance markedly increased. This relation holds in the larger arterial vessels, such as the main pulmonary arteries and the lobar and segmental branches. In smaller vessels resistance rises more sharply at lesser degrees of obstruction.

The implications of these relations to both scan and angiographic studies are substantial. For example, an embolus in the pulmonary artery of the right lower lobe could occlude 50% of the lumen of this vessel without significantly decreasing blood flow to this lobe (Fig. 3). The scan, which measures this flow, will be normal. Indeed, it may remain normal unless the embolus grows or passes to a more distal vessel. Some might say that a normal scan in the face of 50 to 80% luminal obstruction represents a false negative. Actually the scan is doing its job perfectly. It is stating only what it can state: that there has been no significant alteration in the regional distribution of blood flow.

What of the angiogram in partial occlusion? It is subject to the same hemodynamic rules. In the 0 to 80% occlusion range, radiopaque medium would reach the vessels of the right lower lobe in almost normal time and concentration. The astute observer, however, will see the one available diagnostic clue: a filling defect in the artery of the right lower lobe (Fig. 4). He need not question the validity of this filling defect just because distal flow is well preserved.¹¹⁻¹³

These same considerations apply regardless of the cause of the obstruction. For example, in congenital stenosis a substantial degree of narrowing of one main pulmonary artery branch may exist without causing an abnormality in the scan.¹⁴ Again the angiogram will display the stenotic area itself but will appear otherwise normal. Of course, the clinician usually will hear a murmur, and his transmission of this fact to the angiographer may be a key factor in identifying the abnormality.

The second mechanism for alteration of blood flow is vessel destruction. Many diseases, ranging from tuberculosis to bullous emphysema, can obliterate blood vessels. Neither the scan nor the angiogram can identify the cause of the destruction. Both, however, will faithfully reflect the absence of blood flow to the affected lung zones. The angiogram has one distinct diagnostic advantage in this situation: it will identify the size of the vessels involved in the obliterative process. The scan can show only that perfusion is absent to a given lung zone, an event that could be due to destruction of one large vessel or many smaller vessels. The angiogram can distinguish between possibilities. This also applies in pulmonary embolic disease (Fig. 5). For example, if there is no perfusion to the left lower lobe, the scan cannot distinguish obstruction of the artery of the left lower lobe from multiple smaller emboli in the distal branches. The angiogram can supply this anatomic information, which may be critical to clinical decisions.

In assessing destructive pulmonary lesions, the two procedures have an additional point of disparity. When angiography demonstrates radiopaque

Fig. 3 (Left) with less than 50% obstruction of the lumen of a pulmonary arterial vessel, distal flow may be completely undisturbed so that a normal scan will result. With more extensive obstruction (right), flow is decreased and a scan abnormality appears.

Fig. 4 Filling defects on angiogram (arrows) in pulmonary arterial branches to right lower lobe. Such defects may be the only clue to the presence of partially obstructing emboli. [From K. M. Moser, P. Harsanyi, G. Ruis-Garriga, M. Guisan, G. A. Landis, and A. Miale, Jr., Assessment of Pulmonary Photoscanning and Angiography in Experimental Pulmonary Embolism, *Circulation*, 39: 669 (1969).]

material in the major arterial vessels, the conclusion may be reached that flow to this zone is normal. Yet the scan may show sharply diminished (or absent) perfusion to this same area. There is no conflict in these findings. The patency of major arterial vessels does not mean that arteriolar-capillary blood flow is normal. If the pulmonary arterioles and capillaries are severely compromised, this will be reflected in the scan image even though the angiogram documents that the large arterial vessels are patent.

Fig. 5 Both of the embolic (or destructive) situations pictured above will produce the same scan defect: absence of left lower lobe perfusion. Angiography, however, can distinguish between obstruction of left lower lobe artery *per se* (left) and its branches (right).

The third mechanism that compromises blood flow, constriction, is perhaps most subject to interpretive error because it is least often considered. Yet it is extremely common. Constriction occurs chiefly in the smaller arterial vessels, the arterioles. These vessels are rather thin and are poorly muscled in contrast to their systemic counterparts, but under normal circumstances their structure is quite sufficient to contend with the low pressures that exist in the pulmonary circulation. Constriction of these vessels can occur in two ways (Fig. 6). Obviously the muscle in their walls can contract so that flow through them is reduced or blocked, but it has recently been appreciated that they also can be mechanically constricted—compressed, if you will—by the accumulation of fluid in the perivascular space surrounding them.^{15,16} Such accumulation is common in cardiopulmonary disease. Pulmonary edema begins in these interstitial areas. Only after they are congested does fluid finally enter the alveoli themselves to produce the full-blown clinical and radiographic findings of pulmonary edema.

With regard to muscular contraction of the pulmonary arteries, three pathways exist which may instruct these vessels to contract: (1) neural pathways, (2) the bloodstream, and (3) the conducting airways. I will neglect the first because it is the most controversial except to say that reflex vasoconstriction undoubtedly can occur.

The bloodstream can carry a number of materials that induce pulmonary arterioles to constrict or dilate. Acidity of the blood, for example, can cause arteriolar constriction,¹⁷ and there are many clinical situations in which

Fig. 6 Lumen of normal pulmonary arteriole (above) can be reduced by muscular contraction on hypertrophy (left) or by compression as fluid accumulates in the perivascular space (right).

metabolic or respiratory acidosis can appear. Humoral agents also can alter pulmonary vasomotor tone. One of the most widely studied of these agents has been serotonin.¹⁸ This potent vasoactive amine is normally contained in blood platelets. Its release from platelets on the surface of pulmonary emboli has been demonstrated in animals to add a vasoconstrictive element to the mechanical effects of embolism, thus acutely augmenting the degree of pulmonary hypertension observed.¹⁹ Whether this also occurs in man is presently unknown, but there is reason to conclude that it may, at least in some instances.

The third pathway through which pulmonary arteriolar tone can be augmented is via the airways, more specifically, by the partial pressures of oxygen and carbon dioxide in the alveolar gas. Alveolar hypoxia and alveolar hypercapnia both are capable of inducing pronounced arteriolar contraction.^{20,21} This is of considerable importance because there are many clinical conditions in which regions of the lungs are poorly ventilated. Inadequate ventilation, or hypoventilation, as it is called, causes inadequate delivery of oxygen to and removal of carbon dioxide from the region involved. As a consequence the arterioles there will constrict. Therefore on perfusion scan a defect will be seen. Perfusion abnormalities of this type are common in patients with chronic obstructive pulmonary disease; chest pain that causes marked splinting; pleural tumors, fibrosis, or effusions that restrict ventilation; and bronchial tumors or stenosis of sufficient extent to impair ventilation. In short,

any condition that causes a lung region to be inadequately ventilated will cause arteriolar contraction and a perfusion defect. Such effects also will be readily seen by angiography as a failure to visualize the capillary phase. Regional hypoventilation is a particularly tricky cause of abnormalities in the perfusion scan and angiogram because it can occur in the presence of an essentially normal chest X ray. Alveolar hypoxia and hypercapnia leave no telltale imprint on the roentgenogram.

Another closely related circumstance that leads to arteriolar contraction is the development of atelectasis or a process filling the alveoli. Acute bacterial and viral pneumonias are the most common alveolar filling processes. Arterioles entering these areas of lung consolidation are totally deprived of contact with alveolar oxygen and respond by contracting. The same sequence occurs when atelectasis develops. Thus the scan and angiogram again will show regional perfusion abnormalities, though in these situations the chest X rays usually will show the consolidated or atelectatic zones.

Finally, a similar phenomenon occurs in patients with tight mitral stenosis.²² The chest roentgenograms of such patients taken in the erect position show large vessels in the upper zones of the lung and avascularity in the lower. Both the scan and angiogram reflect this same blood-flow distribution, i.e., marked reduction in basilar flow and marked augmentation of apical flow. This is a complete reversal of the pattern seen in normal erect man. The mechanisms responsible have not been fully elucidated, but both constriction, due to perivascular edema in the dependent lung zones, and active contraction appear to be involved. Whatever the mechanisms they are operative chiefly in the erect position because, if the patient is studied in the supine position, the distribution of blood flow becomes uniform apex to base. Thus we are dealing with some acutely reversible process, not vascular obstruction or obliteration.

It is apparent, then, that many clinical disorders can cause defects on the scan and angiogram on the basis of arteriolar contraction. It is of more than academic interest to be able to distinguish those defects due to obstructive or destructive vascular lesions from those due to muscular contraction of arterioles. This has not, as yet, been widely attempted, but work in our laboratory and elsewhere suggests that it can be done by infusion of a pulmonary vasodilator such as acetylcholine.²³ Acetylcholine should improve distinctly the scan and angiographic abnormalities caused by contraction, but it will not change those due to vascular obstruction or destruction.

This review of the anatomic, physiologic, and pathophysiologic factors controlling the distribution of pulmonary blood flow has served to document the fact that neither scans nor angiograms can be interpreted in a technical vacuum. A scan or an angiographic abnormality may arise from a variety of quite different mechanisms. Only the interpreter familiar with these possibilities can offer proper diagnostic assistance. If he is not familiar with them—and that is not to the discredit of men whose lives have not been devoted to a study of

cardiopulmonary physiology—then two solutions present themselves. Either he can consult with a colleague who does have such familiarity or he should describe what he observes without invoking etiology. The latter course is quite acceptable. The experienced roentgenographer has done this for years to avoid misleading his clinical colleagues. An X ray showing consolidation or infiltration is reported exactly that way. It is uncommonly reported as a “consolidation indicative of pneumococcal infection” or “an infiltrate compatible with tuberculosis.” Why, then, should the interpreter of a scan or an angiogram describe an avascular zone of the lung as “a defect compatible with pulmonary embolism.” Of course, it is compatible with that possibility, but it also may be compatible with 50 other diagnoses. There are, of course, instances in which the interpreter of a roentgenogram, a scan, or an angiogram is in possession of additional laboratory and clinical details that enable him to make a useful etiologic suggestion. But, unless this is the case, a descriptive report rather than an etiologic one better serves the patient. The use of anticoagulant therapy threatens to reach epidemic proportions in those institutions in which every defect in a perfusion scan is labeled as “compatible with” or “suggestive of” embolism.

Recognition of the pathophysiology of the pulmonary circulation is not the only variable with which the interpreter of perfusion scans and angiograms must contend. He also must be aware of the technical limitations and artifacts associated with each method and the fact that the abnormalities visualized may have a dynamic quality which changes as the natural history of the disease process unfolds.

The need for attention to technical detail in the performance of both scans and angiograms is now well known. Inadvertent injection of angiographic contrast medium into one main pulmonary artery can suggest total occlusion of the other. A rectilinear scan with background suppression adjusted to moderate the zones of most intense radiation will make poorly perfused zones appear nonperfused. The AP and PA views on both a scan and an angiogram not supplemented by lateral views may lead to misinterpretation. Both scans and angiograms are poor in detecting diffuse obstruction of pulmonary arterioles or venules because such lesions are generally below their resolving capabilities.

These points of technic, however, are less a source of difficulty than failure to consider the natural history of the disorder being studied. This problem can be especially troublesome for such dynamic entities as asthma and pulmonary embolism, in which the regional distribution of pulmonary blood flow can shift rapidly. For example, our experience has disclosed several instances in which the diagnosis of recurrent embolism has been based on serial scan changes which, in fact, were not due to recurrence. This sequence occurs in patients who present with multiple pulmonary emboli, a not uncommon presentation since more than 50% of all embolic events are multiple (Fig. 7). The scan observed in such patients faithfully reflects the distribution of blood flow, which, as mentioned

previously, depends on the resistance to flow. In a patient with total occlusion of several vessels plus partial occlusion of another, the scan would show defects in the totally occluded regions, but the partially occluded region might appear to have relatively normal flow for two reasons: (1) because the luminal occlusion is less than 80% and (2) because diversion of flow from the occluded lung regions increases its share of blood flow. But what would we see in a day or two should

Fig. 7 (Above) multiple emboli, three totally occluding, one partially occluding. Partial occlusion is likely to cause minimal reduction in perfusion by scan. If totally occluding emboli resolve (below) while original partial occlusion persists, partially occluded vessel becomes the "high-resistance" vessel and a "new" scan defect may appear in this lung region, suggesting recurrence of embolism.

there be rapid dissolution of emboli in the totally occluded areas and little dissolution of the partially occluding embolus? This can and does occur in man. A repeat scan at this juncture might show a return of perfusion to the areas in which dissolution was rapid and an apparently new defect in the area of partial occlusion. Thus the new defect does not indicate recurrence of embolism; rather, it merely indicates that the distribution of resistance in the pulmonary vascular bed has changed.

Similarly subject to misinterpretation is the story of embolic resolution. The return of blood flow to a lung zone previously identified as avascular on a scan or an angiogram does not mean that the offending embolus has resolved totally. It means only that radiopaque or radioactive materials can now reach these regions. This can occur when the embolus has partially resolved, even though it

still fills 50% or more of the vessel's lumen. Or the change may mean that a partially dissolved embolus has moved distally to occlude a vessel below the resolution of standard angiographic and scintiphotographic techniques.

Thus far this discussion has dealt only with perfusion scintiphotography and standard angiography. Recently, both scintiphotographic and angiographic-radiographic techniques for assessing cardiopulmonary disease have expanded considerably. Among the radiographic advances are three of particular interest: (1) magnification angiography, (2) tantalum bronchography, and (3) videodensitometry.

The diagnostic potential of magnification angiography has been amply demonstrated.^{24,25} The status of the smaller pulmonary blood vessels, where much of the physiologic and pathologic action is, now is subject to study. Technical advances should bring this method into more general use in the near future.

Tantalum bronchography promises to open similar new horizons with respect to the structure and behavior of airways.^{26,27} The extreme radiodensity of tantalum makes this metal an ideal contrast material. It can be prepared in a variety of particle sizes for inhalation as a powder. Particle size and technic of administration can be altered to control where the tantalum will rain out in the tracheobronchial tree. The particles cling to the bronchial mucosa, permitting repeated radiographic studies over a period of hours, and tantalum insufflation can be accomplished without inducing bronchospasm or cough and without clogging airways, all deficits of current bronchographic methods. With magnification techniques, the smallest airways now can be visualized. What angiographic advance has done for our diagnostic capability with respect to pulmonary vascular anatomy, tantalum promises to do with respect to tracheobronchial anatomy.

Videodensitometry and videofluoroscopy provide additional means for studying the dynamics of respiration.²⁸ Cardiopulmonary events now can be recorded, reviewed, and, to an increasing degree, quantitated. Densitometry may allow statements about regional ventilation, regional blood flow, and the pulsatility of thoracic vessels. The limits of these relatively young and developing techniques are unknown, but their promise is considerable.

Equally fast moving and exciting have been new developments in the application of radioisotopes to the study of pulmonary disease and physiology. Perhaps the two most valuable advances have been the emergence of ventilation scintiphotography and of methods for quantitating radionuclide information.

Ventilation scintiphotography²⁹⁻³¹ has proven to be an extremely powerful tool, not only in enhancing the diagnostic specificity of pulmonary radionuclide studies but also in providing functional information. As has already been indicated, many pulmonary disorders can cause abnormalities in perfusion scans; but, by combining ventilation with perfusion scintiphotography, we can begin to sort the causes of perfusion abnormalities into clinically useful categories. Such categorization is made possible by recognizing that certain diseases produce

rather characteristic ventilation-perfusion disturbances. The pulmonary physiologist has been doing this for some years by analyzing arterial blood and expired gases. Such analyses have established that even in the normal lung ventilation and perfusion are not evenly matched in all regions. Some regions receive too much ventilation in proportion to their blood flow; others receive too little. These mismatches between air and blood in the lungs are referred to as instances of ventilation/perfusion (or $\dot{V}/\dot{Q}$) imbalance. When ventilation and flow are perfectly matched, a $\dot{V}/\dot{Q}$ ratio of 1 is said to exist, and the blood emerges from such an area of gas exchange with precisely normal oxygen and carbon dioxide tensions. In gas exchange regions with a high $\dot{V}/\dot{Q}$ ratio, some ventilation is wasted because the blood exits from such zones with a higher than normal oxygen tension and a lower than normal carbon dioxide tension. In low $\dot{V}/\dot{Q}$ zones the mismatch means that blood exits without having received adequate oxygen and without having given off enough carbon dioxide. That these disturbances in $\dot{V}/\dot{Q}$ relations are the most common cause of arterial blood gas abnormalities in patients with pulmonary disease has been well established by standard pulmonary-function studies, but ventilation-perfusion scintiphotography has provided a new dimension in functional evaluation. It has permitted us for the first time to visualize these areas, to see where they are located in the lungs. Furthermore, as stated above, such visualization of $\dot{V}/\dot{Q}$ relations has direct diagnostic value since certain disease processes alter $\dot{V}/\dot{Q}$ in a characteristic manner.^{3,2}

For example, an acute pulmonary embolus results in a lung region with decreased to absent perfusion, but, until and unless pulmonary infarction has occurred in this zone, which is uncommon and requires some hours to develop, the region remains well ventilated (Fig. 8). Thus a region of high or infinite $\dot{V}/\dot{Q}$ is characteristic of pulmonary embolism and other pulmonary vascular obstructive diseases.^{3,2,3,3} Included in this category are such acquired entities as pulmonary arteritis or obstruction by tumor as well as congenital vascular anomalies, such as pulmonary artery agenesis^{3,4} and severe stenosis^{1,4} of a unilateral pulmonary artery branch.

Contrast this with the ventilation-perfusion pattern anticipated in a zone of lung occupied by a large bullous lesion. Such bullae receive no pulmonary arterial flow and in this regard resemble an embolized lung zone, but, contrary to the embolized lung zone, a bullous area is essentially nonventilated. Thus a bullous lesion will appear as a "No $\dot{V}$ /No $\dot{Q}$ " area when combined ventilation and perfusion scintiphotography is applied.^{3,2}

These are just two of many clinical situations in which an understanding of the ventilation-perfusion relations characteristic of a given disease can be used to diagnostic advantage. If this concept is applied, vascular disorders can be separated from parenchymal diseases of the lungs, and some parenchymal diseases can be distinguished from others. Thus the perfusion scan, which by itself totally lacks diagnostic specificity, gains substantial specificity when combined with the ventilation scan.

Fig. 8 Ventilation-perfusion studies in patient with angiographically documented pulmonary embolism. Posterior perfusion scan (upper left) shows absent perfusion to left lower lobe and a region of the right upper lobe. Ventilation to these nonperfused regions is preserved on the first breath of xenon (upper right) and at equilibrium (lower left). Washout proceeds normally (lower right).

Although the raw images of perfusion and ventilation scintiphography are of diagnostic value, it has been obvious for some time that these procedures could be manipulated to provide quantitative data in addition to the visual data. The only problem has been to devise practical systems for extracting and presenting the digital information hidden in these images. A number of systems are now available which permit such maneuvers, and the state of the art is continually improving.³⁵⁻³⁸ Pulse-height analyzers, magnetic tapes, videotapes, computers, and computer programs now literally surround many scintillation cameras. Visual images are now a starting point, even a by-product, of these

Fig. 9 Equilibrium ventilation scan (above left) with two areas of interest identified by white boxes. Ventilation scan after 6 min of washout is shown at upper right. Note area of delayed washout in left upper lobe. At lower left are computer-generated washout curves from the two areas of interest. At lower right are these two curves plus curve representing composite of xenon washout from all lung regions.

sophisticated analysis systems. Such systems are proving to be more than investigative playthings. They can generate diagnostic and functional information that images alone cannot provide. For example, the clinical physiologist has used such tests as the nitrogen washout to detect the presence in the lung of poorly ventilated regions. Combining ventilation scintiphotography with computer techniques now allows him not only to detect the presence of such zones but also to identify their anatomic configuration and to generate clearance curves from each of them (Fig. 9).³⁹

Computer techniques also can provide invaluable clinical information. For example, quantitation of the contribution of specific lung regions to overall function is critical in assessing a patient for possible thoracic surgery. The decision for lobectomy, pneumonectomy, or no surgery can hinge on such

quantitation. In the past pulmonary-function studies, such as spirometry and blood gas analysis, were performed in such patients. Gas analysis helps describe the overall status of both lungs, and bronchspirometry allows assessment of the contribution of each lung, but it does not permit finer distinctions and is a cumbersome, unpleasant procedure. Ventilation-perfusion scintiphotography, combined with the quantitative analysis techniques, now permits such assessment rapidly and safely.

Finally, computer manipulations of perfusion or ventilation images allow certain diagnostic information buried in the initial image to be extracted (Fig. 10).

In this discussion I have attempted to view the advances in radiographic and radioisotopic techniques from the vantage point of the pulmonary physiologist and clinician. As I indicated at the outset, these techniques, like many others, have shown a tendency to develop an independent existence. Unfortunately, when a technic itself becomes the central focus, the broad reaches of physiology, pathology, and clinical medicine become blurred. Thus a perfusion scan defect becomes an entity rather than an area of decreased pulmonary blood flow potentially related to a whole variety of physiologic-pathologic processes. An angiogram demonstrating an avascular area becomes a finding "compatible with embolism" rather than a beginning point for thinking about the many destructive, obstructive, and constrictive vascular disorders that can lead to the same visual end point.

There is a place in life for visual eroticism, for emotional attachment to images, but that place is in the art gallery or the movie theater, not in the radioisotope laboratory or the radiology department. The images reviewed in these places derive their full meaning only when combined with the full sweep of structural and functional information available from all the other disciplines of medical science.

Admittedly, such broad perspective is difficult to maintain, but such integration, such cross-linking, is the fundamental process by which advance is sustained. It is neither efficient nor useful to have the physiologist describe the gravity dependence of pulmonary blood flow and have this fundamental observation neglected by scintiphotographers who describe the deficiency of apical blood flow as a common "artifact." It is counterproductive to have one compartment of medicine know that the resistance in a vessel is increased minimally until its lumen is narrowed more than 50% only to have scans interpreted as being false negatives in the face of partially-occluding emboli. It is wasteful to have a splendid array of information regarding ventilation-perfusion relations without applying this to ventilation-perfusion scintiphotography.

Granted, these perspectives do not come easily. They require continuous cross-fertilization between the many disciplines of medicine. That is the purpose of symposia such as this one. I hope my contribution has served to further that purpose.

Fig. 10 Ventilation scintiphotograph in patient with recurrent hemoptysis and negative chest X ray and bronchoscopy. Analog scan (left) was essentially normal as was digital scan (center). Computer manipulation disclosed right upper lobe lesion, which was present on manipulated perfusion scan as well. Exploration based on these studies revealed a cystic-bronchiectatic area in right upper lobe which was the source of the bleeding.

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DISCUSSION: LUNG

Shevitz: I would like to ask Dr. Loken a question about his lung scans. We are at a hospital that performs lung scans using the microspheres of technetium supplied by the 3M Company. We have had some problems. I was wondering, Dr. Loken, if you got good results with ^{99m}Tc -macroaggregated albumin (MAA) Would you comment, please?

Loken: We are not making technetium-MAA at present. We did for some time, and, during this period, our results were quite satisfactory. I do not recall exactly our percent yield, but I believe we had a 70 to 80% label. If we controlled the method of heating the labeled albumin, we consistently obtained particle sizes between 20 and 40 μm with very few small particles. With the advent of the microspheres referred to by Dr. Wagner, we have been working with 3M in the development of this product as a kit to simplify the reduction of the particles for use in scanning and to make the labeling relatively simple. I think it should become commercially available before too long. This is a practical approach and the direction to take with albumin microspheres labeled with technetium.

Wagner: I would like to ask Dr. Moser a philosophical question. Do you imply that the person running a nuclear medicine department should not give an interpretation in terms of the probability of the data? I ask this question, and I will try to answer it myself. When somebody in the nuclear medicine department interprets study; he really is not interpreting it for a pulmonary specialist; he is interpreting it either for a general practitioner or for an internist. If he reports that there are bilateral segmental defects, segmental perfusion defects as radiographic abnormalities, I feel this is impossible for a general practitioner or an internist to comprehend. Although the suggestions you advocate are worthwhile, one should expect the nuclear medicine physician to know enough about the field to make reasonable interpretations and do away with such statements as "compatible with" or "consistent with." I deplore these phrases as much as you do. I agree completely that we see tactical errors in the interpretation of studies. I wonder if you really are suggesting that we should

not interpret the studies at all but try to discuss the findings on a functional basis.

Moser: Well, that is what I said for a fact. Obviously, if you misinterpret areas as perfusion defects, etiology to be determined by the physician, you may lose some stature in the eyes of your associates. However, I do not know if this is preferable to the current status of affairs at many hospitals. In many medical centers the interpretation of a defect compatible with a pulmonary embolism is felt to be compelling enough to the physician who is to institute anticoagulant therapy. He simply is not aware of all the other conditions that can cause this particular kind of defect. This is a problem in communication. Very often a scan is interpreted without reference to the X ray, something everybody who has spoken here agrees you cannot do. Nevertheless, that does not mean that the X ray is always looked at in the interpretation of every scan. We like ideal clinical information that helps one to consider multiple probabilities. We showed graphs of the incidence of nausea, dyspnea, hemoptysis, chest pain, etc. Many of us do not even know whether the patient is in a hospital much less whether he has dyspnea, chest pain, or hemoptysis.

My point is that the more clinical information the scintiphotographer has at his disposal, the more he can make a specific statement. The less information he has, the less specific should be his interpretation of the scan or image.

Wellman: I have a question for Dr. Wagner. I think the segmental interpretation of lung scans teleologically has considerable appeal. It seems logical, and this you have advocated. But what objective correlation do you think a blind panel of physicians could make in correlating the segmental interpretation of a lung scan with arteriographic findings that demonstrated segmental defects?

Wagner: The patients who had arteriograms were hospital patients, not urokinase patients. We had as many patients in our own series as there were in the entire urokinase study, and this was a reasonable number. We had approximately 100 patients who had arteriograms. There was at least one segmental defect in 80% of the patients who had specific arteriographic evidence of pulmonary embolism. I emphasize that this is based on rectilinear scanning with adequate collimation and with the highest photon yield.

Wellman: I am not sure if you answered my question. As I understand it, you had a panel of physicians who read lung scans blind, identified a particular area of the scan as representing a segment of lung, and correlated this with blind readings of the arteriogram.

Wagner: There were two radiologists in this study; one of whom is the senior author on this report which is being submitted for publication. They independently read the arteriograms and identified the segment. In the interpretation of our scans, we pick out the particular segments that are involved whenever possible. We do not say that there is just a segmental defect. We train ourselves to understand the segmental anatomy of the lung so that we will say that there is a segmental defect in this particular lung segment or that one. We

have an atlas of heart and lung pathology in which there are overwhelming numbers of examples, ad nauseum examples, of segmental defects in pulmonary embolism (F. H. Deland and H. N. Wagner. *Atlas of Nuclear Medicine*, Vol. 2, W. B. Saunders Company, Philadelphia, 1970). We really do not show numerous arteriograms, but those involved are identified as particular segments.

If we do not see segmental defects, we do not say there is a high probability of tumor or embolism. If we do see segmental defects, we do not say there is a high probability of pulmonary embolism unless we are 100% sure that the patient does not have obstructive lung disease. Before we interpret a scan, we insist on knowing whether that patient has chronic obstructive lung disease. If we cannot get it from his chart or from the history, we do the necessary laboratory studies. I agree with Dr. Moser, you must have all the information. I would emphasize that the concept of segmental defects indicative of pulmonary embolism is the most important single finding for specific interpretation of lung scans. If you do not believe that, you should do what Dr. Moser suggested; just hand the scan to somebody and let him comment.

Adelstein: I want to ask some questions about small clots. First, Dr. Greenspan has described a sequence of events which suggests that under the influence of urokinase small clots may be broken from a huge pulmonary artery thrombosis to produce decreased perfusion distally by occlusion of small vessels. Does he believe or have any evidence that small clots can be produced from more peripherally located thrombi in the lung (with or without urokinase therapy), resulting in the same arteriographic (and scintigraphic) picture? Second, Dr. Moser has described a situation in which a clot occupying less than 80% of the cross-sectional area could, by virtue of not affecting the quantity of blood flow, still allow a normal scan. Is this a theoretical physiological prediction or is there experimental evidence of this? Third, how does he square this with Dr. Wagner's observation (and that of others) that angiographic evidence of embolism has not been seen in the face of a normal scintigram?

Greenspan: I would like to answer the question directed to Dr. Moser first. I personally have never been privileged to see a patient who had a documented pulmonary embolism angiographically and a normal isotopic scan. Everyone says they have one, but I simply have not seen a case. I have observed a number of inadequate scans. In our institution we consider a normal perfusion scan basically to rule out pulmonary embolism. We may be missing 1 or 2% of the people, I do not know. If a patient has a normal perfusion scan, we do not do an angiogram on him before we exclude a pulmonary embolism.

I cannot answer the question about the migration of multiple small emboli directly from the legs to the lungs. I do not know whether these emboli stop somewhere, fragment, and pass further. I know that pathologists on occasion find multiple small emboli in vessels that are below our limits of resolution angiographically. I am not certain whether these are emboli or thrombi that are formed as there is simply no evidence to answer that question. In looking at the data of a study, one is struck by the phenomenon of a large clot disappearing

and the perfusion defect increasing. I proposed this as a possible explanation; I do not really have evidence for it.

When should one do an angiogram? Many times the clinician will consider the patient for 5, 6, or 7 days and then refer the patient for an angiogram to evaluate possible embolism. There is ample evidence in animals and in humans that the rate of lysis of emboli is variable and very fast. The only way angiographers can diagnose embolism is to see the clot. If clinicians refer the patient to us 5 or 6 days after the episode, the odds are that we will not see a clot. We will see some nonspecific abnormalities and maybe some perfusion defects on the scan, but we cannot make a positive diagnosis.

Moser: Your point of view determines how you answer the question about the scan and angiogram correlation. Multiple experiments leave no doubt that you may have a normal scan when you have a partially occluded thrombus in animals. Even if the thrombus loops within the pulmonary arteries, failure to visualize this abnormality may also result in a normal scan. This is a physiologic fact you cannot question. How often it occurs in man is a tougher question. The only time that we actually worry about getting an angiogram in the face of a normal scan, a perfectly normal scan, is when the clinical picture does not fit. If we use a normal scan as a reason not to do an angiogram, we are going to miss 1 or 2% of the patients with centrally placed thrombi. This is why we continue to do angiograms.

Wagner: A couple of points. First, we try to persuade the doctors taking care of these patients to do arteriograms in a patient who has a high clinical suspicion of pulmonary embolism and who has a normal scan. I think you understand the need for this request. At our hospital the angiographers are continually after us to reduce the number of referrals for angiograms. We continually try to get angiographic confirmation of what we see on the scan. So I think it is a true statement that you cannot possibly use pulmonary angiography as the second line of diagnosis of pulmonary embolism. First, it requires cardiac catheterization. There are many small hospitals that lack the facilities for pulmonary angiography. Second, even in a large university hospital, you can easily surpass the ability of that hospital to do pulmonary angiography. The answer to Dr. Adelstein's question referring to 19% of the patients with normal angiograms in whom we said there was a high probability of a positive scan is difficult. I am sure, and this is strictly my guess since I have little data to support this statement, that some of these patients did not have pulmonary embolism. I also believe that some of these patients had pulmonary embolism of the small type, smaller than 2 mm, which is the size of a pulmonary arteriole. We know this happens because some of these patients have had double arteriograms where the first arteriogram was negative and the second was positive. I would suggest then that, if a subsequent arteriogram had shown that the patient had pulmonary thromboembolic disease, there was a reasonable probability that he had a pulmonary embolism with the first episode but the emboli were too small to be seen. When I was in medical school, we thought that cor pulmonale with right

heart failure was a common situation in people who had the disease of multiple showers of small emboli. I have not seen that since I graduated from medical school. Most, but not all, of the patients we see have pulmonary emboli with clots larger than 2 mm. Even those who have this large perfusion defect and large obstruction will have showers of fragmented clots that pass into the circulation. I do not think they originate very often as small emboli. I think they are large emboli that fragment into smaller ones.

Teates: How successful is lung scanning with the aid of ^{133}Xe ventilation studies in diagnosing pulmonary embolism in patients with obstructive lung disease? Similarly, how accurate is pulmonary angiography in the same group of patients?

Loken: This is a difficult diagnostic problem in which we have been reasonably successful using ^{99m}Tc -microspheres for a detailed evaluation of perfusion and ^{133}Xe to study washout of this gas from those areas shown to be poorly perfused on the microsphere study.

We know that regions of lung that are poorly ventilated because of obstructive disease will also be poorly perfused. Thus the probability of embolus being deposited in these areas will be unlikely. Hence we look for regional compromise of blood flow in regions that are well ventilated as an indication of pulmonary embolus in a patient with obstructive lung disease.

Wagner: There is no question that patients who have chronic obstructive lung disease are predisposed to develop superimposed pulmonary embolism. As a result of our experience, we stay clear of making any firm statements as to whether the patient also has superimposed pulmonary embolism. If we exclude the urokinase patients who have had arteriograms in our hospital, the most common indication for doing a pulmonary arteriogram is the patient with chronic obstructive lung disease in whom we are uncertain of the existence of superimposed pulmonary embolism. Dr. Loken's reply makes sense if you can document a ventilation-perfusion imbalance and the ventilation is more normal than that expected on the basis of a perfusion defect. Such an interpretation really makes me nervous, and I think you will encounter trouble with people like Dr. Moser if you make these statements. Even I agree with Dr. Moser on this subject. I would rather pass the problem to Dr. Greenspan. I would like to know what Dr. Greenspan has to say about the arteriographic diagnosis of pulmonary embolism in a patient who has severe, chronic, obstructive lung disease.

Greenspan: Well, in the first place, we do not like to do arteriograms on these patients. They are referred to us frequently. Angiograms are a little more difficult to interpret because they have multiple areas of perfusion defects. You have to demonstrate a clot in those patients and in any patients in whom you are making a diagnosis of pulmonary embolism; showing a nonfilled segment or multiple nonfilled segments does not make the diagnosis. You have to demonstrate the trailing edge of a clot occluding a vessel or, by using contrast media, observe it going around the clot within the vessel. These patients have curly vessels that double back on themselves, and the architecture of their vessels

is warped, making it very difficult to demonstrate a clot. If you keep your interpretation of the angiograms pure, I think you can make the diagnosis in these cases.

Moser: In our discussion about these two patterns, we have to be extremely cautious as soon as we leave the normal patient with normal pulmonary function. Although we are talking about chronic obstructive pulmonary disease, and it is a defined entity, this patient has a whole variety of diseases involving the lung in various, fascinating physiological ways; some involve only the upper lobes, some only the lower lobes, and some every other alveolus. There are about 300 million alveoli, each of which has its own function. When you put chronic obstructive lung disease as a bronchial obstruction etc., into that diagnostic picture, you are getting into a very, very difficult area in terms of pattern differentiation. I would turn the patient over to the angiographer and see if he could diagnose the problem.

Baltax: Dr. Moser, is there regional spasm in the lung in nonembolic disease, and, if there is, what is the mechanism?

Moser: If you have, for instance, a partially obstructed airway anywhere, and smokers have this, that partially obstructed airway causes a regional hypoventilation of the lung. The oxygen decreases in that area of the lung and the carbon dioxide pressure ($p\text{CO}_2$) will rise. Constriction of the pulmonary arteriole in that zone will produce a perfusion defect. This is a very common sequence in an asthmatic. Scan an asthmatic sometime during an acute attack and later after therapy. After the areas of poor ventilation improve, the perfusion defects disappear with great dispatch. So there are very delicate mechanisms in the lung which tell this organ, "for goodness sake, if you aren't putting any air into this region, don't put any blood flow into this area either."

Loken: A question asked of me by several participants relates to the optimal number of regions to consider in evaluation of function. Several considerations may be mentioned. The inherent resolution of our camera collimator system of studies with ^{133}Xe is approximately 7 cm^2 ; thus division of the lung into smaller areas than this would not be worthwhile. The second consideration is count-rate statistics. With a limited amount of photons, even when using 30 mCi of ^{133}Xe for a pulmonary-function study, one must use areas of sufficient size to record sufficient counts per unit time to obtain reliable results. A third consideration relates to the amount of data per patient studied which can reasonably be handled. With computer processing we can accumulate literally reams of data which must ultimately be interpreted for the referring physician. Too much data often serves to cloud rather than clarify appropriate diagnoses. Finally, consideration must be given to the needs of the internist or surgeon who will be called on to treat the patient. How small an area (hence volume) of lung can be effectively treated?

After much discussion of these matters, one group is planning to reduce the number of areas of lung presently being evaluated (18 per lung) to either 6 or possibly 9 per lung.

Buonocore: I wonder whether Dr. Wagner would elaborate on the clinical application for the use of urokinase, particularly in view of several facts. First, Dr. Greenspan informed us that clots will resolve by themselves at a very variable rate. Second, it is very difficult to convince the clinicians to begin prolonged therapy because they feel that the people who die, die very abruptly and not in the later stages. So what can we obtain from the data that have been accumulated by this combined study?

Wagner: Around 1963 or 1964 there was a great deal of interest in pulmonary embolectomies. These procedures were carried out because patients with pulmonary emboli have significant mortalities; in fact, the mortality in the first phase of the urokinase study was approximately 10%. The urokinase study has taught me, and nothing I am saying is meant to reflect the views of anyone else who has had anything to do with the urokinase studies, that urokinase is effective in increasing the speed of resolution of a patient with pulmonary embolism. For many of these patients who have potentially fatal pulmonary embolism, an improvement in 10 or 15% might mean the difference between the patient's dying of right ventricular failure and the patient's not dying. It seems to me that thrombolytic therapy is an effective substitute for pulmonary embolectomy. I would prescribe or want someone to give me thrombolytic therapy if I had a small pulmonary embolism. I would certainly want to be anticoagulated immediately. On the other hand, if the physician taking care of me thought there was a reasonable probability that I was going to die, in other words, that I had persistent hypotension or a great deal of elevated right ventricular pressure or signs of heart failure, I would certainly want to be given urokinase or streptokinase, which is now under study together with urokinase, rather than have a pulmonary embolectomy. I have a feeling, and I think this is true that to a large degree pulmonary embolectomy has gone out of vogue throughout the country.

Some things that can potentially help the patient get over this very critical period, such as maybe a pulmonary embolectomy, fall in disfavor. When Dr. Robert Baker and I analyzed the 13 patients in the series at Johns Hopkins University Hospital, we could match the patient who had a pulmonary embolectomy and survived with people who were equally sick, in terms of manifestations of their disease, who recovered without a pulmonary embolectomy. I hope this answers your question.

Moser: Henry has given his opinion about the urokinase study, and I would like to give mine. I think urokinase can speed the lysis of thrombi. I think there is thus far no indication in the study that urokinase alters the long-term prognosis or the immediate mortality or morbidity of people with pulmonary emboli. This is very important to bear in mind. Now I have been in this urokinase business for 15 years, so these words come very hard for me. We were using streptokinase when other people did not even know that agent existed. In a thrombolytic agent we want a drug which dissolves thrombi but, more

important, one which decreases morbidity and mortality. This is where the hard numbers must come from a study.

I agree with Dr. Wagner; the urokinase study has contributed much information. It has not convinced me and other thrombolytic investigators, however, that this therapy substitutes for anything else. Embolectomy has been abandoned mostly because of the equal, if not better, results obtained with heparin therapy. We have not abandoned embolectomy because we are using no drug other than heparin. I think the urokinase study has caused some consternation, and we will have to see if better things appear.

Wagner: One particularly fascinating group in the Phase I study was the group of patients with massive embolism. As Dr. Greenspan pointed out, there were 8 of these patients, and most of them were treated with urokinase. If you analyze the lung-scan data in these patients, you will note a very dramatic response. Unfortunately some patients were too sick to have a lung scan; thus the study was not properly balanced with an equal number in the heparin group. Statisticians emphasize this point.

I will give you a prediction right now, and I hope it gets recorded in the notes.* I predict that urokinase will prove to be effective, and it will primarily prove to be effective in decreasing the mortality. As Dr. Moser said, there was no difference in the mortality in the two groups, but that was because the sample size was small and the mortality is low; in the medical sense the mortality is high. It is going to take more study to determine whether urokinase will lower mortality. I think there will be a tendency to treat the sicker patients and not treat the patients under analysis, and perhaps it will provide more information on whether there is an effect on mortality.

I call your attention to the patients with massive defects; you will see a very large improvement in the perfusion shown by the scan, not by the angiogram. These patients with perfusion defects as high as 67%, indicating the person is perfusing only 33% of his lung, had very dramatic improvement. In the future, I think we shall see a substantial reduction in mortality. I certainly agree that it has not been shown yet, but I predict, on the basis of observing these data in the past, that it will be shown. When we did an uncontrolled study with urokinase, we described degrees of resolution that we had never seen in a controlled study [D. E. Tow, H. N. Wagner, Jr., and R. A. Holmes, Urokinase in Pulmonary Embolism, *New Engl. J. Med.*, 277: 1161-1167 (1967)]. This was not a precise study because the patients were studied consecutively and not in a "double-blind" protocol; we did not see the degree of resolution in a patient treated with heparin alone that we saw in quite a few of the patients treated with urokinase. Also, in the first phase of the National Cooperative Urokinase Pulmonary Embolism Trial referred to by Dr. Greenspan, the number of patients treated with urokinase was quite small, but it is much larger in the Phase II study.

*We are glad to oblige, Henry. (The Editors)

Another important result of the urokinase study, in my opinion, was the observation that thrombolytic therapy can be given safely. My friend, Dr. Oscar Ratnoff, said before the study was undertaken that the patients receiving urokinase were going to do worse. Clots that were nice and tight would be loosened a little bit, and they would go on to the lung, but this did not happen. Although there were significant bleeding complications, this should make one aware that this is not simple drug therapy. It was shown that these patients could be given urokinase, and now streptokinase, safely. So I just hope you do not get too despondent too soon, Ken.

Moser: Henry, I am not despondent at all. The same prediction you are making today was made 10 years ago by people interested in thrombolytic therapy. If such drugs were beneficial, they would have an effect on people who needed immediate resolution of emboli, i.e., people who had gigantic clots that were causing cor pulmonale. The patient with the little embolus in the left lower lobe would do fine, but nothing has changed. Nothing at all has changed since the urokinase trial except that more people now feel strongly that the same group of patients should benefit from urokinase. I repeat that, although resolution rates are gratifying, the patient could not care less unless he has a lower pulmonary-artery pressure or lives instead of dies.

So, when we read the reports from the study, I am as intrigued by them as anybody. I love to see rapid resolution of the clot. I get a good feeling inside, but I do want to see a reduction in morbidity and mortality as well.

Haynie: Dr. Moser, I enjoyed the presentation of your paper, but, in view of what you said with regard to "false negatives" in diagnosing pulmonary embolism by lung scans, I wonder if you believe that there is such a thing as a false-negative diagnostic test. If so, how do you define it?

Moser: I would think of a false negative as something that does not show an abnormality when there is a reason for it to be there. What I was saying, however, to clarify my point, is that the test is not really a false negative if you are asking a technique to do something that it was never capable of doing. If you ask a perfusion scintiphotograph to show you an area of embolic occlusion 3 mm across, you may call that a false negative if you wish. I would call it a problem with the technique.

If you ask a perfusion scintiphotograph to show you a 50% occlusion in a vessel and the flow past this 50% occlusion is normal, I do object to calling that a false negative. I think that is within the limitations of the technique. A false negative then would be a totally occluded vessel that does not show on the scan, and I do not think that event happens; other situations happen that people might call false negative.

Haynie: If you were doing a diagnostic procedure on a patient, I presume you would be doing the study to try to recognize the disease. If you were doing it to diagnose pulmonary embolism and there is a pulmonary embolism, but it has not sufficiently occluded the artery to cause a perfusion clot or perfusion defect, then we could call it a false-negative test in that patient. The patient had

the disease, but the test just did not show it. For example, we commonly speak of false-negative X rays in cancer of the bone when the tumor has not produced enough decalcification. If I understand what you are saying and follow your line of logic, I will end up not having any false negatives.

Moser: To qualify why something does not show in a particular study is much better than talking about false negatives. If you admit that the angiogram was positive but I did not see a defect on the scan, which you have already said is extraordinarily rare, then you can start talking about another matter than false negatives. If you state that the scan cannot show you a partially occluding defect or that the bone scan cannot show you anything until it is a certain size, then the proper attitude of qualifying the limitations of the technique continues. The people who are dependent on you for keeping them straight start thinking appropriately also.

Wagner: I would like to see if Dr. Moser or Dr. Haynie agree with this attitude. If an arterial blood sample is sent to the laboratory with a request to study $p\text{CO}_2$, that may be all that is asked of you. If the $p\text{CO}_2$ value is correct and if it is a perfect test, you will never have any false negatives or false positives. It is either accurate or inaccurate; it is precise or not precise.

But then the doctor sending you the $p\text{CO}_2$ may say, now look I am a very, very busy general practitioner. I have done my best to keep up with the field, but I have not been able to keep up with the whole field of medicine. I want you to tell me whether my patient has respiratory acidosis. So Dr. Moser must say the patient probably does or probably does not have respiratory acidosis. If he says the patient has respiratory acidosis and the laboratory does an arterial pH on that patient and it comes back 7.5, Dr. Moser has had a false positive. If, on the other hand, Dr. Moser says the $p\text{CO}_2$ is normal and they do an arterial pH which comes back 7.3, Dr. Moser has had a false negative. So it depends on whether you are just measuring a specific function or a specific parameter or you are trying to classify the patient.

False positives and false negatives are intimately associated with the classification of the patient and how a particular person performs in making that judgment. It is an interaction between a disease category and the person deciding whether or not the patient fits in that particular category.

Moderator:
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DYNAMIC ISOTOPIC STUDIES IN CARDIOLOGY

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ABSTRACT

A review of the past role of nuclear medicine in the diagnosis of cardiac pathology and evaluation of heart function indicates a failure to develop useful clinical tools. This may be attributed in part to lack of adequate instrumentation and methods to solve the geometry problem and to failure to develop methods for correcting depth and absorption factors.

However, several recent advances in nuclear medicine show promise of developing into simple, safe, noninvasive methods for the diagnosis and evaluation of cardiac disease. Among these is the development of scintillation cameras with data storage and area-of-interest selection capacity. The latter feature makes it possible to do semiquantitative radioisotope angiography.

In addition, new isotopes with less radiobiological effect and higher photon flux will improve the quality of these studies and make serial studies possible during the course of an illness.

Recently methods based on time-activity curves obtained from camera data have been described for the diagnosis of cardiac shunts. Other studies using electrocardiogram (ECG) gating have made possible visualization of regions of impaired myocardial contractility.

Also, new designs of precordial collimators have made it possible to quantitate such dynamic parameters as cardiac output, stroke volume, volume of the right and left ventricles, and pulmonary blood volume.

In clinical cardiology there is a need for simple, safe, accurate, noninvasive, and relatively inexpensive methods to diagnose cardiac pathology and to evaluate heart function. As the number and types of lesions suitable for surgical intervention and the possibilities of individualized medical management increase, it becomes desirable to accurately describe pathology within the heart as a guide in selecting and managing various types of patients. Although quite accurate data from current X-ray and catheterization techniques are available, these techniques

often cannot be applied to the acutely ill patient and cannot be repeated frequently.

To date nuclear medicine has played a very minor role in identifying surgically reversible situations or as an aid in medical management of the cardiac patient. Studies of heart function have been largely limited to the clinical research laboratory. Although there are probably many reasons for this, a major cause has been limitations in instruments and isotopes. In earlier sessions of this symposium, you heard about some of the new isotopes and cameras which, I believe, will change this situation. It can reasonably be predicted that the nuclear medicine of the future will play an important role in the evaluation and management of the cardiac patient. I will cover briefly some of the highlights of past attempts to apply radioisotopes to measurement of heart function, to explain why these methods have not achieved more dramatic results, and to discuss the potential value of nuclear medicine in clinical cardiology.

The first clinical study of heart function performed with radioisotopes was the measurement of circulation time with radium-C by Blumgart¹ in 1927. In these early experiments simple ionization chambers and recorders were used. The method was too complicated to attract wide use, and I doubt that the equipment was either highly sensitive or reliable.

The next major contribution was made by Prinzmetal² in 1949. Using a precordial probe and ^{24}Na , he and his associates described a number of tracings made through a rate meter and strip-chart recorder. These were termed "radiocardiographs." In the normal individual the precordial detector would "see" the bolus as it passed sequentially through both chambers of the heart, giving curves with sharp peaks on the strip-chart recording. On the other hand, in the failing heart or in the heart with valvular disease, the sharp peaks were lost and the bolus moved slowly through the central circulation, giving low, flattened curves.

These studies were repeated in numerous laboratories, and many attempts to quantitate the data were made. The first real quantitative studies came from the laboratory of Veall.³ Veall defined the conditions under which cardiac output could be determined with a precordial probe and emphasized the need for a relatively narrow collimator which did not necessarily see the entire heart. He introduced the theoretical concept of quantitating the curves from the equilibrium value and demonstrated that the method could be applied to a multicompartment system, i.e., one in which the probe saw more than one heart chamber, and a double peaked curve was obtained. The equilibrium value could be applied to the calculations as long as the geometry was unchanged during the study so that geometry factors cancelled out and the Stewart-Hamilton principle could be applied.

When cardiac output is measured by Veall's modification of the Stewart-Hamilton formula for the determination of cardiac output by indicator dilution, the cardiac output is calculated by the expression

$$\text{Flow rate (liters/min)} = \frac{1}{\text{Area under the dilution curve}} \quad (1)$$

where the denominator is expressed as (fraction of the dose per liter) $\times$ (time in minutes); the general mathematical expression of which is

$$F = \frac{1}{\int_0^{\infty} C \cdot dt} \quad (2)$$

When properly carried out with a relatively narrow collimator placed over the precordium and seeing primarily the arch of the aorta, cardiac output measurements by this method compare favorably with direct arterial sampling using the Stewart-Hamilton principle.

The major problem challenging the investigator who wished to obtain true quantitative data from radiocardiographic techniques was the geometry of what the precordial detector saw. The standard narrow-angle probe used for precordial measurements saw the two heart chambers with different sensitivity and also varying amounts of noncardiac tissue. If the collimator was placed at an oblique angle so that the heart chambers could be seen with equal efficiency, then the amount of extracardiac tissue usually increased. A variety of methods using single probes with long precordial collimators⁴ or dual probes⁵ were developed to attempt to solve this problem, but these were not applicable to the equilibrium-value concept because the retrocardiac space was seen with similar efficiency.

A comparison of the textbook by Veall and Vetter³ published in 1958 with the latest texts in 1971 shows little dramatic progress during the intervening period and few studies that come within the scope of this course. Some recent textbooks barely mention heart function. Those studies which have been made are best classified as clinical investigative methods rather than as practical procedures applicable to clinical nuclear medicine or cardiology.

When we analyze this situation, there seems to be no question that good tests of cardiac function are needed and that good investigators have worked on the problem. They have produced excellent theoretical analyses, but simple, practical applications to the routine clinical problem have not been developed, with the exception of measurement of cardiac output and, possibly, the diagnosis of shunts.

Reasons for failure to develop useful clinical tools include lack of adequate instrumentation and methods to solve the geometry problem, i.e., inability to determine what the detector is actually seeing, and failure to develop methods for correcting depth and absorption factors. There is also a need to build a backlog of experience by numerous investigators which would show the limitations of the theoretical approaches.

Recently Bosnjakovic⁶ developed a precordial collimator with a special inner core which gives a flat field over any heart of normal size (Figs. 1a and 1b). With

this collimator it is possible to calculate cardiac output, stroke volume, rate of emptying of the right ventricle, volumes of the right and left ventricles, pulmonary circulation time, and pulmonary blood volume.

Scintillation cameras with data storage and area-of-interest capability also offer the possibility of solving some of the geometry problems. Much extraneous tissue can be eliminated by selecting areas of interest for analysis. The depth problem remains and can be partially corrected by (1) the use of an appropriate area over the right chest to correct for activity in the chest wall or deep vessels, (2) use of separate equilibrium values obtained from each area of interest, and (3) using nuclides emitting high-energy photons (over 300 keV) to reduce tissue absorption of radiation arising from the posterior heart.

New radionuclides will make a great deal of difference in studies of heart function. Some of the early nuclides had serious technical limitations. Sodium-24, for example, rapidly equilibrates in lung extracellular space and is difficult to collimate since it emits extremely high-energy gamma rays. Iodine-131 as the iodide or as an albumin tag had serious limitations, primarily due to the long biological half-life, which gave a significant radiobiological effect long after the study was completed and prevented repeat or serial studies. Rubidium-84 also presented problems with its long half-life and high-energy photons.

New short-lived radionuclides will offer several important advantages to studies of heart function:

1. Less radiobiological effect, which will permit the use of larger doses.
2. Higher photon flux from larger doses of the short-lived nuclides, resulting in better counting statistics and more reliable data. The higher count rates also permit the application of the regions-of-interest technique to small areas that otherwise have such low count rates that they are entirely inadequate for diagnosis by visual analysis.
3. The possibility of doing serial studies during the course of disease or during the evaluation of a drug.

Among the new nuclides which have been used in angiography or scanning and which offer real promise for function studies are: ^{99m}Tc , ^{133}Xe , ^{43}K , ^{129}Cs , ^{13}N , ^{11}C , and ^{15}O .

An excellent example of the quality of images that can be obtained by radioisotope angiography has been demonstrated by Martin and Kriss⁷ in a study on mitral stenosis and mitral insufficiency. Other lesions, such as aneurysms, dilatation of the heart chambers, obstruction of vena caval blood flow, and intracardiac shunts, have been clearly visualized by this type of angiography.

Extension of the method to problems where visual analysis of the angiographic data is inadequate for diagnostic purposes has led to the development of methods based on time-activity curves obtained from the scan data stored in computers or visual tape systems [Figs. 2(a) and 2(b)]. Two

Fig. 1a Precordial collimator with a special inner core to give a flat field.

groups have applied this approach to the diagnosis of small heart shunts. In 1966 Braunwald⁸ proposed that the time-activity curve obtained from a probe over the lung field could be used as a screening procedure for heart shunts. A prolonged downslope of the curve was found in all patients with significant left-to-right shunts. Recently, Alazraki and associates⁹ have used a scintillation camera with computer and area-of-interest capability for this measurement.

Fig. 1b Isoresponse curves with collimator shown in Fig. 1a over the normal-size heart (2 mCi $^{99\text{m}}\text{Tc}$ -sulfur colloid).

Bosnjakovic and associates¹⁰ have demonstrated both right-to-left (Fig. 3a) and left-to-right (Fig. 3b) shunts by a dual-isotope technique. In this method a scintillation camera is placed in a modified left anterior oblique position. Information is stored on video tape for later analysis using the region-of-interest feature to generate time-activity curves over both the left and right chambers of the heart. A saline solution of ^{133}Xe is used to visualize the venous or right side of the heart since over 95% of the material will be cleared by a single pass through the lungs. Appearance of ^{133}Xe in the left side simultaneously with passage of the bolus through the right side of the heart is diagnostic of a right-to-left shunt.

Fig. 2a Normal time-activity curves with ^{133}Xe in a patient with a repaired septal defect.

Fig. 2b Normal time-activity curves with 2 mCi of ^{99m}Tc -sulfide.

Fig. 3a Abnormal ^{133}Xe time-activity curve in a patient with a large right-to-left shunt. The ^{133}Xe appears simultaneously on both sides of the heart.

Fig. 3b Abnormal $^{99\text{m}}\text{Tc}$ -sulfide curve with a second peak on the right side at the time of filling of the left ventricle in a patient with a left-to-right shunt.

Tchnetium-99m as the sulfide of albuminate is used to visualize both the right and left sides of the heart. Distortion of the normal emptying curve for the right side of the heart at the time of arrival of the bolus in the left side of the heart is characteristic of the left-to-right shunt. Sensitivity of the method at the present time appears to be equal to conventional catheterization.

When the albuminate is used and equilibrium values are obtained for regions of interest, it is possible to calculate shunt size to within approximately 10% of the values obtained at catheterization.

Zaret and associates¹¹ have recently described the application of the Anger camera to the evaluation of myocardial wall function in patients with previous coronary-artery occlusions. Regional ventricular dysfunction (asynergy) was demonstrated by making electrocardiographic controlled cardiac images in end-systole and end-diastole. Then, by superimposition of the end-systolic and end-diastolic traced images, an assessment of left ventricular wall contraction was made and the extent of wall movement was quantified. The results showed a good correlation with contrast radiographic techniques. This quite simple, noninvasive technique should become a useful method in evaluating the patient who is convalescing from an acute myocardial infarction as well as the patient with chronic coronary heart disease.

In 1958 Sapirstein¹² reported his studies on fractional cardiac output in rats and dogs using the clearance of ⁴²K and ⁸⁶Rb. The principle of the method is that for a rapidly cleared substance the initial uptake of the tracer in an organ is proportional to the fraction of the cardiac output reaching the organ. Applied to the coronary circulation and myocardium, the coronary blood flow can be estimated from the expression

$$\frac{\text{Coronary blood flow}}{\text{Cardiac output}} = \frac{\text{Myocardial uptake of isotope}}{\text{Total body uptake of isotope}} \quad (3)$$

In the experiments the animals were killed at short intervals after injection with the nuclide, and the radioactivity of each organ was determined. If one attempts to obtain the same information by external body counting, different geometry problems are encountered, i.e., what is the detector seeing and what are the effects of variations in distance of various portions of the organ from the detector?

Several groups have worked on the application of this principle and on the development of an accurate and practical clinical method. Probably the most satisfactory method to date uses a dual coincidence system and ⁸⁴Rb, a positron emitter. In this method one coincidence system looks at the heart silhouette and the second at a corresponding right-chest area to obtain background measurements for estimation of the ⁸⁴Rb in the chest wall and other noncardiac tissues. Values for this method give a good correlation of myocardial blood flow with the Fick principle. Unfortunately the method does not distinguish between patients with coronary-artery disease and normal subjects unless the patients are

subjected to stress such as isoproterenol hydrochloride infusion. An excellent paper giving the current status of the method was recently published by Knoebel.¹³

In summary, a group of safe, relatively simple, noninvasive tests of heart function appear to be in the developmental stages. As these or other tests are perfected, they will probably find wide use in nuclear medicine clinics and intensive-care units.

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SCINTIGRAPHY OF MYOCARDIAL PERFUSION WITH RADIOACTIVE MACROAGGREGATED ALBUMIN

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ABSTRACT

Myocardial-perfusion scintigrams have been performed in 205 patients after direct coronary injection of macroaggregates without demonstrable sequelae. The methods for the preparation and quality control of the radiopharmaceuticals are discussed as well as the technique for coronary injection and the computer-oriented instrumentation for imaging. Normal myocardial-perfusion anatomy is presented. The distribution of the radioactive macroaggregated albumin (MAA) from the injection in the left coronary artery corresponds to what might be expected and follows the outline of the vessels. However, radioactive MAA from the injection in the right coronary shows intense concentration in the distribution of the posterior descending and posterior lateral branches but little concentration anteriorly in the region of the right ventricular wall. These studies provide information not obtainable by standard coronary angiography alone, namely, the myocardial perfusion distal to a severe stenosis, the adequacy of collateral perfusion, and the status of myocardial perfusion in symptomatic patients with normal coronary angiograms. We have demonstrated normal myocardial perfusion in patients with greater than 95% stenosis of a major coronary artery. Patients with completely occluded coronary arteries may or may not have adequate collateral perfusion. This determination is readily made with the perfusion study. The most common pattern is an occluded right coronary artery with collateral perfusion to the inferior myocardium from the left coronary injection. Patients with normal myocardial perfusion distal to a severe stenosis or with satisfactory collateral perfusion distal to an occlusion should be considered ideal candidates for coronary bypass surgery. The group of patients with normal coronary angiograms but with other signs of myocardial ischemia may be further elucidated by myocardial-perfusion studies. Indeed, a few such patients demonstrated to have impaired myocardial perfusion have shown abnormalities of lactate production. Postoperative reevaluation is necessary to determine the predictive value of these studies. However, we anticipate that scintigrams of myocardial perfusion will be valuable in the evaluation of patients with proven or suspected coronary-artery disease.

Coronary heart disease is the leading cause of mortality in the United States,¹ responsible for 80% of the cardiac deaths in persons between the ages of 35 and 65 years. Indeed, one of every three persons in this age group succumbs to this disease.

An increasing number of patients with coronary disability are being selected for surgical palliation of the disease, and the coronary arteriogram is routinely being used to evaluate these patients. This procedure is capable of demonstrating anatomic abnormalities in the coronary arteries which are as small as $100\ \mu\text{m}$; however, coronary-artery filling is not necessarily synonymous with myocardial perfusion. Likewise, coronary blood flow commonly does not reflect myocardial perfusion. Because of this the selection of patients for coronary revascularization procedures cannot be based solely on demonstrated coronary anatomy or even on measurement of blood flow. Since it is useless to deliver additional blood to heavily scarred myocardium, a method is needed to evaluate perfusion at the capillary level. There are also a few patients who clinically have myocardial ischemia and have a normal coronary arteriogram. We suspect that these patients have an alteration in myocardial perfusion which is beyond the level of the present imaging ability of the coronary arteriogram.

Endo and coworkers² have reported the use of labeled macroaggregates in the evaluation of patients with myocardial ischemia. Ashburn and his associates³ have reported in this symposium and elsewhere their experience in injecting radioactive particles directly into the coronary arteries to visually portray regional myocardial perfusion. Utilizing this technique, with some variations, we have studied the myocardial perfusion of 205 patients undergoing coronary arteriography.

METHOD AND INSTRUMENTATION

Macroaggregates are labeled with ^{99m}Tc and ^{131}I to separate the myocardial perfusion of the left and right coronary arteries. The technetium-labeled particles are prepared by a modification of the method of Cragin.⁴ Our method is: to a sterile 10-cm^3 vial, we add 2 ml of ^{99m}Tc eluate, 0.3 ml of 1% sodium thiosulfate ($1.9\ \text{mg}\ \text{Na}_2\text{S}_2\text{O}_3$), and 0.2 ml of 1.0N HCl. We place the vial in boiling water for 90 sec and then cool it in a water bath for 90 sec. We then add 0.25 ml (6.25 mg) of diluted albumin and 0.1 ml of 0.05% phenol red followed by 0.1N NaOH titrated to a faint permanent pink color (approximately 2 ml). To this we add 0.2 ml of 0.1M citrate buffer with a pH of 5.0. The mixture is placed in boiling water and gently agitated constantly for 75 sec and then cooled under running water. Particle size is reduced by forceful passage of the mixture through a 22-gauge needle. Stringy and oversized particles are removed by passing the mixture through a special filter (thin film of glass wool over a stainless-steel disk with $75\text{-}\mu\text{m}$ holes) into a sterile, rubber-stoppered, test tube. The filtrate is centrifuged for 12 sec in an International clinical centrifuge model CL. The supernatant is discarded, and the particles are resuspended in 0.9% NaCl. By this technique 20 to 30% of the original activity is recovered in the form of usable particles of 10 to $80\ \mu\text{m}$, with an average of $35\ \mu\text{m}$. The dose range for the left coronary injection is 1.0 to 1.5 mCi of ^{99m}Tc sulfur colloid

macroaggregated albumin (SCMAA) consisting of 300,000 to 800,000 particles and 0.1 to 0.3 mg of albumin.

A commercial preparation of ^{131}I -macroaggregated albumin (MAA) for the right coronary injection may be used as received, but often there is an excess of small particles that must be removed by the centrifuge technique. We have found that the remaining large particles are most stable when resuspended in the original fluid; thus the supernatant is filtered through a $0.45\text{-}\mu\text{m}$ Millipore filter and reconstituted with the macroaggregates. By this technique the dose of ^{131}I is maintained at approximately $100\text{ }\mu\text{Ci}$ without exceeding 800,000 particles.

The macroaggregates are injected into the coronary arteries after the completion of the contrast study of each coronary artery. The particles are first injected into a 10-cm^3 syringe containing 8 cm^3 of N saline; after gentle agitation to ensure adequate suspension, the injection is made manually through the coronary catheter at the rate of $3\text{ cm}^3/\text{sec}$. The technetium-labeled particles are usually injected into the left coronary artery and the iodine-labeled particles into the right coronary artery. This provides the left coronary system with the most favorable counting statistics. Continuous electrocardiographic and coronary pressure monitoring is maintained. After the catheter has been removed, the patient is transferred to the Nuclear Medicine Department for myocardial imaging. The biologic half-life of the macroaggregates of 4 to 6 hr provides sufficient time for delayed imaging.

Anterior, right anterior oblique (RAO), left anterior oblique (LAO), and left lateral views are obtained on each patient. The RAO is a 20° projection from the anterior view, and the LAO is a 20° projection from the left lateral view.

Images of the myocardial perfusion are obtained with an Anger camera integrated to a data acquisition, storage, processing, and display system. The system includes analog-to-digital converters, a PDP-8L computer, teletype, tape transport, and a multichannel analyzer for storage and display. It provides two 64- by 64-channel matrixes with a storage capacity of 4096 counts per channel.

The raw-data images are acquired and stored on tape and subsequently transferred to the multichannel analyzer. Computer-image processing includes a nine-point smooth routine, multiplication of each channel of one image by the factor required for normalization of the images, and channel-by-channel summing of the two images. The left, right, and summed myocardial images are then photographed from the display oscilloscope. A computer-controlled system has been developed for producing images in color to enhance contrast, to extend dynamic range, and to make information quantitative at a glance.⁵

CORRELATIVE ANATOMY

The normal myocardial-perfusion anatomy is demonstrated in Fig. 1. Each view shows the distribution of perfusion superimposed over the corresponding

Fig 1 Normal myocardial-perfusion patterns of the right and left coronary arteries as seen from two projections. R.C., right coronary artery; L.C., left coronary artery; RAO, right anterior oblique; LAO, left anterior oblique.

coronary artery. The distribution of the radioactive MAA from the injection in the left coronary artery corresponds to what might be expected and follows the outline of the vessels. However, the distribution of the radioactive MAA from the injection in the right coronary artery shows intense radioactivity inferiorly but little radioactivity anteriorly (lighter shaded area). This means that there is intense perfusion in the distribution of the posterior descending and posterior lateral branches of the right coronary artery but little perfusion to the right ventricular wall. If multiple views are used, the areas perfused by the three major vessels, namely, the anterior descending, circumflex, and posterior descending arteries, can be identified. There is partial overlapping of the distribution of the left anterior descending and circumflex arteries as seen from the anterior and RAO views, but distinction can be made quite readily in the LAO and left lateral

views. The anterior descending projects anteriorly and the circumflex, posteriorly on these views. The posterior descending distribution projects inferiorly on all four views but is best delineated in the LAO and left lateral views.

DISCUSSION

There is no doubt that patients with suspected coronary heart disease require evaluation by coronary arteriography. This is especially true when surgery of the coronary artery is contemplated. Although coronary angiography clearly delineates coronary artery abnormalities, it provides only indirect evidence of myocardial perfusion. Thus several questions arise. First, do symptomatic patients with severe stenosis of a major coronary artery have sufficient myocardial perfusion to warrant venous bypass surgery? Second, do patients with complete occlusion of a major coronary artery have adequate collateral perfusion to have maintained enough viable but ischemic muscle to justify bypass surgery? Third, do symptomatic patients with other evidences of coronary heart disease but a normal angiogram have abnormal myocardial perfusion? To date 205 patients have been studied without any demonstrable sequelae. In the vast majority of cases, there is good correlation between the angiogram and the myocardial-perfusion scintigram. However, we have demonstrated normal myocardial perfusion in patients with greater than 95% stenosis of a major coronary artery. These patients, in most instances, should be ideal candidates for coronary bypass surgery. The 95% stenosis undoubtedly results in relative myocardial ischemia, but the normal perfusion pattern suggests persistence of viable myocardium. Patients with completely occluded coronary arteries may or may not have adequate collateral perfusion. This is readily determined with the perfusion study. The most common pattern is an occluded right coronary artery with collateral perfusion to the inferior myocardium from the left coronary injection. These patients should also be good candidates for coronary bypass surgery.

Postoperative patients must be restudied to determine the predictive value of myocardial-perfusion scintigrams. Only a few such cases have been reevaluated to date. Incidentally, we have studied two patients with a previous Vineberg procedure, neither of whom demonstrated significant myocardial perfusion even though the graft was patent.

The group of patients with normal coronary angiograms but other evidence of myocardial ischemia may be further elucidated by myocardial-perfusion studies. Indeed, a few such patients demonstrated to have impaired myocardial perfusion have shown abnormalities of lactate production.

We feel that ultimately patients with symptomatology suggestive of coronary heart disease will not be considered completely evaluated without a myocardial-perfusion study.

SUMMARY

Myocardial-perfusion scintigrams have been performed in 205 patients after direct coronary injection of macroaggregates without demonstrable sequelae. The methods for the preparation and quality control of the radiopharmaceuticals are discussed as well as the technique for coronary injection and the computer-oriented instrumentation for imaging. These studies provide information not obtainable by standard coronary angiography alone, namely, the myocardial perfusion distal to a severe stenosis, the adequacy of collateral perfusion, and the status of myocardial perfusion in symptomatic patients with normal coronary angiograms. Postoperative reevaluation is necessary to determine the predictive value of these studies. However, we anticipate that myocardial-perfusion scintigrams will be valuable in the evaluation of patients with proven or suspected coronary-artery disease.

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SCANNING APPROACHES IN THE EVALUATION OF HEART DISEASE

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ABSTRACT

The application of nuclear medicine imaging procedures in the evaluation of patients with cardiac disease is viewed with increasing interest by specialists both in nuclear medicine and in cardiology. This paper reviews a number of clinically established radionuclide imaging procedures, such as "blood-pool" scanning for the demonstration of pericardial effusion, as well as a number of newer procedures that are being developed. In the category of "static" imaging procedures, the following topics are covered: blood-pool imaging with and without electrocardiogram gating, myocardial imaging with such agents as ^{125}I and ^{43}K , and perfusion imaging of the myocardial capillary bed following the intracoronary injection of labeled particles similar in size to those used for lung-perfusion scanning. "Dynamic" imaging is discussed and refers to those studies in which sequential images of the heart and great vessels are obtained after the intravenous injection of a small volume of a short-lived and physiologically inert agent, such as $^{99\text{m}}\text{Tc}$ -pertechnetate. Although the detail of these "radionuclide angiocardiograms" cannot approach that obtainable with modern, radiographic contrast angiography, important information concerning cardiac function and morphology can be obtained with virtually no risk to the patient. Thus these procedures can be used on an outpatient basis for screening selected patients with suspected cardiac anomalies prior to more definitive diagnostic tests, such as cardiac catheterization, or in studying, on a serial basis, very ill patients, such as those with acute myocardial infarction, in whom contrast angiography may be associated with a significant risk. The future diagnostic applications of these newer radionuclide imaging procedures are discussed.

If it can be said that the years between 1960 and 1970 will be remembered as the period when imaging techniques in nuclear medicine did much to aid in the evaluation and management of cancer patients, then the next decade may well be remembered as the one in which nuclear imaging techniques served to aid in the evaluation and management of man's number one killer, heart disease. Since many of the most recently introduced scanning techniques that have shown promise in cardiovascular diagnosis have not yet had the opportunity to stand the test of time, it is difficult to judge their ultimate clinical value. Some of

these procedures will become useful clinically and others will eventually have only historical interest.

In considering scanning approaches to cardiovascular diagnosis, we should note that it is often difficult to determine when a scanning approach ends and a functional study begins. For simplicity we will divide the discussion into those approaches where individual or static images provide the necessary information about some aspects of cardiac function and those techniques in which serial images are used to describe dynamic aspects of cardiac performance.

STATIC IMAGING

The cardiac blood-pool scan is perhaps still the most widely used radioisotopic procedure for demonstrating certain cardiac anomalies.¹⁻⁹ This procedure necessitates the intravenous administration of a radiopharmaceutical, such as albumin labeled with ^{131}I or $^{99\text{m}}\text{Tc}$, which is cleared from the vascular compartment relatively slowly. Whether the imaging is performed with a rectilinear scanner or a stationary camera device, this type of study is of definite clinical value in demonstrating a variety of conditions that alter the normal relations of the cardiac chambers and great vessels. The primary attractiveness of the procedure is that it is essentially noninvasive and does not require the administration of relatively large quantities of substances, such as radiographic contrast agents, which may on occasion alter cardiac performance. In addition, because of its simplicity, it can be performed on an outpatient basis. During the past few years, our experience with blood-pool scanning has shown it capable of demonstrating such things as relative cardiac chamber enlargement, ventricular aneurysms, intracardiac filling defects (e.g., tumors and thrombi), and, most importantly, the presence of moderate to large amounts of pericardial effusion (Fig. 1).

It is of unquestioned clinical value to be able to demonstrate a separation between the cardiac blood pool and the pulmonary vascular bed due to the interposed pericardial effusion. Also, the quality of cardiac blood-pool scanning has improved in recent years since the introduction of newer, short-lived radiopharmaceuticals, such as $^{99\text{m}}\text{Tc}$ -albumin and $^{113\text{m}}\text{In}$. A number of critical comparisons,¹⁰⁻¹² however, between blood-pool scanning, cardiac angiography (CO_2 and radiopaque agents), and ultrasonic techniques have revealed the limitations of the radionuclide technique when used to detect the smallest effusions.

Some laboratories have attempted to further improve the quality of the cardiac blood-pool scan in order to study the anatomy and function of specific chambers in greater detail.^{13,14} Although it might seem more appropriate to determine the morphology of a specific chamber by contrast angiography, it is becoming apparent that certain high-risk patients, such as those with acute myocardial infarction, are not ordinarily suitable candidates for cardiac

catheterization and angiography. Furthermore, since cardiac catheterization requires a specially trained team and a special facility, serial determinations of cardiac chamber volume and morphology are not practical in many situations. Therefore noninvasive methods, such as radioisotopic imaging, are viewed with increasing interest.

Fig. 1 Pericardial effusion. The separation "halo" between the ^{99m}Tc -albumin within the cardiac blood pool and that in the pulmonary vascular bed is due to the nonlabeled pericardial fluid. A direct comparison in size is possible between the labeled cardiac blood pool and the cardiac silhouette identified on the chest X ray obtained in the same projection (AP supine) and adjusted for magnification.

One of the most widely used techniques to improve the quality of the image of the cardiac blood pool involves the use of an electronic "gate" triggered by the electrocardiogram (ECG). After the patient has received an appropriate intravascular radiopharmaceutical agent, such as ^{99m}Tc -albumin, he is examined with a stationary imaging device. The ECG is also recorded and used to limit acquisition to only those periods during each cardiac cycle which correspond to either end-systole or end-diastole.^{15,16} In practice, all the end-diastolic images are integrated into a single image as are all the end-systolic images. The ECG gating technique can be applied either during the "live" acquisition or later if both the raw-image data and the ECG are recorded simultaneously on a suitable recording medium, e.g., magnetic tape. One can obtain as many views as are needed, and, in the appropriately "gated" images, one can clearly observe a definite change in size of the ventricular chamber between systole and diastole (Fig. 2). When we apply techniques similar to those used to determine left ventricular volume on single-plane angiocardiograms, we can calculate for the left ventricle both end-diastolic volume and end-systolic volume¹⁷ as well as stroke volume, cardiac output, and ejection fraction.

Of equal if not greater potential importance is the ability to identify local areas of abnormality in the left ventricular wall as demonstrated either by absence of observable change between systole and diastole or by paradoxical motion, such as may occur in areas of nonviable myocardium or ventricular aneurysms. Although we recognize the potential of these procedures in the

Fig. 2 Electrocardiogram gated images (see text) integrated for approximately 600 sequential cardiac cycles during each 100 msec (short horizontal line beneath the ECG) corresponding to end-systole (left) and end-diastole (right). The original 10-min recording made in the left anterior oblique position followed the I.V. administration of 10 mCi of ^{99m}Tc -albumin. Note the minimal change in volume of the dilated left ventricle between systole and diastole, indicating a low-ejection fraction in this patient with an acute anterolateral myocardial infarction, in contrast to an easily observed change in right ventricular volume (arrows) during the cardiac cycle.

evaluation of patients with acute myocardial infarction, we will have to accumulate additional data before we can determine their usefulness.

Worthy of practical consideration is the problem of how to obtain the required data on acutely ill patients. Since the patient with an acute myocardial infarction cannot be studied in the nuclear medicine laboratory, we must have a method for transporting our imaging and recording equipment to the bedside. In Fig. 3 we see an approach that allows a scintillation camera and magnetic-tape recording system to be rather easily transported.

In recent years myocardial scanning has received increasing attention. Since Carr¹⁸ in 1964 demonstrated that it was possible with ^{131}Cs and would permit one to distinguish between normal and infarcted myocardium, a number of investigators¹⁹⁻²² have used other radionuclides, such as ^{82}Rb , ^{129}Cs , and ^{43}K , and have shown encouraging results. These monovalent cations, which concentrate in normal myocardium as well as in the liver, muscle, and other organs, are excluded from regions of infarcted myocardium and probably concentrate in reduced amounts in ischemic heart muscle (Fig. 4). Although some of the early

Fig. 3 Scintillation camera modified so that it can be transported to the coronary intensive care unit or cardiac catheterization laboratory to study patients that cannot be brought to the nuclear medicine laboratory due to the severity of their illness or the nature of the examination.

published examples of scanning with these agents show poor image quality, the fact remains that a noninvasive technique for assessing the extent of myocardial damage is very attractive, particularly in the patient with an acute myocardial infarction.

It is entirely possible that myocardial scanning will find its greatest application in following the course of patients shown by other means to have

focal myocardial damage rather than as a screening procedure to document regions of ischemic or infarcted myocardium.

Work is already under way in an attempt to measure by myocardial scanning the size of infarcts. If sensitive enough to demonstrate small serial changes in size, these techniques may prove to be of great value in the management of patients with acute myocardial infarction since surgical and other interventions are occasionally attempted in those showing extension of the lesion. Myocardial imaging techniques may someday be useful in the operating room since our surgical colleagues cannot always determine the boundary of normal and infarcted myocardium at the time of open heart surgery, in which case it may be difficult to decide how much, if any, nonviable heart muscle should be excised after completing a myocardial revascularization procedure.

Other methods for demonstrating the extent of myocardial damage have been reported. Early investigations have shown that certain intravenously administered radiopharmaceuticals, such as ^{203}Hg -chlormerodrin (Ref. 23) and labeled fluorescein (Ref. 24), concentrate in what appears to be infarcted myocardium. Little if any clinical use has come from these observations, possibly because of the inconsistent and low specific labeling of the damaged myocardial tissue. Nevertheless, this early work suggests that we may, in the not-too-distant future, have radioactive compounds that will help us differentiate between normal, ischemic, and infarcted myocardium. A number of laboratories are exploring the possibility of rapidly synthesizing short-lived, biologically active compounds incorporating such radionuclides as ^{13}N and ^{11}C as well as using the ultra-short-lived radioisotopes of cesium and rubidium to permit more frequent serial examinations in the acutely ill patient with myocardial infarction.

Still another scanning approach in the evaluation of myocardial disease is the myocardial-perfusion scan.²⁵⁻²⁸ This procedure is not normally used on patients with acute myocardial infarction, but it has been safely used at the time of coronary arteriography in well over 500 patients with suspected coronary artery disease, many of whom have had previous myocardial infarctions. The principle is similar to perfusion scanning of the lung. In this case, however, the particles of labeled albumin are injected directly into the coronary circulation by selective catheterization of the coronary artery. The imaging can be performed at any time within the next several hours and need not be done in the cardiac catheterization laboratory. Although certainly not a noninvasive technique nor a substitute for coronary arteriography, the quality of the images is quite satisfactory, permitting the cardiologist to clearly define regions of reduced myocardial blood flow (Fig. 5). Since different labeled particles can be injected (e.g., $^{99\text{m}}\text{Tc}$ particles into the left coronary artery and ^{131}I particles into the right coronary artery), an evaluation of collateral perfusion and the distribution of perfusion from each major coronary artery is possible. Several centers have combined coronary arteriography with myocardial-perfusion imaging in the evaluation of candidates for myocardial revascularization procedures; in this

Fig. 4 Normal (A) and abnormal (B) ^{129}Cs myocardial images in the anterior projection. Each patient received 1 mCi and the recordings were for 30 min each using a converging collimator (inverted Nuclear-Chicago diverging collimator). Note the cardiac enlargement in patient B and a large, rather well-demarcated region (arrows) of reduced concentration of ^{129}Cs in an area corresponding to a known anterolateral myocardial infarction. Imaging was begun 30 min after the I.V. injection.

Fig. 5 Abnormal myocardial-perfusion images in the anterior projection from a patient with complete obstruction of the anterior descending branch of the left coronary artery and approximately 80% narrowing of the right coronary artery. The recordings follow the injection of approximately 100,000 carefully prepared and examined ^{131}I -albumin particles (10 to 60 μm in diameter) into the right coronary artery and a similar number of $^{99\text{m}}\text{Tc}$ -albumin particles into the left coronary artery while the patient was in the cardiac catheterization laboratory. Using pulse-height discrimination, separate images (left and middle) were stored in a 4096 magnetic core memory and subsequently transferred to digital magnetic tape. Individual images depicting the relative distribution of myocardial perfusion from each major coronary artery were combined to produce a composite image (right) showing a large, well-outlined region of virtually absent perfusion in the anterolateral aspect of the heart. Normally, multiple views are obtained to define the extent of the reduced perfusion.

situation the myocardial-perfusion scan is helpful in evaluating myocardial perfusion as influenced by the condition of small vessels, whereas coronary arteriography is used to determine the patency of the larger coronary vessels.

With all the many possible techniques used to image specific heart defects, the ultimate usefulness of each study depends to a significant degree on the quality of the recorded images. This is particularly true in assessing the extent of myocardial damage. Thus considerable effort is being made in the development and application of various techniques with computer enhancement which may eliminate, where appropriate, the subjective nature of scan interpretation and provide consistency in determining such things as changes in the extent of damage between one examination and the next. This may be of special importance to acute myocardial infarction patients in whom a documented change in infarct size, in either direction, might be a significant observation and for whom contrast angiography is a significant risk.^{2,9}

Last, we would mention the possibility that special labeling techniques as well as new scanning methods (such as fluorescent scanning) may be eventually utilized to demonstrate such things as intracardiac thrombi,^{30,31} damage to heart valves caused by bacterial endocarditis, the condition of valve prostheses, cardiac tumors,³² and many other problems that are not easily studied by other indirect methods.

DYNAMIC SCANNING APPROACHES

In cardiology we would describe as dynamic scanning approaches those procedures which record sequential images during one or more changing events within the heart. In addition to recording and viewing these serial images, we can often obtain valuable information from curves representing the time—course of count rates derived from various anatomical regions of interest within the heart and lungs (see the following paper).

The most familiar of these dynamic imaging techniques has been variously referred to as radionuclide angiocardigraphy, isotope angiography, or nuclear angiography. These terms, though describing what is actually performed, are sometimes construed as suggesting that these procedures are in competition with or substitutes for radiographic angiography. Wish as we might that these radionuclide imaging procedures could provide the anatomic detail achievable with high-quality selective contrast angiography, we must accept the fact that even the best radionuclide angiograms are generally capable of demonstrating only the grossest changes in morphology and alterations in cardiac function. On the other hand, radionuclide angiography is safe, causing no apparent alteration in cardiac performance, and is relatively simple to perform. This means that it can be an outpatient procedure as well as a means of studying the seriously ill cardiac patient.

In recent years radionuclide angiography using stationary imaging devices and performed after the intravenous administration of a bolus of a short-lived agent, such as ^{99m}Tc -pertechnetate, has been successfully used to study a variety of acquired and congenital cardiac abnormalities.³³⁻³⁸

As a matter of convenience, the injection of the radioactive bolus, which is rarely greater than 1 ml, is usually made into an arm vein. Alternatively, if it is desired to keep the bolus reasonably intact, it may be injected into a femoral or jugular vein. Although somewhat less convenient, injection into a central venous catheter advanced to the superior vena cava provides the greatest assurance that the bolus will remain compact and avoids a delay before the bolus passes into the heart. Positioning the patient is important; most laboratories prefer the left anterior, oblique projection in which the detector is directed somewhat caudally, providing an opportunity to separate the right and left chambers of the heart on review of the serial images.

After one gains a little experience in viewing these admittedly "photon-deficient" sequential images, he can begin to recognize significant abnormalities, such as enlargement of an individual cardiac chamber, abnormal chamber position (Fig. 6), various anomalies of the great vessels,^{39,40} aortic and ventricular aneurysms,⁴¹ pericardial effusion,⁴² altered flow patterns secondary to acquired valvular disease particularly in mitral and aortic valvular lesions,⁴³ right-to-left shunting of the injected bolus through congenital defects,⁴⁴ and focal areas of abnormal heart-wall motion.

One might question the necessity for performing this kind of study when contrast angiography is unquestionably better able to define the anatomical features of the beating heart. In many cases radionuclide angiography may serve as a screening procedure in helping to select those patients who might benefit from the more difficult procedures, particularly in those institutions where high-quality catheterization and angiographic procedures are not available. Similarly, for the ill infant in whom the question of primary pulmonary disease vs. congenital heart disease is raised (Fig. 7) or in the patient with a myocardial infarction in whom a progressive alteration of left ventricular performance is of concern, radionuclide angiography may be of real value and permit selection of patients who might benefit from the more elaborate diagnostic procedures that can be performed only in the cardiac catheterization or angiographic laboratory.

Over the years we have observed a definite improvement in the quality of radionuclide angiograms. Whereas we once had to depend on hand-pulled Polaroid prints, we can now record on a variety of media, such as 35- or 70-mm film, with little loss of image information between frames. Similarly, a recording can be made on magnetic tape so that images can be reconstructed to provide serial, individual, or composite images representing any desired time interval.⁴⁵ We can watch the replay of an angiographic sequence forward and backward, and even in slow or fast motion. Although we do not expect that this is going to compete with the Sunday afternoon football game, we do recognize some interesting possibilities in being able to better define regions of abnormal motion

Fig. 6 Transposition of the great vessels is easily recognized in this study following the injection of 2 mCi of ^{99m}Tc -pertechnetate into the femoral vein of a child. Note the oblique direction of the aorta arising from an anteriorly positioned ventricle (anatomically the right ventricle). Each sequential image exposure was for approximately 1 sec, and the entire outpatient procedure was completed in less than 15 min.

of the heart wall and rates of change in ventricular contractility, as well as other subtle functions, particularly if these data are further processed by computer techniques.

The last type of dynamic imaging we should mention may well be called radionuclide coronary angiography. Two approaches have been reported. The first involves the intracoronary injection of ^{99m}Tc -pertechnetate, during which time rapid-sequence images are obtained. Although the image resolution cannot

Fig. 7 Anomalous pulmonary venous return in an infant in whom the differential diagnosis of primary pulmonary disease vs. congenital heart disease was being considered. Flow of the ^{99m}Tc -pertechnetate through the pulmonary artery and into the pulmonary vascular bed is followed by appearance of the bolus in the liver and subsequently back to the right heart. Although the image detail is insufficient to identify the anomalous pulmonary veins carrying the pulmonary venous return to the liver, the diagnosis is nevertheless obvious and in this case was the crucial bit of evidence needed to initiate plans for making this infant, of Jehovah's Witness parents, a ward of the court in order that cardiac catheterization and possible open heart surgery could be undertaken.

approach radiographic detail, the overall dynamics of the flow through the myocardial vascular bed can be observed.^{4,6} The procedure does, unfortunately, require that an imaging camera be located in the cardiac catheterization laboratory.

Of perhaps greater current interest is the substitution of an inert gas, such as ^{133}Xe , dissolved in saline which is injected into the coronary artery at the time of cardiac catheterization. Recording the sequential flow patterns with a stationary imaging camera is reported to provide a gross visual estimate of regional perfusion,^{4,7} and a regional analysis of the rate of xenon washout from the extravascular spaces of the myocardium can be used to calculate regional myocardial blood flow. Although certainly not a noninvasive technique, in those institutions that are fortunate enough to have a scintillation camera in the cardiac catheterization laboratory, it does offer a way of determining regional myocardial blood flow. Again, the possibility of a portable scintillation camera is attractive.

Finally, as was mentioned previously, many of these new and exciting techniques have not yet had the opportunity to stand the test of time in clinical cardiology. Which ones will ultimately become useful is anybody's guess and will depend on the continuing interest of both the cardiologist and the nuclear medicine specialist. This interest will be sustained by the promise that we will someday have better radiopharmaceuticals as well as higher capabilities of resolution image and that, unfortunately, we will not run out of patients with heart disease in the foreseeable future.

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APPLICATION OF RADIONUCLIDE PROCEDURES IN CLINICAL CARDIOLOGY

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ABSTRACT

Because nuclear medicine procedures for testing the cardiovascular system are receiving increasingly greater attention, it seems timely to examine their practical value in solving clinical problems. Older, longer established techniques, such as scanning of the cardiac blood pool and measurement of cardiac output, have had sufficient critical analysis for us to appreciate their more useful applications and the more significant sources of error. The frequency with which these noninvasive techniques are requested varies with such local factors as the expertise and attention of the nuclear medicine physicians, the appropriate selection of patients and correct use of the test data by the referring physicians, and the reputation of nonnuclear medicine procedures capable of evaluating the same cardiovascular functions.

Myocardial infarct scanning, imaging of coronary perfusion, and radionuclide angiography are exciting new approaches to testing of cardiac disorders. These can provide important information about the location and extent of myocardial infarcts, areas of the heart not receiving direct arterial blood supply, dyskinetic portions of myocardium, size and shape of individual cardiac chambers, congenital cardiac defects, and the effects of valvular disorders. Although careful critical analysis and correlation with follow-up information have not yet been completed, it seems that, on the basis of underlying principles and the great need for this information in many patients, these new techniques will receive widespread appreciation.

In general, tests of the cardiovascular system using radioactive tracers provide significant information about a variety of cardiovascular functions and disorders in a facile and nontraumatic manner. More thorough testing of each new technique must be performed and great care must be exercised in the procedure for each patient lest some appeal is lost from these exciting means of studying functions of the heart and blood vessels.

Cardiovascular procedures using radioactive tracers are undergoing a phase of particularly rapid development and evaluation. Because of the great need for more accurate diagnostic information on patients with symptoms suggesting cardiovascular disorders, it is exciting to conjecture on continued growth of nuclear medicine in this direction.

Other authors have described and evaluated some diagnostic procedures in use for 5 to 10 years. In nuclear medicine that is a rather long time on which to base judgment regarding the clinical worth of a procedure. On the other hand, the newer techniques described seem now like extremely valuable additions to our diagnostic armamentarium but will have to survive critical, objective laboratory evaluations and practical clinical appraisal before we can appropriately decide on their merits.

The scan of the cardiac blood pool, as described by Ashburn (this volume), has become a frequently requested procedure over the past 10 years. The problems of diagnosing pericardial effusion occur fairly often in acute-disease hospitals and to a lesser extent in chronic-care institutions. The procedure has a high diagnostic accuracy,¹ but the frequency of its use is dependent mainly on certain local factors. One of these, of course, is the eagerness and expertise of the local nuclear medicine practitioners and technologists. They should avoid using contrast enhancement during scanning because this could lead to an erroneously small image of the cardiac blood pool. Also, they should know the importance of obtaining the related roentgenogram with the split-film technique² or with the patient in the same position as for the scan and with a tube-to-film distance of at least 6 ft to minimize the magnification of the cardiac outline on the roentgenogram. Either of these potential errors could lead to an erroneous indication of an increased pericardial space. Usually a knowledgeable nuclear medicine person must accompany the patient to the radiology suite to obtain the roentgenogram desired. As an alternative to this special chest X ray, one should consider a chest transmission scan,³ which would provide knowledge of the cardiac outline but without the magnification of an X ray.

The accuracy and usefulness of cardiac blood-pool scanning⁴ depends also on the local capability of labeling human serum albumin with ^{99m}Tc . One could use commercially available ^{131}I -albumin, but this would be a significant compromise in count rate, resulting in longer scan time and lower information density. Also, one may have to wait a day to receive the shipment. The use of ^{99m}Tc -pertechnetate has been advocated,⁵ but one must hurry and finish the scintigram to avoid obtaining any information that might be confusing and lead to a false interpretation.

The frequency of requests for the cardiac blood-pool scan depends also on the availability and trust local clinicians have for the use of ultrasonic cardiography, a procedure even less traumatic than the radionuclide scan. Cardiac ultrasonography is as accurate as the scan except in some patients with obesity or pulmonary emphysema and when pericardial fluid pools more laterally or posteriorly rather than over the anterior surface of the heart.⁶ This procedure must be carefully and knowledgeably performed and interpreted to have the claimed diagnostic accuracy. Special talents are required also for the radiographic procedures with carbon dioxide or other contrast materials. These carry some risks and complications, but their frequency is small in the hands of expert radiologists.

When the preceding factors are favorable for cardiac blood-pool scans, the laboratory of a medium-size general hospital can expect to perform over 50 tests per year. A correct diagnosis can be of dramatic clinical assistance. For instance, a 48-year-old man was treated for acute myocardial infarction for 2 days because of the fairly sudden onset of severe substernal pain accompanied by nausea, vomiting, and diaphoresis. Pulse was 130 and blood pressure 110/82 with a narrow blood pressure and a 15-mm paradox, but the ultrasonic cardiogram was normal. The electrocardiogram was abnormal but not diagnostic. Because of difficulty over 2 days in maintaining the blood pressure and because of the paradoxical pulse, the diagnosis of pericarditis with effusion was considered. Therefore an emergency cardiac blood-pool scan was obtained and revealed the presence of a clinically significant amount of pericardial effusion (Fig. 1). The removal of 750 ml of effusion fluid a few minutes later provided dramatic improvement and disappearance of the patient's symptoms. Furthermore, the ominous diagnosis of severe myocardial infarction suddenly became very unlikely.

Ashburn has described the cardiac blood-pool scan as an easy means of detecting an aneurysm of the ventricular wall or of the great vessels. A very dramatic example of this fact is depicted in Fig. 2. The photoscan reveals a large aneurysm at the apical portion of the left ventricle, which in a subsequent surgical procedure was found to be partly filled with clotted blood.

The use of electrocardiographic gating, as described by Ashburn and as developed also by the Johns Hopkins group,⁷ provides a significant advance toward increased usefulness of cardiac blood-pool imaging. As has been shown, this innovation can provide sufficient definition of cardiac chamber outline during end-diastolic and end-systolic periods so that akinetic or dyskinetic portions of the ventricular wall can be correctly identified. This information, which can thus be obtained in a facile and relatively nontraumatic manner, will, I predict, become extremely beneficial in the management of patients with myocardial infarction. It is indeed fortunate that this advance in instrumentation is occurring at a time when rapid strides are being made also in surgical procedures for patients with acute or chronic myocardial infarction.

Most cardiologists would agree that there is great clinical need for an imaging procedure that can depict injured portions of the myocardium. In patients suspected of suffering acute myocardial infarction on the basis of historical or physical findings, presently available diagnostic tests are often of limited value in substantiating or ruling out myocardial infarction. Myocardial scans may well aid in this recurring dilemma and, in addition, indicate the location and extent of tissue injury. This would be of immense value in the selection of appropriate intensity of medical management and referral for myocardial revascularization.

Myocardial scans with ^{129}Cs -chloride, as described by Yano et al.,⁸ and by Ashburn, or with ^{43}K -chloride, as announced recently by Hurley et al.,⁹ are being evaluated in patients suspected of having acute myocardial infarction. The

Fig. 1 Chest radiogram and cardiac blood-pool scan of patient being treated for acute myocardial infarction prior to diagnosis of pericardial effusion from scan. Note zones of decreased tracer concentration between intracardiac and hepatic or pulmonary blood pools. Diagnosis based also on discrepancy between sizes of intracardiac blood pool on scan and cardiac silhouette on X ray. Dose of 2 mCi of ^{99m}Tc -albumin administered via indwelling left-axillary-vein catheter. Note partial adsorption of tracer on irritated venous endothelium.

Fig. 2 Chest radiogram and cardiac blood-pool scan of patient with large left ventricular aneurysm (near apex) and loculated pericardial effusion. Tracer: 2 mCi of ^{99m}Tc -albumin.

physical and chemical properties of these two tracers provide significant advantages over radioactive chemicals that have been previously tried for this purpose. Monovalent cations are avidly sought by healthy cardiac (and skeletal) muscle and permit injured myocardium to be demonstrated as an area of decreased tracer concentration. We have been participating in the clinical evaluation of ^{43}K , which is provided by Oak Ridge National Laboratory. Figure 3 is a rectilinear scan of the first patient on whom we tried this procedure. This patient had chest pain, electrocardiographic changes, and blood-enzyme abnormalities diagnostic of acute myocardial infarction starting

16 days before this scan, with evidence of further extension of the infarct 8 days before this scan. The left anterior oblique view reveals a fairly definite area of decreased tracer concentration compatible with the possible appearance of an anterolateral infarct. At first we thought this area of decreased tracer concentration might represent a central clear area where the myocardial wall was not seen on edge; however, experience with subsequent patient studies indicated that this scan was abnormal.

Another patient, whose scan appears in Fig. 4, had history and laboratory information strongly suggestive of an acute myocardial infarct with extension and had electrocardiographic abnormalities which indicated the infarct to be in the inferoposterior portion of the left ventricle. The scan suggested the infarct to be apical and lateral. Thus the electrocardiogram correlates with the presence of an infarct, but there is lack of agreement on the location. In another patient there was complete agreement. His electrocardiographic abnormalities were very similar to the last patient's, and his scan (Fig. 5) reveals an abnormal area of decreased tracer concentration in the postero-inferior portions of the myocardium.

Another experience was in a patient thought to have suffered an acute myocardial infarction on the basis of sudden onset of severe substernal pain, nausea, vomiting, transient ST-segment deviation on his serial electrocardiograms, and transiently elevated blood-enzyme levels. His myocardial scan, however, revealed no areas of decreased tracer concentration (Fig. 6). Although this test is not yet being used for diagnostic purposes, it did raise a question for the cardiologists caring for the patient. As a result, the patient had coronary arteriography and an exercise test, both of which were normal. Present clinical opinion is that the patient probably had reasons for his symptoms other than acute myocardial infarction.

Our experiences so far indicate that this is a relatively simple, nontraumatic and noninvasive procedure that can be performed on patients with acute myocardial infarction. Doses of 0.5 to 1.5 mCi of ^{43}K are given intravenously and scans are performed within the ensuing 30 min, each view requiring about 6 min. The 375-keV main peak is suitable for rectilinear scanning with focused collimators designed for ^{131}I . The physical half-life of 22.4 hr helps to keep the radiation exposure within low levels and makes it possible to perform serial scans. Valuable information regarding the presence, location, and extent of damage can be provided by this test; however, more extensive clinical evaluations must be performed before we know the type of tissue damage that is revealed by this tracer. The supply of this radionuclide is still limited and the doses are very expensive, but, with increased popularity, the cost should decrease.

Imaging procedures that map out the distribution of coronary blood flow have been described in animals¹⁰ and recently in patients with coronary artery disease.¹¹ These procedures, described at this symposium by Ashburn and

Fig. 3 Left anterior oblique scan after 1.0 mCi of ^{43}KCl in patient with acute myocardial infarct. Note area of decreased tracer concentration near right anterior border of heart.

Fig. 4 Scan of myocardium after 1.5 mCi of ^{43}KCl in patient with acute myocardial infarct. Electrocardiogram indicated injured areas to be in posterior and inferior portions of myocardium. Scan indicates damage to be in left lateral and apical portions.

Jansen, involve the injection of ^{131}I -macroaggregated albumin (MAA) and/or $^{99\text{m}}\text{Tc}$ -MAA via coronary arterial catheters. As we heard, the technique is customarily combined with coronary angiography. Although information about regions of decreased blood supply is extremely valuable the need for catheterization will limit the growth in popularity of this procedure. Also, it must be remembered that this procedure does not indicate the presence or extent of actual ischemic damage to the myocardium.

Fig. 5 Radioactive potassium scan in patient with myocardial infarct. Electrocardiographic and scan abnormalities indicated infarct to be in posterodiaphragmatic region.

Fig. 6 Normal scan of heart after ^{43}KCl in patient thought to have acute myocardial infarct by history and laboratory tests. Subsequently found to have normal coronary arteriogram and normal response to exercise test.

I predict that 2 or 3 years from now the following procedures will be performed on most patients with coronary artery disease:

1. Coronary arteriography and ventriculography.
2. Myocardial scans or scintiphotos with ^{43}K or ^{129}Cs .
3. Myocardial scans or scintiphotos with ^{131}I -MAA and $^{99\text{m}}\text{Tc}$ -MAA.
4. Cardiac blood-pool scintiphotos to demonstrate dyskinetic portions of the myocardial wall.

Ashburn and Bennett have described clearly some of the newer techniques for the detection of intracardiac shunts, featuring use of new, short-lived tracers

and stationary imaging instruments and representing outgrowths of previously heralded techniques for shunt detection with single or multiple, collimated, external detectors. The new modifications seem to be clinically useful but in their present form have not been completely evaluated or used under more routine circumstances. It is too early to answer three questions that pertain to the clinical value of any diagnostic procedure: Is the test still being used in the hospital where it was initially heralded? Is the procedure used in a number of other hospitals at this time? Are the costs required to perform the test borne by the clinical revenues that can be collected for this procedure?

The radionuclide precordial counting technique for measurement of cardiac output was described by Bennett. It is a simple procedure for determination of an important variable of the cardiovascular system. It can be performed in very sick patients or in outpatients, once or oftener. No cardiac catheterization or arterial puncture is required. One wonders, therefore, why this procedure is not more frequently performed in clinical settings. The first explanations that come to mind are that the test is not being advertised by nuclear medicine practitioners and that it has not been mentioned much in recent literature. Also, one could justifiably say that cardiologists are naturally oriented toward the catheter laboratory where cardiac output is traditionally determined by the Fick principle or by dye-dilution curves. However, a more likely reason relates to its simplicity. The instrument and the tracer are readily available in most nuclear medicine laboratories, and it has been easy for physicians to try the procedure. It has been so simple in fact that they have felt little need to read the pertinent literature or to seek supervised experience. Probably the procedure was often left to the technician and a resident to perform. In any case the procedure was tried a few times in a laboratory and found not to be accurate compared to determination of cardiac output by one of the longer established techniques. It is possible also that measurement with a Fick or dye method was done in the same patient at another time or on another day than the radionuclide procedure. The situation may be analogous to the many errors in the thyroid uptake procedure which were recognized when Brucer^{1,2} sent a mannequin around the country to have its thyroid uptake measured by various laboratories. You will recall the wide range of erroneous results and how this convinced laboratory staffs that more care was required in standardizing that seemingly simple procedure.

We might mention a few of the more frequent sources of error that become recognizable and avoidable by the more critical and experienced laboratory worker. Usable indicator-dilution curves can be obtained by a well-collimated detector centered in front of the precordium (Fig. 7). Such a curve will be a composite of contributions from tracer flowing through the right and left sides of the heart. As Bennett mentioned, there is an essential requirement for narrow-angle counting to minimize radioactivity contributed to the detector by extracardiac blood. The same counting geometry must be compulsively

Fig. 7 Simultaneously recorded cardiac output curves over precordium and right internal carotid artery after 20 μ Ci of ^{131}I -albumin. Rate-meter scale 100,000 counts/min for precordial detector and 10,000 counts/min for carotid detector.

maintained from injection of tracer to the end of the equilibrium recording. In addition to precordial detection, it is possible to obtain a fairly pure arterial curve without significant capillary or venous contribution by detecting over the internal carotid artery on the side of the head (Fig. 7). With an intravenous injection of tracer, one can measure cardiac output, but this location is not commonly used. We might mention that cerebral blood flow cannot be measured in this manner. The concentration-time curve indicates cardiac output, not cerebral blood flow.¹³

I consider the extrapolation of the indicator-dilution curve past the start of recirculation as the most frequent but avoidable source of error of the precordial counting technique. This cannot be performed with sufficient accuracy and reliability by laying a French curve on the recorded downslope and then guessing the correct extrapolation. Although this is quick and simple, it is fraught with serious potential error even in the hands of experienced persons. A popular, acceptable means of extrapolation is to plot the downslope on semilog paper where it takes the form of a straight line. This is then easily extended past the start of recirculation with a straight edge, and this extrapolation is then replotted on the original rectilinear graph for measurement of the area under the

curve by a polar planimeter. This means of extrapolation is accurate but takes time and is quite tedious. We found several years ago that it was simple to construct and use an underlay of a family of single exponential curves.¹⁴ The recorded downslope of a particular curve can be matched to one of the family of curves on the underlay, and it can then be extrapolated in an exponential manner. This is as simple and rapid to use as the laying on of a French curve but matches the accuracy of semilog extrapolation and replotting.

The influence on cardiac output and the shape and area of the precordial dilution curve by exercise or change in the body's position with respect to gravity is illustrated in Fig. 8. These serial determinations on one patient represent measurements of cardiac output at rest, supine; at rest, sitting; and while exercising on a bicycle ergometer in the sitting position. Cardiac index was 4.3, 2.6, and 5.6 liters/min/m², respectively. We should note that the peak concentrations are approximately the same because of the fortuitous combination of factors such as cardiac output, central blood volume, tracer dose and volume, and rate-meter scale setting and time constant. This demonstrated the well-known fact that peak concentration by itself is of little significance. It is the area under the primary dilution curve which is important and which is seen to vary inversely with the cardiac output. Figure 9 illustrates the effect of following the intravenous administration of the radioactive tracer with a flushing dose of physiologic saline solution. The serial cardiac output values were approximately the same in this patient, and the areas under the two primary dilution curves are approximately equal. By comparing their shapes, however, one observes that the peak concentrations and mean circulation times are quite different. The saline flush has hastened the tracer toward the heart, thereby reducing the transit time from the point of injection to the site of precordial detection.

The precordial counting technique is subject to the same limitations of accuracy as the dye-dilution procedure at low levels of cardiac output. Figure 10 illustrates a normal cardiac output curve with an easily discernible start of recirculation. The other curve, however, is in a patient with low cardiac output and indicates that the point of recirculation, though recognizable, is not as sharply deviated from the downslope. With further decrease in cardiac output and still slower transit through the central recirculation, the start of recirculation may not be accurately recognized. The primary dilution curve would then include early recirculated tracer, causing the dilution-curve area to be erroneously high and the calculated cardiac output to be erroneously low.

The underlying principles of the precordial technique for measurement of cardiac output can be better appreciated by studies with a glass model of the central circulation and known levels of flow across the field of the detector.¹⁵ Such a model is presented schematically in Fig. 11 and includes right and left "hearts" and pulmonary and systemic circulations. Water was circulated through the system by a Sigma motor pump. Its flow rate could be measured accurately with a stopwatch and a graduated cylinder. Flow was determined also

Fig. 8 Serial precordial cardiac output curves in patient (a) at rest, supine; (b) at rest, sitting; (c) exercising, sitting. Chart travel was left to right in each.

Fig. 9 Precordial cardiac output curves (a) without and (b) with flushing dose of physiological saline solution after intravenous ^{131}I -albumin. Note similarities in area of primary dilution curve and differences in shape.

Fig. 10 Precordial time-concentration curves in patients with (a) abnormally low and (b) normal cardiac outputs. Note greater difficulty in extrapolating correctly past start of recirculation in left curve.

Fig. 11 Schematic diagram of glass-model circulation used to study underlying principles of precordial technique. (a) reservoir; (b) Sigma finger pump; (c) inflow tube; (d) right heart chamber; (e) pulmonary circulation; (f) left heart chamber; (g) outflow tube; and (h) scintillation detector. Insert shows usual positions of detector and two heart chambers. [From R. Gorten and J. C. Gunnefs, Isotope External Counting Method for Cardiac Output Analyzed in Glass Model Circulation, *J. Appl. Physiol.*, 16: 267 (1961).]

by using the primary-dilution-curve area, equilibrium level, and chart speed. Repeated observations indicated that flow could be accurately measured even though the tracer was presented to the detector twice during the initial circulation. The reason that cardiac output was equal to, rather than half as much as, the actually measured flow could be better appreciated when one of the "heart" flasks was removed from the circulation or when it was kept in the circulation but was prevented from contributing to the detection of radioactivity by being enclosed in a lead glove (Fig. 12). It was noted that the equilibrium level was reduced to the same extent as the diminution in the dilution-curve area. The basic principle demonstrated is that with the precordial technique counts from the right heart and from the left heart contribute to a similar extent to the primary dilution curve and to the equilibrium level. When one recalls that the equilibrium level is in the numerator of the equation for cardiac output and the primary-dilution-curve area is in the denominator, it will be realized that the technique has its own self-correcting features for individual differences in body build and detector placement. Understanding of these concepts emphasizes the need (not just convenience) for substituting the equilibrium level (and blood volume) in the calculation for the amount of indicator injected. These concepts serve to underscore also the importance of maintaining exactly the same counting geometry between the heart and the precordial detector from the start of the primary dilution curve to the end of the equilibrium-level recording.

Although the precordial counting technique works well for cardiac output, it cannot be used to calculate central blood volume from the product of cardiac output and mean transit time. This calculation works when serial arterial sampling is used to determine the primary dilution curve. The shape and mean transit time of the precordial counting curve are determined in part by nonphysiological factors, such as collimation and rate-meter time constant, for which corrections are extremely difficult. Figure 13 demonstrated three primary dilution curves at the same rate of flow but with different time-constant settings. The area under the curve remains the same, but the shape and, therefore, the mean transit time change markedly.

Comparisons in normal human volunteers between the precordial technique and the longer established dye-dilution method also assure us that the newer technique could be used with reliability when certain limiting factors are kept in mind. Comparisons at rest and during hyperdynamic states revealed good agreement between the two methods,^{1,6} as good as is found with any two methods or with two consecutive measurements using one technique. This correlation applies to injection of the radioactive tracer into the antecubital vein only, however (Fig. 14). With injection of the radioactive tracer into the femoral vein, the agreement was rather poor, as demonstrated in Fig. 15. A plausible explanation for this surprising observation is related to the streaming effect by tracer and blood when the injection is made too close to the right heart. Because of the rapid transit from a femoral-vein injection, the tracer might arrive in the heart without being uniformly mixed in the blood with which it travels and

Fig. 12 Comparisons of primary-dilution-curve areas and equilibrium levels when (a) one or (b) two cardiac chambers were contributing to counts recorded with the model shown in Fig. 11. Volume of each chamber was 205 ml; flow was 2.4 liters/min for both recordings. See text.

Fig. 13 Effect of different time-constant settings of the count rate meter on the shape of the dilution curve. From left to right, respective time constants were 0.5, 1.5, and 3.5 sec. Calculated flows from left to right were 2.3, 2.4, and 2.5 liters/min. Mean transit times were 12.5, 13.8, and 14.8 sec, respectively. [From R. Gorten and J. C. Gunnells, Isotope External Counting Method for Cardiac Output Analyzed in Glass Model Circulation, *J. Appl. Physiol.*, 16: 269 (1961).]

Fig. 14 Relation between cardiac outputs calculated from simultaneous injections of blue dye into superior vena cava (SVC) and radioiodinated albumin into antecubital vein. Time-concentration curve of albumin was determined by external counting and that of dye by arterial sampling. Values are distributed randomly about line of agreement. [From J. C. Gunnells and R. Gorten, Effect of Varying Indicator Injection Sites on Values for Cardiac Output, *J. Appl. Physiol.*, 16: 263 (1961).]

therefore might stream first toward one portion of the right heart and next time in another direction. With the precordial technique the right side of the heart contributes significantly to the primary dilution curve. On the other hand, when the tracer is injected into the femoral vein and arterial sampling methods are used, complete mixing would be achieved in the pulmonary circulation and left heart before detection of the entire primary dilution curve in a systemic artery. Therefore the accuracy of the precordial counting technique as demonstrated by antecubital-vein injection cannot be extrapolated to injections of tracer closer to or into the heart.

Another reason why this easy and readily adaptable technique is not more popular has to do with the practical value of knowing a patient's resting cardiac output. This is usually of limited benefit to the patient because the wide range of normal overlaps to a considerable degree abnormally high and low levels of cardiac output. Definitely high or low cardiac output values would occur mainly in people in whom one can make a correct estimate by physical examination. Measurement of cardiac output during exercise is sometimes beneficial for evaluating patients with limited cardiovascular reserve, but the interpretation is not really complete without knowing the simultaneously determined arterio-venous oxygen difference.

Fig. 15 Relation between values for cardiac output calculated from simultaneous injections of blue dye into superior vena cava (SVC) and radioiodinated albumin into femoral vein. Time-concentration curves of dye were plotted from data obtained by arterial sampling and those of albumin from external counting. All but one point fall below line of agreement, indicating a consistently higher value for method involving femoral injection and precordial detection of radioactive tracer (difference in means, 1.8 liters/min; standard deviation, ± 0.9 liter/min; $p < 0.01$). [From J. C. Gunnells and R. Gorten, Effect of Varying Indicator Injection Sites on Values for Cardiac Output, *J. Appl. Physiol.*, 16: 263 (1961).]

The use of ^{131}I -labeled albumin in the precordial counting technique requires thick lead shielding and collimation to exclude (as much as possible) extracardiac blood contributions to the activity detected from intracardiac transit of tracer. This makes it impossible to attach the detector to a patient's chest. The detector must be attached to a sturdy stand, but then it is difficult for most patients to maintain the required constant counting geometry during sitting or horizontal bicycle exercise. A technique developed to circumvent these limitations features the use of ^{125}I -albumin, an isotope that emits only low-energy photons.¹⁷ A small thin crystal can be used efficiently, and the customary lead shielding and collimation are not required to exclude scattered activity. This permits the use of a light-weight probe¹⁸ that can be attached to the chest (see Fig. 16). The cardiac output response to a moderate exercise assignment by a group of healthy adult males is illustrated in Fig. 17. Such measurements would be useful in work rehabilitation evaluations but would have limited popularity with physiologically oriented cardiologists. The cardiac

Fig. 16 Lightweight scintillation detector attached to subject's anterior chest during bicycle ergometer exercise. [From R. J. Gorten, A Small Lightweight Counter for Determination of Cardiac Output, *J. Appl. Physiol.*, 20: 1364 (1965).]

output response to exercise depends not only on the ability of the heart to pump more blood but also on the redistribution of cardiac output to supply more blood to active parts of the body. The latter factor and greater peripheral oxygen extraction are in part functions of physical training.¹⁹

The greatest usefulness of the precordial counting procedure is for special clinical problems that do not require cardiac catheterization for other reasons and for serial measurements of cardiac output. Some cardiologists and other physicians would find it useful to measure cardiac output serially in patients recovering from acute myocardial infarction.^{4,20} Others might find it useful to measure cardiac output in a serial manner on the same day and thereby monitor the cardiovascular response to a particular drug. The procedure is useful for certain preoperative evaluations. For instance, the effect of surgical correction of

Fig. 17 Cardiac outputs supine, sitting, and exercising (bicycle ergometer, 50 watts, 40 rpm) in group of untrained, healthy adult males.

an arteriovenous fistula can be easily predicted in this manner. As an example, the cardiac output in a patient with a femoral arteriovenous fistula was 11.6 liters/min with the fistula open and 6.8 liters/min with the fistula manually compressed. This proved the presence of a high cardiac output state and that increased work of the heart could be reduced by ligating the fistula.

In summary, the radionuclide precordial counting technique for the determination of cardiac output has certain clinical advantages because of its simple and nontraumatic features and its facile adaptability to serial measurements, but one needs to be aware of certain sources of error to provide meaningful results.

I have related my reflections on the value of certain tests of the cardiovascular system using radioactive tracers. The general approach I have

conveyed is that nuclear medicine techniques provide important information in a variety of problems. The cardiologist must know when and what to request and how to use the results to benefit his patient. The nuclear medicine specialist must be knowledgeable, experienced, and careful to provide correct and meaningful information.

EDITORS' NOTE

The cardiac blood-pool scan is particularly helpful in distinguishing a solid mass from one that contains blood [J. Bonte et al., Scintillation Scanning in Differential Diagnosis; Thoraco-abdominal Midline Masses, J. Amer. Med. Ass., 175: 221-224 (1961)]. It may be used as an alternative to contrast angiography in the differential diagnosis of midline masses of the chest, such as delineating a solid tumor or clot-filled aneurysm from an aneurysm or other abnormal blood-containing space. Another very reliable sign of pericardial effusion is the separation of the cardiac blood pool from the hepatic blood pool, particularly in rectilinear scan images (F. H. Deland and H. N. Wagner, Jr., Atlas of Nuclear Medicine, Volume 2, Lung and Heart, p. 267, W. B. Saunders Company, Philadelphia, 1970).

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DISCUSSION: HEART

Powell: I wonder what Dr. Judkins expects of the radioisotope laboratories in the work-up of the patient with coronary artery disease. The angiograms of the coronary arteries that you showed were beautiful, and I can see their eventual value to us in diagnosis and treatment. However, is the information obtained from coronary angiography presently being used in management of the patient?

Judkins: We definitely are using this information in the management of the cardiac patient. I tried to point out in my presentation the importance of cardiac angiography because I think right now nuclear medicine has been catapulted into this field of investigative cardiology. In our learning to interpret these examinations, we are probably at the same stage now that we were when we did the first 200 chest X rays.

Wellman: The radioisotope laboratory, in cooperation with the Division of Cardiology at the University of Cincinnati, primarily through the work of Dr. Daurel Weller, has had preliminary experience with injections of ^{99m}Tc -human albumin microspheres into the coronary vessels of six patients; this was after doing a large series in dogs. These studies showed unusual clarity in the demonstration of myocardium. They give a somewhat different appearance from macroaggregated albumin. First, in a normal case I think the most dramatic difference is in the heart, particularly the left anterior oblique projection, which shows a view simulating a cross section of ventricular myocardium. Second, in a patient who had an anterior myocardial infarction 3 months earlier, one would see no definite cutoffs of large-vessel abnormalities on the coronary arteriogram. On the right lateral there may be an area in the myocardial wall which has increased activity or decreased distribution. One may see a perfusion abnormality of the apex of the left ventricle. These studies appear to be significantly different from the pattern of the coronary vessels after macroaggregated albumin injections shown by Drs. Judkins and Ashburn. I wonder if either of these speakers would care to comment on this difference.

Ashburn: I think those studies are very elegant, Dr. Wellman. I think we have to remember that you injected a technetium bolus into each of the coronary

arteries. When we use ^{131}I , we have to use very small amounts of iodine; we have various problems such as low photon yield. The only way to do your study, Henry, is to inject indium particles into the right coronary artery and technetium into the left coronary artery and then add the two for interpretation. I get the impression from the work at Loma Linda that the ability to separate the portion of heart perfused by the right coronary artery from that by the left is needed to supply additional information, not just the fact that we have a defect.

Br... The measurement of cardiac output and radiotracer dynamics from individual cardiac chambers is complicated by the broad field seen by the external radiation detectors used in these studies. Using the camera-type imaging systems coupled to computers, one can select cross-section projections, and this helps a little. The first transit of radioindicator is limited to the cardiac and major pulmonary vessels, whereas in subsequent transits material is also present near and below these structures. Because the efficiency of detector response varies with depth, the counts obtained during the early and late portions of the study have different numerical significance, and this greatly complicates quantitative analyses. The recent availability of high-resolution semiconductor detectors has provided a new tool that may be of great external use in quantitative cardiovascular studies. Drs. Welch and Ter-Pogossian have used the X-ray-fluorescent system for measuring cerebral blood flow and circulation transit times. The method involves the measurement of characteristic X rays from an intravascularly injected stable high Z tracer, such as iodinated oils used in radiography, as they pass through the intersection of the fields of view of the X-ray beam and collimated lithium-drifted silicon detectors. I am told that the nuclear medicine group at the University of California in San Francisco recently reported, at a local chapter meeting, their preliminary studies with this technique in dogs. They found that more than adequate sensitivity is available for quantitative analyses. Using the principle of this technique, we should be able to sample the tracer's transit through well-defined anatomical regions in the body and quantitate flow with accuracy.

Powell: Dr. Leon Kaufman of our group reported the information to which you referred at the meeting of the California chapter of the Society of Nuclear Medicine. He described the need for a multichannel analyzer to observe K-alpha and K-beta X rays and Compton scatter in an area between background and the organ to make the data completely independent of the animal's geometry.

Wellman: I would like to return to the comment of Dr. Ashburn. There is no doubt that the separate administration of two radiopharmaceuticals into the coronary vessels is important information. However, I would wonder if the availability of a higher resolution image of myocardial defects might be more desirable.

Powell: I would like to ask Dr. Ashburn whether he thinks there will be any competition between nuclear medicine laboratories and cardiac catheterization laboratories in studying a patient with heart disease.

Ashburn: I do not believe competition will exist with the cardiac catheterization laboratory. If we find anything that looks important, the nuclear medicine laboratory will try to apply its techniques to obtain the most accurate information possible in conjunction with the cardiac catheterization laboratory. People who do not want to come to the cardiac catheterization laboratory, such as some children or the elderly, will find the nuclear medicine laboratory an adequate substitute.

Gorten: The radionuclide studies offer also the advantage that they can be readily repeated, whereas studies in the cardiac catheterization laboratory do not lend themselves to frequent determinations.

Moderator:

Frank Comas

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GENERAL

LOCALIZATION OF TUMORS WITH RADIOISOTOPES

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ABSTRACT

Tumor scanning already is an important diagnostic tool in the clinical management of cancer patients. Although many tumors can be located with organ-scanning procedures, there is a need for more-general tumor-scanning agents. Many radioactive compounds have been proposed for this purpose. Apparently most of these gain access to the tumors as labels of the plasma protein pool, but they are then fixed in the tumors by a variety of mechanisms. Gallium-67 and possibly ^{111}In now appear to have the best prospects for wide clinical application. Tumor uptake of ^{67}Ga given as the citrate was detected on scans in approximately half of the 140 patients scanned. The histologic type, degree of fibrosis or necrosis, and location of a tumor appear to be important determinants as to whether it will take up gallium and be detected on the scans. Despite the inconsistent uptake from one tumor to another, occult tumors not detectable by other means often can be demonstrated by scanning with gallium. This procedure appears to be particularly useful in the posttreatment evaluation of cancer patients, especially those treated with radiotherapy for Hodgkin's disease and other lymphomas.

At the present state of the art, with a few notable exceptions, the only cancer treatments offering hope for cure are those directed at the neoplasm locally—i.e., ablation either by surgical excision or radiation as opposed to systemic chemotherapy. A second truism of cancer therapy is that cures or long-term remissions require early diagnosis and treatment. So long as these statements are true, there will be a continued need for improved techniques of locating tumors. It is not surprising, therefore, that a large part of the newest discipline of medicine, nuclear medicine, should be devoted to this particular problem. A recent survey indicated the three most common scanning procedures were for the thyroid, brain, and liver.¹ Most of these are done for tumor detection or localization. Obviously, much of the subject suggested by the title of this paper is covered elsewhere in this symposium. One cannot discuss brain scanning, liver scanning, thyroid scanning, and bone scanning without talking

about the significant clinical contribution these procedures have made in locating tumors.

TUMOR-SCANNING AGENTS

Despite the relative success of these organ-scanning techniques, investigators in nuclear medicine have not discarded their dream of a "magic bullet" that would permit detection of tumors irrespective of their histologic type or location. Although this dream remains only a dream, the search for the missile has not been altogether unrewarding.

As early as 1946 relative tumor specificity² had been demonstrated for ^{32}P . Since then various devices have been contrived in an effort to use either the rather potent beta emissions or the associated Bremsstrahlung rays of this nuclide to detect internal cancers. Better agents for tumor scanning have of course been sought from among the gamma-emitting nuclides. Table 1 shows a partial list of the agents that have been proposed. The agents range from simple salts of radioactive nuclides, such as $^{197}\text{HgCl}_2$, to complex immunoproteins with a radioactive label. The limited success so far has been characterized as much by chance observations and serendipity as it has by meticulous scientific investigation based on deductive reasoning.

Basically there appear to be two aspects to the problem of getting differential tumor localization of any radioactive tracer: (1) the delivery of the nuclide to the tumor and (2) the residence time of the nuclide in the tumor. It is probable that each of these agents listed in Table 1 is delivered preferentially to tumors as a result of the increased vascular pool and increased permeability of the tumor. Furthermore, each of the agents, with the exception of cesium and quinoline derivatives, is either protein in nature or known to be quickly bound to the plasma proteins after injection. Cesium probably enters the tumor cells along with the other alkali metals potassium and rubidium, both of which are known to be more highly concentrated in tumors than in other tissues.³

One characteristic of malignant tumors is their great influx of proteins from the plasma.^{1,6} Therefore those radioactive agents acting as plasma-protein-pool labels would be expected to preferentially enter the tumors along with the proteins of the plasma. This increased uptake of the radioactive label in the tumor should be apparent on scans, provided the scans are made during the residence of the label in the tumor. Efforts to further increase the delivery of the nuclide into tumors by selective intra-arterial injection and regional oxygenation have been made^{1,7} but are not very helpful in the search for unknown lesions. Greater tumor uptake has also been achieved by using chemical forms of the nuclides which result in increased residence time in the tumors. For instance, ^{131}I becomes highly concentrated in functioning follicular carcinoma of the thyroid because much of the iodide delivered to it is incorporated into the hormone synthesized by the tumor. Likewise, the prolonged residence time of

TABLE 1
RADIOACTIVE TUMOR-SCANNING AGENTS

Nuclide	Half-time	Principal radiations	Chemical forms
^{32}P	14.3 days	β^- 1.7	Phosphate ²
^{131}Cs	9.6 days	γ 0.030	Acetate ³
^{197}Hg	2.7 days	γ 0.077	Chloride ⁴
		γ 0.069	Chlormerodrin ⁵
and ^{203}Hg	46.6 days	β^- 0.21	
		γ 0.279	
^{75}Se	120 days	γ 0.265	Selenite ⁶
		γ 0.136	Selenomethionine ⁷
		γ 0.280	
^{99m}Tc	6 hr	γ 0.097	Pertechnetate ⁸
^{131}I	8 days	β^- 0.80	Iodinated serum albumin ⁹
		γ 0.364	Iodinated rabbit- antihuman fibrin ¹⁰
and			Iodinated analogs of chloroquine ¹¹
^{125}I	60 days	γ 0.035	Iodo-MNDP ¹²
^{206}Bi	6.2 days	γ 0.803	Acetate ¹³
		γ 0.880	
		γ 0.516	
		γ 1.72	
^{111}In	2.8 days	γ 0.247	Citrate ¹⁴
		γ 0.173	
^{67}Ga	3.2 days	γ 0.093	Citrate ¹⁵
		γ 0.184	
		γ 0.296	
		γ 0.388	

*6- ^{131}I -iodo-2-methyl-1,4-naphthaquinol bis (diammonium phosphate), a vitamin K related compound.

^{75}Se -selenomethionine has been achieved because the labeled compound is incorporated into proteins synthesized by the tumor cell⁷ while radioactive-labeled derivatives of quinoline are selectively deposited along with melanin in malignant melanomas.¹¹ Since some tumors are known to contain an abundance of fibrin, radioiodinated heterologous antibodies to human fibrin or fibrinogen have been produced and used to demonstrate tumors by scanning.¹⁰ Likewise, some success has been reported in producing radioactive-labeled heterologous antibodies to human tumors which have shown selective localization in the tumor after intravenous injection.¹⁸

At present little is known about the mechanism of localization of the radioactive derivatives of vitamin K. In some instances it appears that the iodine label is detached and attaches itself to plasma proteins and thus is handled much like iodinated serum albumin. Iodine, pertechnetate, selenite, bismuth, indium, and gallium are all bound to proteins in the plasma and presumably also in tumors. However, there does appear to be a great difference in the number and strength of the tumor binding sites available to each, giving different residence times and therefore different tumor concentrations. Because of superior radiation characteristics and generally better tumor localization than the others, ^{67}Ga and possibly ^{111}In appear to hold the greatest promise of continued clinical usefulness.

GALLIUM

Gallium is a group III metal which until recently had been thought to have little or no biological significance. In the late 1940s Dudley¹⁹ discovered it to be deposited where new bone is being formed, i.e., at tumor sites, and suggested a possible clinical use of radioactive gallium in locating and treating neoplasms of the bone. At that time ^{72}Ga was readily available from the Oak Ridge graphite reactor, but therapeutic and diagnostic trials with this nuclide in patients with osteogenic sarcoma were generally disappointing here at Oak Ridge²⁰ and elsewhere. There was a resurgence of interest in radioactive gallium with the introduction of a long-lived generator (^{68}Ge) for another isotope of gallium, ^{68}Ga . This short-half-life (68 min) isotope was used in the ethylenediaminetetraacetate chelate form as a brain-scanning agent²¹ and in the citrate form with added stable carrier gallium as a bone-scanning agent.²² In neither case did these compounds demonstrate superiority over existing agents available for the same purpose, and they have largely been abandoned.

The most recent interest in radioactive gallium followed experiments with still another isotope, ^{67}Ga . When given intravenously as citrate in the carrier-free form to a patient with Hodgkin's disease (Fig. 1), this nuclide localized in the Hodgkin's lesions well enough to clearly demonstrate them by scanning. Subsequent studies have shown concentrations of gallium in other types of tumors.^{15,23}

DISTRIBUTION AND EXCRETION

A tracer amount of gallium, when injected intravenously as citrate, is believed to be bound immediately to plasma proteins and rapidly distributed throughout the body. It leaves the blood fairly rapidly at first and then more slowly (Fig. 2). At 40 hr approximately 5% is still in the blood, and at 5 days about 2% is still circulating. In the meantime some is excreted into the bowel (approximately 10%) and some into the urine. Urinary excretion is greatest

Fig. 1 Anterior photoscan of the neck of a 73-year-old woman with Hodgkin's disease showing ^{67}Ga concentrated in neoplastic cervical lymph nodes.

during the first 24 hr after infusion, about 10 to 15% of the injected dose (Fig. 3). A similar amount is excreted over the next 5 to 6 days, leaving about 65% of the injected dose remaining in the whole body after a week. In the 18 patients counted in our whole-body counter, this figure varied from 35 to 81%.

In a series of autopsies on patients who had received recent doses of carrier-free ^{67}Ga , Nelson²⁴ found the average concentration of the nuclide in the spleen to be greater than that in other organs not involved with tumor. Brain and spinal fluid show the lowest concentration, suggesting exclusion of the nuclide by the blood-brain barrier. Like the whole-body retention, the amount of gallium retained in the individual organs or tissues is quite variable. Other tissues with significant levels of activity include the renal cortex, bone marrow, liver, and bones (see Table 2).

As shown in Table 3, the concentration of ^{67}Ga found in tumors has ranged from 1.6% of the injected dose per kilogram of tumor to 68% per kilogram. Tumors of the same histologic type have shown greatly different concentrations of gallium from one patient to another and also within the same patient. Part of this variation can be explained on the basis of differences in viability of the tumors. Those which show necrosis or fibrosis will generally take up less gallium than the more cellular and viable-appearing ones. Although even the lowest assay value for viable tumor (2.1% per kilogram) is greater than the average whole-body retention (100% of the injected dose per 70 kg of body weight or

Fig. 2 Mean blood level of ^{67}Ga following intravenous injection of diagnostic dose of carrier-free ^{67}Ga as citrate. The percent of the dose in the entire blood volume is estimated by assuming the whole blood volume in liters to be equivalent to 7% of the body weight in kilograms.

Fig. 3 Average daily urinary excretion of ^{67}Ga after intravenous injection of the carrier-free nuclide as citrate.

TABLE 2
CONCENTRATION OF ^{67}Ga IN TISSUES
OBTAINED FROM AUTOPSIES*

	Percent of injected dose per kilogram adjusted for 70-kg man	
	Mean	Range
Spleen	4.1	0.4 to 10.2
Renal cortex	3.8	0.7 to 8.4
Bone marrow	3.6	0.7 to 9.9
Liver	2.8	0.6 to 5.2
Bone	1.4	0.04 to 3.5
Muscle	0.2	0.03 to 1.1
Brain	0.1	0.00 to 0.7

*Adapted from: Ref. 24.

1.43% per kilogram) and can thus be said to represent concentration of the nuclide, we have found it difficult to detect tumors containing less than 5% per kilogram unless they were very favorably located.

Although the mechanism for the concentration of gallium in tumor tissue is unknown, studies at our institution have shown that the nuclide is located intracellularly rather than in the intercellular spaces.^{2,5} Electron-microscopic autoradiograms of murine tissues and neoplasms have further shown that the

TABLE 3
GALLIUM-67 CONCENTRATION IN BIOPSIED TUMORS

Tumor	Interval, days	Concentration, % dose/kg	Ratio* of tumor to blood
Malignant lymphoma			
Pleomorphic	1	11 to 19	22 to 38
Burkitt-type	1	49 to 68	25 to 34
Poorly differentiated	4	26 to 43	87 to 143
Hodgkin's disease			
Mixed cellularity	4	8.0† to 51	
Nodular sclerosis	7	2.9‡ to 16	7 to 40
Adenocarcinoma, metastatic	2	11‡ to 39	15 to 55
Squamous carcinoma of the lung	9	12 to 14	
Fibrous histiocytoma	8	2.1 to 4.5	
Leiomyosarcoma	2	1.6† to 6.9	

*The range of values results from multiple varying samples of tumor.

†Tumor was largely necrotic.

‡Tumor was fibrotic.

nuclide is mainly concentrated in intracytoplasmic dense bodies resembling lysosomes.²⁶ In some tissues the nuclide appears mostly in the macrophages. Unlike some other metals—e.g., copper, zinc, magnesium, and manganese—gallium is not known to be involved in any enzyme or to participate in any intracellular metabolic pathway. Why it should be concentrated in macrophages or lysosomes generally is still a mystery.

RADIATION DOSIMETRY

The radiation exposures received by patients from any radioactive isotope depend on the characteristics of the radiations involved in its decay, the size of the dose injected, and the rate at which it is excreted. Although recognizing that the latter varies widely from patient to patient, Cloutier²⁷ has calculated that approximately 20% of the dose is eliminated from the body with a half-time of 43 hr and 80% with a half-time of 638 hr, or effective half-times of 27.6 and 69.5 hr, respectively. Using these figures and assuming uniform distribution, he estimates the whole-body radiation dose to be 0.27 rad/mCi of injected dose. The dose to the specific organs or tissues is even more variable than that in the whole body. Using organ assays from Nelson's autopsy data and taking into consideration the cross-radiation from adjacent organs, Cloutier has calculated radiation doses of 0.5 rad/mCi to the liver, 0.6 rad/mCi to the spleen, 0.5 rad/mCi to the kidney, and 0.6 rad/mCi to the marrow. Again these figures include the assumption of uniform distribution of the nuclide within organs, a situation that in fact does not exist.

CLINICAL STUDIES

Gallium-67 has a half-life of 78 hr. It decays by electron capture, giving off four principal gamma rays: 93 (40%), 184 (24%), 296 (22%), and 388 (7%) keV. The nuclide is produced at the Oak Ridge National Laboratory by bombarding a zinc target with a beam of accelerated protons. The ⁶⁷Ga is then extracted from the zinc target and prepared as a citrate solution. After being sterilized and tested for pyrogens, the doses are injected intravenously. We are presently using a dose of 0.035 mCi per kilogram of body weight (approximately 2.5 mCi for a standard man of 70 kg). After more than 200 doses of ⁶⁷Ga, we have seen no significant reactions attributable to the radiopharmaceutical. Because approximately 10% of the dose is excreted in the stool, where it can appear in the scan of the abdomen, patients are given laxatives and enemas to encourage elimination of the activity from the bowel. Routinely we wait 48 hr before scanning, although serial profile scans show there is very little redistribution of the nuclide within the body after 24 hr. For our scans we have used a spectrometer window setting of 160 to 320 keV bridging the two medium-energy gamma emissions.

Having tried to avoid scanning patients without active neoplastic disease, we have had little experience with "normal" gallium scans. However, there are tissues and organs that are regularly identified on scans as sites of increased activity, although they are not involved directly with tumor. From these findings we conclude that the "normal" gallium scan will have a diffuse body background of activity showing the body outline, provided the scans are not made with a large background-erase factor. Against this level of body background, we can often see the skeleton, especially the skull, vertebral column, sacro-iliac joints, and the ends of the long bones. These are especially prominent in growing children and less so in elderly and osteoporotic adults. Other organs apparent on the scan with levels of activity approximating that of the skeleton are the liver, spleen, and kidneys. The anterior view of the head shows regularly a site of increased activity corresponding to the location of the nasopharynx. At times the lacrimal, salivary, and mammary glands may be visible, although not necessarily symmetrically. Gallium has been demonstrated in human milk.²⁸ In the pelvis activity is usually seen in the perineal area; some of this may be due to staining from excreta, but some appears to be actually localized in the vulva and penis. The gallium present in the bowel is by far the most troublesome in reading a scan. It often appears as the greatest concentration of activity on the scan, and we have not been able to consistently prevent this.

RESULTS

We have now scanned 140 patients with a variety of tumors. Some patients have been scanned serially, thus accounting for the excess of doses over patients. The patients included in this study are drawn from the patient population at the Medical Division of Oak Ridge Associated Universities or referred by area physicians specifically for the study. As such there is a definite bias in this series with a relatively larger number of patients with malignant lymphoma compared to other tumors and more patients with advanced and metastatic disease than untreated primary tumors.

Of the initial scans, 53% have shown evidence of sufficient tumor concentration to be judged clinically useful (Table 4). Although each patient was thought to have malignant neoplastic disease at the time of the scan, the subsequent course of the disease or later findings have now led us to believe that 9 of these 140 patients had no neoplasm when scanned. As indicated in Table 4, two of these patients gave positive scans which are regarded as false-positive tumor scans.

Since gallium is a bone seeker, bone metastases are frequently seen, probably often without actual uptake of gallium by the tumor. Although we have not yet had the opportunity to scan a patient with primary breast cancer, Lavender et al.²⁹ found no gallium concentration in 8 of 10 patients with primary breast carcinoma. Of our 10 positive scans in patients with breast cancer, at least 8

TABLE 4
INITIAL ^{67}Ga SCANS

	Positive	Negative	Total
Hodgkin's disease	19	8	27
Other malignant lymphomas	14	10	24
Carcinoma of the lung	11	9	20
Carcinoma of the breast	10	4	14
Miscellaneous	18	28	46
Probably no tumor	2	7	9
Total	74	66	140

TABLE 5
SCAN RESULTS IN PATIENTS WITH CARCINOMA OF THE LUNG

	Positive	Negative	Total
Squamous	7	1	8
Undifferentiated	2	5	7
Adenocarcinoma	1	2	3
Unspecified	1	1	2
Total	11	9	20

showed only bone metastases. On the other hand, Ito³⁰ has reported positive scans in 4 out of 4 patients with breast cancer, 1 of which may have had only bone metastases.

The histopathology of the cancer seems to be of considerable importance in our series. Seven of the eight patients with squamous carcinoma of the lung had positive scans compared to the total of only 11 of 20 patients with all types of lung cancer (Table 5). To a limited extent the importance of the histology is apparent also in scans of malignant lymphomas. We have seen consistently good localization of the radionuclide in histiocytic and poorly differentiated lymphocytic lymphomas (Table 6). On the other hand, the well-differentiated lymphocytic lymphomas have given positive scans much less frequently. Results in patients with mixed lymphocytic and histiocytic lymphomas and Hodgkin's disease are somewhere in between. Although the number of our cases of Hodgkin's disease is still small, as yet we can see no relation between the gallium uptake and the histologic classification in this disease (Table 7).

Table 3 shows a wide patient-to-patient range of gallium uptake for tumors of the same histologic type within the same patient. This inconsistency is illustrated by the scan of a 44-year-old woman with untreated Hodgkin's disease (Fig. 4) showing activity in tumors of the mediastinum and hilum of the left

TABLE 6
GALLIUM-67 SCANS OF PATIENTS WITH MALIGNANT LYMPHOMA

	Positive	Negative	Total
Lymphocytic			
Well differentiated	2	6	8
Poorly differentiated	4	1	5
Histiocytic	3	0	3
Mixed lymphocytic-histiocytic	3	3	6
Undifferentiated			
Pleomorphic	1	0	1
Burkitt-type	1	0	1
Total	14	10	24

TABLE 7
SCAN RESULTS IN HODGKIN'S DISEASE BY HISTOLOGIC TYPE

	Positive	Negative	Total
Mixed cell	11	4	15
Nodular sclerosis	4	2	6
Lymphocyte predominant	1	1	2
Lymphocyte depleted	0	0	0
Not classified	3	1	4
Total	19	8	27

lung but none in tumors of the iliac lymph nodes. Subsequent biopsy and assay revealed concentrations of less than 3% of the injected dose per kilogram of the pelvic tumor.

The obvious conclusion is that seeing gallium concentrated in only one tumor on the scan does not preclude the existence of other tumors. Hence it has been suggested that a tabulation of the actual number of lesions according to whether they were detected on scans would be more informative than merely recording as either positive or negative the scans for each patient on the basis of finding a single lesion. However, we believe that such a tabulation would introduce a bias of its own and would likely be even more misleading because of its guise of precision. Scans detecting only the most superficial lesions, such as cervical lymph nodes, are of little clinical use, yet these lesions are often numerous and are most readily detected on scans. If gallium scans have any role in the detection of tumors, it must be for locating lesions that are difficult or impossible to detect by other means. A tabulation of all known lesions, including those easily palpable or visible on routine X rays, would be strongly

Fig. 4 (a) Anterior photoscan of a 44-year-old woman with untreated Hodgkin's disease showing abnormal accumulation of ^{67}Ga presumably in tumors of the mediastinum and the hilum of the left lung. (b) Chest X ray of the same patient showing tumor of the hilum of the left lung. (c) Anterior photoscan showing no accumulation of ^{67}Ga in tumors of the left iliac chain of lymph nodes in the pelvis, although these could be palpated and were apparent on the lymphangiogram. (d) X ray of the abdomen and pelvis of the same patient after lymphangiogram and intravenous pyelogram showing distortion and blockage of the left iliac lymphatics due to tumors of Hodgkin's disease.

biased by the omission of those which are either impossible or difficult to detect, thus making gallium scanning appear more reliable than it actually is. It is against these difficult lesions that gallium scanning must be evaluated, and for this reason we look forward to studies comparing gallium scanning to other specific methods of detecting tumors in specified sites (i.e., the abdominal and pelvic lymph nodes and the central nervous system).

Gallium has been reported to concentrate in certain inflammatory lesions.^{29,30} These include pulmonary tuberculosis, lung abscess, and pneumonitis. We have seen three such examples of scans in which the gallium appeared to be concentrated at sites of inflammation and thus were interpreted as false positive for tumors. One was a man with multiple myeloma and a history of extramedullary tumors who developed an abdominal mass with bowel obstruction. Subsequent events have led us to believe the mass had been an abscess (Fig. 5). Another example was a woman with pseudolymphoma of the stomach thought to be due to a cytomegalic inclusion virus. Only after careful histologic examination was the correct diagnosis made. The third patient was a young man with Hodgkin's disease; a pulmonary infiltrate was seen on X ray at the time he was receiving chemotherapy. An area of abnormal activity seen on the scan corresponded to the infiltrate seen on X ray and was interpreted by the radiologist as acute pneumonitis.

CLINICAL USES

The inconsistent tumor uptake apparent from patient to patient and the differences between metastases within the same patient greatly restrict the usefulness of gallium scans in the initial staging of tumors. Clearly it should not be relied on alone to answer such crucial questions as whether a person has Hodgkin's disease involving the abdominal nodes. Nevertheless, some tumors that are very difficult or impossible to detect by other means short of exploratory surgery can be easily demonstrated by scanning with ^{67}Ga and without additional risk to the patient. For this alone gallium scans should be of considerable clinical use.

Deep in the midepigastrium near the celiac group of lymph nodes is an area of particular interest. A scan (Fig. 6) of a 9-year-old boy with a Burkitt-type lymphoma shows a tumor in this region in addition to tumors palpable in his neck and groin. At laparotomy the scan findings were confirmed, and the tumor was found invading the pancreas. The two pale areas on the picture are tumor nodules within an otherwise normal pancreas. The concentration of radioactivity in the tumor is evident on the gross autoradiograms. Radioassays showed the concentration of gallium in the tumor to vary from 49 to 68% of the injected dose per kilogram of tumor compared to 7% in the liver and 6% in the spleen and in the uninvolved adjacent lymph nodes. Later the same patient developed signs and symptoms of spinal cord compression. Lumbar punctures yielded no

Fig. 5 (a) Anterior photoscan of a 47-year-old man with a palpable mass in the lower abdomen which was probably an abscess due to ruptured diverticuli of the colon. (b) Anterior photoscan of the abdomen of a 66-year-old woman with a pseudolymphoma involving the stomach and omentum which was probably due to cytomegalic inclusion virus.

Fig. 6 (a) Posterior whole-body scan of a 9-year-old boy with Burkitt-type malignant lymphoma showing ^{67}Ga concentrated in palpable tumor of the neck and right inguinal area plus presumed tumor of the mediastinum and upper abdomen. (b) Biopsy specimen obtained at laparotomy on the same patient showing two distinct nodules of tumor (pale areas) embedded in the tail of the pancreas. (c) Gross autoradiogram of the same tissue showing the distribution of the radioactivity (dark areas) to correspond to that of the tumor in the biopsy specimen.

cerebrospinal fluid until after he had been treated with teletherapy, presumably because of extensive tumor of the spinal meninges. Scans failed to show the location of the tumor, or at least we were unable to distinguish it from the activity in the spinal vertebrae. In two other patients scans failed to show tumors affecting the central nervous system. One was a metastatic adenocarcinoma of uncertain origin located in the midthoracic region and the other was a glioblastoma of the brain. At autopsy the gallium concentration in the

glioblastoma was less than that in the blood. These cases raise, but do not answer, the disconcerting question as to whether ^{67}Ga will cross the blood-brain barrier to concentrate in tumors of the central nervous system. If not, this is quite different from the other tumor-scanning agents that are presumed to be transported bound to plasma proteins.

We believe a particularly important role for gallium scans will be in the assessment of treatment, especially radiotherapy, and in the periodic post-therapy evaluation of patients. Figure 7 shows the scans of a 66-year-old man treated elsewhere for squamous carcinoma of the lung with an inadequate dose of cobalt teletherapy. Although ostensibly told he had been cured of his tumor, he was seen by a second physician who advised him to have further evaluation, including a gallium scan. The scan clearly shows increased concentration of the gallium in the left lung. One week later a pneumonectomy was done which revealed a viable carcinoma at the site indicated on the scan. Assays of the surgical specimen showed a tumor concentration of 13 to 14% of the injected dose per kilogram of tumor compared to 2% in the surrounding atelectatic lung and 1% in the normal lung tissue.

The two scans shown in Fig. 8 show the unfortunate progress of a malignant lymphoma of mixed histiocytic-lymphocytic type in a 52-year-old woman. The first scan was made just before radiation therapy. She then received 2500 rads of ^{60}Co teletherapy to the area indicated in the scans. The second scan shows no evidence of gallium concentrated within the field of irradiation, but clearly a great deal is in tumor located outside the treatment area.

Kaplan³¹ and others have advocated extensive or even total lymph node irradiation for stages I to III Hodgkin's disease. With this form of therapy, greatly improved survival rates and frequent cures have been reported. After approximately 4000 rads, all the tumor within the irradiated areas is believed to have been eradicated, and any recurrences are presumed to be due to a failure to include all the tumors in the field of radiation. It is for this reason these investigators have recommended exhaustive staging procedures to ensure that all the tumor is exposed to the curative dose.

Nevertheless, there continue to be cases that relapse after a brief period of apparent remission. Many of these must have foci of disease outside the fields of irradiation and too small to be detected by present techniques. Since ^{67}Ga is unlikely to extend our ability to detect tumors down at the level of a few cells, it may not add a great deal to a thorough exploratory laparotomy and lymphangiography for assessment of abdominal involvement. However, lesions outside the abdomen, for instance, in the mediastinum and bone marrow, may be found with the gallium scan and completely missed by other staging procedures. After therapy an exploratory laparotomy every 3 to 6 months in search of recurrences is not feasible. We believe gallium scanning will play a significant role in detecting small solitary lesions that can still be treated with local radiation without causing further bone-marrow depression as often occurs when chemotherapy is begun after extensive marrow irradiation.

Fig. 7 (a) Posterior whole-body scan of a 66-year-old man with residual carcinoma of the left lung following an inadequate dose of teletherapy. The scan shows an accumulation of ^{67}Ga in the tumor in contrast to the remainder of the atelectatic lung. (b) Anterior photoscan of the chest of the same patient.

(a)

(b)

Fig. 8 (a) Anterior photoscan of a 52-year-old woman with a malignant lymphoma, mixed cellular type, showing ^{67}Ga concentrated in tumors of the left axilla and supraclavicular regions. She was subsequently treated with 2500 rads of ^{60}Co teletherapy to the areas included in the broken lines. (b) Scan made 6 weeks after the completion of the radiation therapy shows more tumor now involving the mediastinum and right axillary lymph nodes but no tumor uptake of gallium within the radiation fields.

Figure 9 shows a scan of a woman treated with ^{60}Co teletherapy at doses of 4000 rads to all lymph-node-bearing areas of the trunk and the neck for stage III Hodgkin's disease. Three months following completion of the therapy, a scan was made which showed an area of increased activity near the anterior-superior-iliac spine outside the radiation field. Careful X-ray examination later confirmed the presence of a lesion in the bone. The lesion was subsequently irradiated, and the patient continues to do well.

Fig. 9 Anterior photoscan of a 45-year-old woman who had just completed a course of extensive ^{60}Co teletherapy as treatment of stage III Hodgkin's disease. The scan shows a small focus of activity near the left iliac crest which was later detected as tumor on X ray but not previously suspected.

The 30-year-old woman shown in Fig. 10 was initially treated for stage II Hodgkin's disease with 4000 rads to the cervical, supraclavicular, axillary, and mediastinal areas. She was later shown to have involvement of the para-aortic lymph nodes. The radiotherapist retreated her with 4000 rads of cobalt teletherapy to the para-aortic, iliac, and inguinal lymph node areas. To avoid a "hot spot" where the mediastinal and epigastric ports might overlap, he allowed a 2-in. gap between the ports. One year later the patient was sent to us for scans because of systemic symptoms suggesting a relapse of her disease. The scans showed a distinct focus of activity located precisely in the gap between the two ports of irradiation. On exploratory laparotomy the scan findings were confirmed, and she obtained relief of her symptoms with excision of the tumor followed by radiation to the area.

Fig. 10 Anterior photoscan of the chest and upper abdomen of a 30-year-old woman treated for stage III Hodgkin's disease with irradiation to all lymph-node-bearing areas but at different settings and with the upper abdominal radiation ports separated from the mediastinal port to avoid overexposure to the overlapping fields. The scan shows ^{67}Ga accumulated in tumor involving lymph nodes precisely in the area between the two fields of radiation.

SUMMARY

Scanning augments the diagnostic armamentarium of clinicians treating cancer patients. Although many tumors can be located by scanning specific organs (i.e., brain, liver, and bones), others are better demonstrated with more-general tumor-scanning agents. Of these, ^{67}Ga and possibly ^{111}In hold the greatest promise of continued clinical usefulness. Gallium-67 appears to show greater tumor uptake in certain lymphomas and squamous-cell carcinoma of the lung and will probably find its greatest clinical application in detection of occult neoplasms and in the posttreatment follow-up evaluation of cancer patients, especially those with Hodgkin's disease and other lymphomas following radiotherapy.

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RADIOLOGIC METHODS IN THE DIAGNOSIS OF NEOPLASTIC DISEASE

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ABSTRACT

Four radiologic modalities can be used in the diagnosis of human disease: roentgenography, nuclear imaging, ultrasound, and thermography. The roentgen radiographic system is comprised of image-forming and image-recording systems. These systems are described, and the diagnostic method applied by the radiologist is reviewed. Examples illustrative of the use of roentgenography in modern cancer diagnosis are given, and the history of roentgenography in screening of populations is reviewed. Roentgenography and nuclear imaging are briefly compared as to their effectiveness in certain instances, and areas for future attack are indicated.

Four principal modalities can be used for human diagnostic radiography: roentgenography, nuclear imaging, ultrasound, and thermography. Although interesting observations have been made about the properties of the last two, roentgenography and nuclear imaging are the techniques of major clinical importance in the discovery and identification of neoplastic disease. I will consider some of the general and special roentgenographic tests for detecting cancer.

The radiographic system is comprised of the image-forming system, which consists of an emission tube and the patient, and the image-recording system.

In the image-forming system, a vacuum emission tube sends a beam of photons of variable energy and quantity toward the part of the patient's body which is to be examined. Collimators and cones are used in an effort to confine the radiation beam to the tissue volume of interest. As the collimated beam of photons passes through the patient, some photons are absorbed and some are not. Those photons which are not absorbed pass through the patient and are removed by a device, such as a grid, which is used to remove stray and scattered radiation. The photon beam next strikes a sensitive recording surface, such as a film, a fluorescent screen, or the input phosphor of an electronic image

amplifier, and an image is registered that shows the pattern of transmission and absorption of the photon beam. Dense, and therefore highly absorbing, structures cast shadows on such a radiograph. Less-dense structures produce less-intense shadows, generating a range of densities on a roentgenogram which records exquisitely fine anatomic detail. There may be, for example, 10^5 to 10^6 information bits per square centimeter on a chest film.

Most roentgenographic diagnoses are made with static images recorded on photographic film. In a given examination a third dimension may be supplied from exposures made in several anatomic projections, as, for example, anteroposterior and lateral or stereoscopic. A fourth dimension, time, occasionally furnishes additional useful information.

There are also occasions when it is necessary to know whether a certain organ or tissue has maintained its inherent motility and pliability. Under these circumstances a continuously visualized or dynamic image, such as might be obtained with fluoroscopy, is used. Fluoroscopy may also be used when circumstances require the passage of a catheter to provide contrast opacification of the cavity of a viscus or of the lumen of a blood vessel. Fluoroscopic images are of relatively low information content compared with static roentgenograms because of the need to minimize the radiation dose to the patient during a long, continuous exposure. However, fluoroscopic images can be amplified by an electronic system, and these amplified images can then be presented on a television monitor for viewing. Hence permanent records of a fluoroscopic examination may be recorded on video tape or cinefilm.

In performing his interpretation, the radiologist acquaints himself with the patient's relevant history and with his physical and laboratory findings. He then displays the record of a given examination and scans it visually, looking for significant asymmetries and inappropriate density edges. He compares the sum of what he sees with his entire recall of the variations of normal in the system he is studying. His first decision is whether the patient's condition is normal or abnormal. Having established a certain pattern as abnormal, the radiologist attempts to classify the finding by determining whether the patient's abnormality is congenital or developmental or acquired (traumatic or of physical origin, inflammatory or granulomatous, metabolic or endocrine, vascular, or neoplastic). If one of the logical compartments is neoplastic, the radiologist then attempts to determine whether it is benign or malignant (primary or metastatic). Thereafter he attempts to identify his finding as a tumor, which logically might be found in the area under study. The diagnostic process is a systematized one involving the selection of entities on the basis of probability. It therefore lends itself to computer analysis, as Lodwick and his colleagues¹ have shown with

Figure 1-10.

What are the findings that lead an observer to the conclusion that he is dealing with a neoplastic process? They have to do with the nature of cancer itself.

Neoplasia has been defined by Fallis² as an autonomous new growth of tissue that is excessive and uncoordinated with the rest of the body. There is no definite limit to the growth, and the resultant mass of tissue is not useful to the body. In fact, the mass is usually detrimental and may be highly injurious or fatal. The growth of the mass may be more rapid than normal. A distinction between benign and malignant tumors is that malignant ones will invade neighboring tissues directly and may spread to distant sites through lymph channels or via the bloodstream.

If a tumor is situated wholly within its primary site on an outer surface of the body, a roentgenographic study contributes little to the assessment of its properties. However, if the tumor is beneath a body surface or if it is on an inner surface, this modality becomes cardinally important.

Tumor appraisal in its simplest form is illustrated in Figs. 1a, 1b, and 1c. Figure 1a is a roentgenogram of a normal female breast. One sees shadows of differing densities attributable to the air that surrounds the breast, the skin that covers it, and the various fatty, stromal, and parenchymal tissues that comprise its structure. Figure 1b differs from Fig. 1a in that an inappropriate density edge appears at the arrow, within an otherwise normal breast, and it therefore represents some sort of new growth. The tumor shadow is round in outline, and its edge is smooth. It appears only to displace the surrounding normal tissue, and therefore it has the properties of a benign tumor. Histologically it was a fibroadenoma. Figure 1c also shows a mass, but it has ill-defined margins with processes that extend in an irregular manner into adjacent soft tissue. It is possible to envision this shadow as one cast by a growing mass invading neighboring tissue. This property is shared by several kinds of disease, including certain inflammations and infections, but it might also represent a malignant neoplasm.

In the chest film of the patient shown in Fig. 2, there is an asymmetry in the appearance of the two lung fields which is principally represented by a mass shadow within the upper right lung. Certain granulomatous and inflammatory lesions might present this appearance, but a neoplasm is the most ominous possibility. The radiologist also takes into account whatever pertinent secondary findings are available to him. Here the right lung appears emphysematous compared to the left one, and there is relative depression of the right diaphragmatic leaf with respect to its anticipated normal height. Could this represent air trapping, the result of bronchial compression by an otherwise invisible mediastinal lymph-node metastasis from a bronchogenic carcinoma? The radiologist would undoubtedly report to his referent that bronchogenic carcinoma was the most likely diagnosis and that tumor spread might already have occurred.

In Figs. 1a to 1c breast fat provided a background that supplied contrast and permitted the observer to distinguish the abnormal mass shadows cast by both the benign and malignant tumors. For the lung, air furnished contrast for the identification of the edge and of the different density of the tumor mass.

For an osseous tumor, the surrounding soft tissue and the bone itself may supply contrast, but in very few other locations within the body are there normally occurring differential densities that may reliably be used to find mass lesions. Natural contrast must therefore be enhanced in some manner so that the mass lesion can be visualized more or less directly. Air or other gases of lesser absorbing density, such as carbon dioxide or nitrous oxide, may be used occasionally, but contrast is usually created by introducing into the body a substance containing an effective absorber of radiation. The heavy elements barium and iodine are the most commonly used. Agents containing these materials can be swallowed by the patient, insufflated into the upper airway and bronchial tree by the physician, or introduced retrogradely into the large bowel or the urinary tract. Direct introduction of radiopaque contrast material was originally used to study tumors located on or about accessible internal body surfaces.

By way of illustration of this concept, Fig. 3a shows the ordinary range of air, soft tissue, and bone densities available in a frontal projection of the neck. The delicate structure of the larynx, composed of cartilage and soft tissue, cannot be seen. However, when an opaque material, such as an iodized oil, is introduced skillfully in the upper airway, the remarkable detail seen in Fig. 3b comes into view. Note the excellent definition of the regions of the true cords, ventricle, and false cords shown in this contrast laryngogram made during phonation. With the knowledge of normal anatomy gained from this roentgenogram, the abnormalities inherent in Fig. 3c (arrows) become readily apparent. The upper three arrows show that the folds and convolutions representing the true and false cords and ventricle have been obliterated by some sort of mass process that also has elevated and displaced the partially contrast-filled left piriform sinus. The lowest arrow shows a contrast-coated tumor projecting into the subglottic tracheal lumen. As a result of its impingement upon and obliteration of normal structures, we have been able to deduce the presence of an extensive, but otherwise roentgenographically invisible, laryngeal squamous-cell carcinoma.

Physicians and experimentalists have long studied the gastrointestinal tract of man by introducing radiopaque suspensions both from above and below. Although bismuth was the original radiopaque principle, barium sulfate is now the usual agent for identifying neoplasms that arise on or near the surface of the gastrointestinal tract.

Figures 4a and 4b show the compelling need for additional contrast in evaluating that part of the gastrointestinal tract which lies within the abdomen. Figure 4a represents an anteroposterior roentgenogram of a normal abdomen. Note the relatively homogeneous soft-tissue detail with but slight contrast afforded by body-wall fat and swallowed air. Figure 4b is a dramatic demonstration of the contrast method for identifying a disease process involving the colon. Barium sulfate was introduced in a retrograde manner. The patient in question had had a right colectomy in the past for neoplastic disease, and certain

Fig. 1b

Fig. 1a

Fig. 1a Lateral view of the left breast. Note normal detail defined by breast parenchyma, fat, and fibrous connective tissue.

Fig. 1b Lateral view of the left breast showing normal structures except for peripherally well-defined nodule at arrow. Biopsy diagnosis, fibroadenoma.

Fig. 1c Lateral view of the left breast showing a nodular lesion (arrow). Note that its margins are indistinct and that stellate processes extend into the surrounding breast fat. Biopsy diagnosis: adenocarcinoma of the breast.

Fig. 1c

Fig. 2 Posteroanterior view of the chest, one of a series made to study the growth of the round mass above the hilum of the patient's right lung. Supraclavicular lymph-node biopsy diagnosis was squamous-cell bronchogenic carcinoma.

clinical findings suggested that a second primary neoplasm might have developed in his colon remnant. That one is probably present is confirmed by the presence of a lesion (arrows, Fig. 4b), which behaves as if it involves the colon circumferentially, narrowing its lumen, distorting its normal mucosal pattern, and bulging into the barium column above and below the lesion. This behavior is characteristic of adenocarcinoma of the colon, and this lesion was so identified after its subsequent removal.

Note also in Fig. 4b that there are areas of lesser radiographic density in the splenic flexure and in the sigmoid, representing air or retained normal bowel content. Although these areas might, in fact, represent solid lesions within the

colon, the examining physician had already ascertained that they did not because he had performed the study in question not only with films but also with the fluoroscope. During the fluoroscopic portion of the examination, he had determined to his satisfaction that the various areas of diminished radiographic density were freely movable within the lumen of the bowel and even miscible with the barium sulfate suspension. He had also observed that the area of tumor involvement of the bowel was not movable, but it seemed fixed to surrounding structures as he palpated it during the course of his fluoroscopic examination.

Esophageal, gastric, and small bowel tumors may also be identified by the same general sorts of findings. Fluoroscopy is often important in the examination of the stomach because some carcinomas do not bulge into the lumen but instead insidiously infiltrate gastric walls, and these may be manifested only by impairment of normal gastric pliability.

The urinary tract is also accessible from an external body surface, and contrast material can be injected into it in a retrograde fashion for the study of pelvocalyceal systems, ureters, and bladder. However, the urinary tract is more commonly studied after the intravenous administration and selective urinary excretion of one of a number of iodine-containing radiopaque contrast materials. The excretory urogram has become the preferred screening test for anatomic visualization of the urinary tract in all kinds of disease states, including suspected neoplasia.

Figure 5 shows the urogram of a young woman with hematuria. Note the excellent definition of normal calyces and the renal pelvis on the patient's left side; also note the displacement of the calyces of the right kidney by something that has the characteristics of a spherical soft-tissue mass (arrow, Fig. 5). Although there are occasionally some other signs, such as the presence of visible calcium deposits, which can serve to indicate to the radiologist whether or not he is dealing with a malignant tumor, there is very little more he can do on the basis of the urogram to help his referent decide whether he is dealing with a benign process or a malignant one. By opacifying the renal vasculature, however, he can acquire the additional information he needs to make this decision, as we shall see later.

The biliary system presents even more formidable problems. Radiopaque material can be introduced into the biliary duct system by inserting a needle through the skin into the substance of the liver, but this technique has limited applications. Instead, a group of pharmaceuticals has been developed that may be administered by mouth or intravenously. These drugs, which also contain iodine as their opaque component, are secreted preferentially by the liver into the biliary system and are concentrated by the gall bladder. Cholecystography and cholangiography have been used extensively as diagnostic screening procedures for the evaluation of tumors in and about the liver and the head of the pancreas.

Fig. 3c

Fig. 3a Anteroposterior film of the neck showing a normal range of osseous, soft tissue, and air densities. The air is in the midline within the tracheal and laryngeal structures. Little soft-tissue anatomic detail is present.

Fig. 3b Anteroposterior laryngogram made after the insufflation of an oily, iodized contrast material. This substance coats the surfaces of the upper airway, revealing soft-tissue detail, such as the arytenoid, true and false cords, and ventricles. Compare with lack of visible detail in Fig. 3a.

Fig. 3c Anteroposterior contrast laryngogram of a patient with chronic hoarseness. Note obliteration of normal anatomic detail along patient's left, as indicated by the three arrowheads. This represented a proven squamous-cell carcinoma of the larynx involving arytenoid, true and false cords, and obliterating of the ventricle. The tumor bulges into the subglottic trachea, and its inferior margin can be seen at the single arrow.

Fig. 4a Anteroposterior film of a normal abdomen. Note the range of contrasts and densities afforded by soft tissue and bone. Further detail is provided by air in the upper and lower gastrointestinal tract. Except for fortuitous contrast circumstances, even large tumor masses can escape detection.

All the tests described in this paper are commonly used, and they have been further modified and improved by the incorporation of such techniques as three-dimensional filming, body-section radiography, cinefilming, video-tape recording, and others.

The emergence of contrast angiography and its development from a general to a selective technique has been one of the most important contributions to oncologic radiology. Angiography, with rapid serial filming, is the definitive method for the diagnosis of most intracranial tumors; it ensures the decision between the benign and malignant nature of renal masses, it contributes significantly to the identification of hepatic neoplasms, and it lends some aid in the identification of pancreatic tumors. Angiography has been applied to the study of almost every kind of neoplasm, and important information about tumor blood supply and the extent of tumor growth has been derived from this kind of study.

Fig. 4b Example of a malignant neoplasm presenting upon an internal body surface. This film was made during the course of a barium enema and shows the "apple-core" deformity of an annular adenocarcinoma of the large bowel (arrows). Some esophageal, gastric, and small bowel tumors have this appearance. Note the rounded dense, soft-tissue shadow in the patient's right upper quadrant. This is the site of a colostomy remaining after the removal of a previously identified adenocarcinoma of the cecum.

Figure 6 illustrates the way in which angiography can be used to identify a tumor. The neoplasm, a meningioma, is easily seen because of the abundant contrast material within its profusion of capillaries (arrows, Fig. 6). However, most intracranial neoplasms are not so richly vascular, and they are usually identified only by displacement of opacified arteries. These displacements may be so minor as to be perceptible only to a physician with a profound knowledge of the anatomy of the central-nervous-system vascular tree.

Fig. 5 Anteroposterior film of the abdomen made during the course of a retrograde urogram after withdrawal of the ureteral catheters. Left pelvocalyceal system, both ureters, and the air- and contrast-filled bladder are normal. Note air bubbles in the upper left ureter. The right pelvocalyceal system is deformed by a round mass which displaces calyces and which has partly obstructed the upper pole calyceal system, evidenced by calyceal dilatation.

Another common field in which selective arterial angiography is used is in the study of renal masses. Figure 7 shows such a mass arising from the lower pole of the right kidney. On a preceding excretory urogram, it would merely be identified as a mass, as in the study shown in Fig. 5, but the important decision of whether it is malignant or benign could not be made. The arteriogram in Fig. 7, however, shows many abnormal vessels about the margin of the mass and those entering its substance (arrows). These are "tumor" vessels and identify the mass as a hypernephroma.

The venous system may be studied selectively as well. In the examination illustrated by Fig. 8, the radiologist has advanced a catheter into the left inferior adrenal vein, and by this route he has injected contrast material into the vascular bed of a functioning (aldosterone-producing) adrenal cortical adenoma whose margins are indicated by the arrow.

Fig. 6 Lateral view of internal carotid arteriogram made after the direct injection of an iodized water-soluble contrast material through a needle introduced into the internal carotid artery. Many opacified arteries are shown. An indistinctly margined, but obvious, "pool" of density, indicated by the arrows, constitutes opacification of the rich capillary bed of a proven meningioma.

Figure 9 is the venous phase of a selective splenic arteriogram; it shows that the spleen is opacified and that contrast material has filled the splenic and portal veins. The only abnormal finding in this study is indicated by the arrow, which points to an impression on the inferior surface of the splenic vein near the body midline. Although it is the sole available evidence of the presence of a pancreatic carcinoma, it is significant evidence that led to the identification and removal of this otherwise obscure neoplasm.

Many neoplasms metastasize through the lymphatic system, and, therefore, it was logical that a diagnostic radiologic technique would be developed for the study of lymphatics and lymph nodes. This technique is called lymphangiography and is widely practiced; it contributes to the appraisal and clinical staging of various entities, such as lymphomas, testicular tumors, and cervical carcinomas. Figure 10 shows a woman with recurrent Hodgkin's disease; lymphatics of both feet have been cannulated, and an iodized oil has been injected into the lymphatics of the lower limbs. A chain of normal lymph nodes appears on the patient's right side (reader's left). Note that they are compact and finely granular. However, the lymph nodes on the patient's left are abnormal because of changes produced by Hodgkin's disease. They are large, irregular in

Fig. 7 Selective right-renal arteriogram showing normal arteries supplying a normally opacified right-renal upper pole. A mass arises from the lower pole of the right kidney, and an arcade of irregular vessels (arrows) enters the upper portion of this mass. These are tumor vessels within a proven renal adenocarcinoma.

outline, and have lost the homogeneity of texture that characterizes the normal nodes on the opposite side.

These, then, are illustrations of the ways roentgenography can be used in the diagnosis of tumors.

But one may ask, if roentgenologic studies are effective for discovering occult neoplasms, why not develop survey techniques to be used for the detection of various kinds of tumors in large population groups? As a matter of fact, experiments of this sort have been conducted for more than 30 years.

On many occasions chest physicians and radiologists have proposed chest X-ray surveys for the identification of lung cancer. At one time such surveys were by-products of population studies aimed at the detection of tuberculosis. Recently, however, radiologists have begun to question indiscriminate use of even diagnostic quantities of ionizing radiation, and physicians in general have

Fig. 8 Selective left-adrenal venogram. Note opacification of a small oval tumor (arrow), which was later shown to be an adrenal cortical adenoma. This was an aldosterone-producing tumor.

begun to turn to skin testing as the medium for tuberculosis surveys. Restudying the yield of lung cancers from tuberculosis chest film surveys of all kinds indicates that, although the unit cost per examination is relatively low, the cost per cancer discovered, about \$1,000, is rather high.³ It is likely that chest roentgenography might better be used as part of periodic health maintenance examinations of patients in appropriate age groups and with histories of exposure to lung carcinogens.

Some interesting experiments have been conducted with routine survey for the detection of cancers of the gastrointestinal tract. It was realized that the symptoms of carcinoma of the stomach were not proportional to the extent of the disease, and it seemed that, if resectable, curable cancers were to be discovered, some sort of routine survey of an asymptomatic population would have to be undertaken.

Several such studies were indeed performed, including extensive ones conducted by Morgan⁴ and by Sherman⁵ and their groups. These investigators used photofluorographic survey films made after the ingestion of barium sulfate, followed by routine examination of the upper gastrointestinal tract by more conventional methods in those patients in whom such follow-up seemed to be indicated. In each of these two series, the yield of gastric carcinomas was less

Fig. 9 Anteroposterior film of upper abdomen which was part of a series made after the intra-arterial injection of contrast material through one of the catheters seen in the abdominal midline. The contrast material is in its venous phase, and the principal vessels opacified are the splenic and portal veins. The arrow points to a smooth impression on the inferior surface of the splenic vein by a later proven adenocarcinoma of the pancreas. Note contrast material in the renal collecting systems from previous arterial contrast studies.

than one-half of one percent of the patients studied, and, in terms of modern economics, the cost per cancer discovered might be of the order of \$20,000 or more. Not only were these studies expensive but they also required the services of a very large number of health professionals, including physicians.

Amberg et al.,⁶ reporting the results of the Minnesota group, found a higher yield of carcinomas, especially early operable ones, when survey methods were used selectively in patients who had such ominous findings as achlorhydria and melena. The number of operable cancers was still small. Finally, Bonte and Friedell⁷ studied a group of symptomatic patients. Although our yield of carcinomas was about 1.5%, many of the lesions discovered were late, inoperable ones. Because of these discouraging results, broad population surveys for upper gastrointestinal neoplasms did not flourish, and the gastrointestinal series has been returned to the work-up of patients showing pertinent early signs. Furthermore, the pressure for the development of a screening method for the detection of gastric carcinoma has diminished because of the apparent decline in the incidence of this form of cancer.

Fig. 10 Right posterior oblique film of the pelvis made during the course of lymphangiography (see text). The chain of normal nodes at the reader's left is compact, coalescent, and finely granular. The nodes at the reader's right are coarsely mottled, and some are fragmented. Others present an inhomogeneous "foamy" appearance. All are abnormal and are involved by the patient's known Hodgkin's disease.

Although as many as three-fourths of the rectal and colon cancers can be detected by digital or conventional endoscopic examinations, the remainder are too high to be found in this manner. In 1951 Wyatt⁸ attempted to develop a survey technique involving self-administration of a small-volume barium enema; photofluorograms were made after evacuation. Technical problems and a low yield of positive diagnoses combined to halt this effort as well.

After many years of dormancy, mammography was finally popularized as a survey technique to be applied against a population of women with breast nodules. Gershon-Cohen and Strickler⁹ and Egan¹⁰ demonstrated the value of this procedure, and it is a valuable part of modern tumor radiography.

As you have observed, roentgenography is not an omnipotent tool for the discovery of occult neoplasms. For example, nuclear imaging affords a superior method of screening patients thought to have intracranial space-occupying lesions. The colloid liver scan remains a better screening method for the detection of hepatic neoplasms than more costly and morbid roentgen alternatives. Neither has provided a thoroughly satisfactory approach to such entities as primary tumors of the pancreas, soft-tissue sarcomas, and certain

mediastinal lesions. Therefore, although a great deal has been accomplished and many sophisticated techniques have been developed, much remains to be done in the field of radiologic diagnosis of neoplastic diseases.

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EDITOR'S NOTE

Discussion of valuable techniques, such as thermography and biopsy procedures under fluoroscopic guidance, has been omitted. The former seems to be the best available test for the detection of minute nonpalpable breast carcinomas that do not cast an abnormal shadow on mammograms. The latter has proven to be the best technique for cytological confirmation of bronchial carcinomas when sputum, bronchoscopy, and bronchial-washing studies have failed to establish the nature of a lung abnormality. Recent technical refinements of fiberoptic instrumentation (duodenoscope and colonoscope), assisted by fluoroscopy, will provide preoperative positive histology of gastrointestinal neoplasms; at present only a presumptive diagnosis can be made from the conventional radiological examinations.

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DISCUSSION: GENERAL

Comas: Dr. Edwards, have you tried to image lymph nodes by giving ^{67}Ga or some other isotope intralymphatically?

Edwards: Yes we have. One of the problems of detecting small lymph nodes in the abdomen is the fact that the small tumors compete so unfavorably with the large liver and bowel. We thought this could be resolved by giving the gallium directly intralymphatically. Then we might deliver larger concentrations of gallium to the abdominal lymph nodes than to these other organs that have access to the gallium after intravenous injection. In the five or six cases done so far, we cannot claim any great success. Our first attempt was very naive; we gave ^{67}Ga as the citrate directly into the lymphatics, and the gallium never reached the inguinal lymph nodes because the lymphatic ducts are so permeable. The gallium quickly diffused into the blood. Later we mixed gallium with the patient's serum in vitro to get it bound to plasma proteins. By injecting this preparation, we were able to fill the lymph nodes in the upper abdomen as seen with the Anger camera. Over the next few hours, however, gallium left the lymph nodes. Later we found no difference in distribution from that after an intravenous dose. In fact, lesions far from the chain of lymphatics concentrated the gallium every bit as well as those in the nodes of the pelvic chain.

Comas: Apparently the answer is that it really does not work.

Ross: We are interested in the instrumentation problems involved in these radionuclides. Indium-111 has come to the attention of some investigators as a possible tumor-seeking agent, but it has two advantages and one disadvantage. One advantage reported to me at the Miami meeting last week was that ^{111}In (half-life, 2.8 days) localizes well in human tumors but, unlike gallium, does not hang up in the normal gut. If this can be substantiated, its advantage over gallium in the abdominal area might be considerable, especially since the gamma emission of ^{111}In should be less troublesome in scanning procedures, and thereby a second advantage, than that of ^{67}Ga . Against this, work in the smaller animals (if I remember it correctly) indicates that the concentration ratios of tumor to normal tissue are considerably less favorable with indium than with gallium. Has anyone here information that would help weigh the pros against the

cons regarding the use of ^{111}In in human neoplastic disease? If this nuclide looks promising, perhaps our group at Oak Ridge National Laboratory should carry out a scattering study similar to that done with ^{67}Ga (D. A. Ross, W. J. McClain, J. K. East, and P. R. Bell, Multiple-Window Spectrometry for Gallium-67, USAEC Report ORNL-TM-3260, Oak Ridge National Laboratory, 1971) with the aim of determining an optimum spectrometer policy for the scanning of ^{111}In in human patients. A fairly simple system should be possible.

Wagner: I would like to ask about studies that have been done in patients comparing ^{111}In with ^{67}Ga . It seems to me that there is a need to do paired studies in the same patient because we all know that there are considerable differences in the behavior of human neoplasms and animal tumors. Dr. Edwards, have you done such a comparative study in humans?

Edwards: I regret that we have not. I would second what you said, Dr. Wagner, that there is considerable difference in species. Of course, chemically indium is very closely related to gallium, and it occurred to us quite early that indium might do just as well as gallium. Dr. Hayes quickly went to the animal model, and we studied several animal tumors in this regard. In all the animal tumors, gallium was superior to indium in terms of tumor/nontumor ratio. For this reason we did not embark on a comparative study. At that time we were not really aware of the other studies going on with ^{111}In . Also, on the basis of animal data in the literature, there was no reason to suspect that indium would not be excreted in the bowel, and it is news to us that indium does not follow gallium in this regard. Again we have no human data on this matter. In the rat it is not true since a great deal of indium is excreted in the bowel. Our animal tumor model may be quite different, and the behavior of indium in terms of excretion in the rat bowel must be quite different from that in humans.

Chairman:

S. James Adelstein

*Peter Bent Brigham
Hospital*

Henry Wagner, Jr.

*Johns Hopkins Medical
Institutions*

Harry Mellins

Harvard Medical School

PANEL DISCUSSION

DETERMINING THE UTILITY OF NUCLEAR MEDICAL AND RADIOLOGIC PROCEDURES

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ABSTRACT

This paper attempts to focus on some criteria for determining the utility of roentgenographic and nuclear medical procedures. These include the demonstration that the procedure provide new diagnostic information in the clinical settings in which it is used and that the new information be translated into improved patient care, at least in some instances. In addition, the statistical validity of each test should be appreciated by the referring physicians; a method of tabulating the statistical validity is supported which expresses the conditional probability that a given interpretation indicates the presence or absence of disease. Last, it is suggested that in a world of finite medical resources it is not only necessary to define the relative utility of various diagnostic tests but it is also desirable to identify the clinical situations in which they are likely to be most useful.

The objective of this symposium has been "to help the practicing physician evaluate the usefulness of radioisotopic methods as compared with radiologic techniques and laboratory tests." The focus has been on the relative value, the limitations, and the failures of individual procedures. The format has been that of advocacy with a radiologist, one or more practitioners of nuclear medicine, and a physician or surgeon sharing the platform. The representatives of nuclear medicine and radiology as producers have shown wares and confronted each other in attitudes ranging from complementarity to competitiveness. The internists and surgeons have served as critics and consumers. Their interest is in fulfillment (or lack thereof) rather than of promise, and they provide the practical perspective for a critical comparison of diagnostic techniques.

In this final panel session we shall attempt to establish criteria for the evaluation of radioisotopic and roentgenographic procedures and to determine the circumstances and timing for their application.

The contemporary methodology of nuclear medicine and radiology epitomizes the application of technology to clinical medicine. In a country now

beginning to realize that its medical resources are not infinite and that the march of technology is not always beneficial, it is reasonable to ask searching questions of these two specialities. The position has been succinctly stated by John Knowles:¹ "... the hazards of excessive technologic development are perhaps nowhere better demonstrated than in the field of radiology [including nuclear medicine]. On the one hand, technologic developments make new things possible or facilitate the achievement of present objectives and events ... [On the other hand] the substitution of the means of technologic development for the ends of improving the health of the American people so that technologic development and the mass production of X-ray examinations become the end measure of our effectiveness is a constant danger." Thus practitioners must be constantly on their guard to avoid the "capacity fallacy":² the notion that because we can do something we necessarily ought to do it.

The development and application of costly and time-consuming techniques should be based on a priori justifications and necessities. In the applied science of medicine, it is not sufficient to strive for a goal just because it is achievable, nor is it justifiable to maintain a procedure that is obsolete or uninformative. One clearly must establish developmental priorities with regard to time, manpower, and money. Once a procedure is developed, it is imperative that its clinical value be realized in the shortest interval. It must be determined whether the new procedure provides new diagnostic information, whether the new information will affect patient care, and to what extent the examination is statistically valid.

Various approaches have been used to determine the extent of new diagnostic information provided by a particular test. In one such evaluation we measured the extent to which the thyroidal radioiodine uptake test provides new diagnostic information.³ The ability of clinical manifestations to predict the outcome of the test was determined by having both a programmed computer and several physicians evaluate a list of 39 signs and symptoms relating to thyroid disease for each patient. On analysis of the list, the computer was able to predict the test result 79% of the time and the physicians only 60% of the time. It was clear that this test was providing new information not readily derived from the history and physical examination alone in 21 to 40% of patients suspected of having a thyroidal disorder.

If the information provided by the new tests leads to more appropriate management, the procedure can be deemed beneficial as well as informative. For example, the new information provided by some nuclear medical procedures is often used as a determinant for further testing or for hospital admission. In these instances a normal study (or a study in which deviations from normality are readily explained by previously recognized disease) not only reassures the physician but also may save the patient and his fellow consumers a costly and time-consuming hospitalization.

We test for new diagnostic information under the assumption that the new information is correct. Actual determination of statistical validity requires

further analysis. This subject has been the object of considered analysis.⁴ In his Shattuck lecture on roentgenographic diagnosis, Sosman⁵ attempted to assign some probabilities for his ability to demonstrate disease and to identify it etiologically or histologically. In the lung he felt he could detect 95% of lesions capable of producing or apt to do harm to the patient; in the gastrointestinal tract he estimated the detectability as 80 to 85%. Of the demonstratable lesions in the lung, 75 to 80% could be identified correctly, whereas in the gastrointestinal tract, 90% of those found could be appropriately designated. Of course, these figures describe the chances of detecting and identifying a disease entity given that it is present; they fail, as do all such statistics, to estimate the probability that a patient has a specific disease entity given certain roentgenographic findings.

TABLE 1
HEPATIC SCINTIGRAPHY IN PATIENTS SUSPECTED
OF HEPATIC CANCER*

	Scintigraphic signs of cancer	
	Present	Absent
Total with hepatic cancer (351)	333	18
Total without hepatic cancer (197)	69	128
True positive = $P(s+ c+) = \frac{333}{351} = 0.95$; false negative = $P(s- c+) = \frac{18}{351} = 0.05$		
False positive = $P(s+ c-) = \frac{69}{197} = 0.35$; true negative = $P(s- c-) = \frac{128}{197} = 0.65$		

*From W. M. Nagler, M. A. Bender, and M. Blau, Radioisotope Photoscanning of the Liver, *Gastroenterology*, 44: 36-43 (1963).

An identical situation exists in nuclear medicine. An example is the use of liver scans for the diagnosis of hepatic malignancy.⁶ In this study 1034 cases were referred for scintigraphy because cancer of the liver was suspected. Of these, 950 were followed, and a definitive diagnosis was established in 548. The results are summarized in Table 1 and are not very different from the results obtained by others. The data have been entered in a decision matrix, and the fractional true positive, false positive, false negative, and true negative, calculated. These elements have also been assigned their appropriate conditional probability notations where s+ means scintigraphy positive, s- means scintigraphy normal, c+ and c- mean that cancer was or was not present, respectively, at surgery or autopsy. Thus $P(s+|c+) = 0.95$ reads: given that the patient has cancer, the probability of the scintigram being positive is 95%. This statement is the equivalent to Sosman's estimate that he could detect 95% of significant pathology in the lung.

For operational purposes it is clear that we require the inverse of the probabilities shown on the table [e.g., $P(c+|s+)$, or, given a positive scintigram, what is the probability that a patient has cancer?]. To derive this probability we need to know the true incidence of cancer in the population of those referred for liver scanning because of suspected cancer. Of course, it could be assumed that the disease is distributed among the entire referred group in accordance with those listed in the table, but, with only 548 of 1034 patients listed, there is clearly room for bias and a reasonable suspicion that the percentage of patients without disease may be underestimated. Nevertheless, the calculations of these probabilities are instructive. They are

$$P(c+|s+) = 333/402 = 0.83 \quad P(c-|s+) = 0.17$$

$$P(c-|s-) = 128/146 = 0.88 \quad P(c+|s-) = 0.12$$

If the study population reflects the real patient population, then 83% of positive scans represent cancer and 17% represent other disease or no pathology. Conversely, 88% of the negative scans reflect the absence of cancer in this patient population, whereas 12% of the negative scans are from patients with the disease. It is to be expected that these latter probabilities will vary from institution to institution and from time to time with the composition of the patient population. Nonetheless, it behooves each laboratory to make a best estimate of these values for work-a-day purposes realizing the difficulties inherent in doing so.

Last, we come to a question that I hope will become a focal point of our discussion: the role of the radiological and nuclear medical specialist as a physician in the diagnostic process. This subject has been analyzed many times, but one may ask whether the recent past has seen some changes in the perception of this role by the specialists themselves and other practitioners. In the more distant past, the referring physician had well calibrated the few radiologists with whom he worked. Today the opposite is more likely: the radiological staff being large, the measure of the several radiologists is less certain. Radiologic and nuclear medical examinations, like all laboratory tests, are noted as objective findings and given appropriate weightings in decision making. Indeed, as the trend to computer-assisted diagnoses goes forward, the nuclear medical and radiologic results will and should be weighed in accordance with an established data base to calculate the probabilities of the differential diagnosis.^{7,8} There is an inherent complication to this if radiologists continue to practice as they are at present, and I presume that nuclear medicine suffers the same limitations.

This situation has most clearly been elaborated by Lusted,⁴ who has called our attention to the receiver operating characteristics (ROC, a term borrowed from radar system development) of roentgenographic interpretation. Stated qualitatively the ROC shows the dependence of the percentage of true positives

as a function of the false positives; such curves show the cost in terms of false positives that one must pay for any level of true positives. A number of studies have shown that several radiologists (or the same radiologist at several times) may operate at different parts of the curve depending on the conservativeness of liberality of their readings. In a given situation where the payoff for the detection of a lesion is high, the radiologist may operate at one point on the curve (e.g., 95% true positive, 15% false positive); in another situation where the cost or hazard of treating is high, he may operate at another point (e.g., 85% true positive, 5% false positive). It is clear that the radiologist as a consultant bases his interpretation on both the inherent detectability of the signals and his judgment as a physician. In so doing he is likely to obfuscate even the most sophisticated computer unless both he and the computer appreciate his index at detectability (i.e., the shape of his ROC curve) and where on the ROC he is operating.

One obvious alternative is to isolate the nuclear and radiological specialist from the other clinical data (and hope that his interpretations are not susceptible to the vagaries of mood and weather). At the present state of the art, this would have some severe shortcomings even in the technical conduct of the examination where it is obviously helpful to know what type of disease is suspected. In nuclear medicine, however, it might be possible to move toward such "blind" readings, especially as scintigraphy becomes more quantitative. In this instance the result, at times, would be the equivalent of providing a cardiac catheterization report with a physiological interpretation based on the numerical results.

A corresponding sticky question concerns the role of the radiologist and nuclear medical specialist in the selection of patients for examination. Given a request to do a colloid liver scan to distinguish alcoholic from postnecrotic cirrhosis, many of us would not hesitate to inform our colleagues that this procedure is incapable of such subtle distinctions. On the other hand, considering the cost of many procedures and the impending shortage of resources, one would like to see some additional guidelines for the most effective utilization of nuclear medical and radiologic procedures. How should these be developed and by whom? Should we confine our inquiries to the probability that an examination will provide new information with a reasonable likelihood, or should the referring physician be confronted with other challenges as well. These might include a definition of the course of action that will be taken based on the outcome of the procedure or the assurance that the payoff is maximized by placing this examination in the diagnostic sequence at a particular time.

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NUCLEAR MEDICINE AND THE DIAGNOSTIC PROCESS

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ABSTRACT

Radioactive tracers permit medical practitioners to measure body functions which enable them to define the problems of a patient with greater precision. These agents help physicians to be more certain of specific diagnoses and to exclude other diagnoses. They contribute toward reducing errors and thus lower the cost of patient care. New information provided by some nuclear medical procedures is often used as a determinant for further testing or for hospital admission. Considered with the medical history (patient communication), physical examination, and other laboratory studies (referring physician communication), nuclear medicine procedures, when properly interpreted, increase diagnostic accuracy and aid decision-making for management of patients.

Improvement in the quality of the day-to-day practice of nuclear medicine is worthy of our best efforts. Among the important decisions to be made are:

Is it necessary for the physician to examine every patient prior to the performance of a tracer study?

Need the physician see the patient at all?

What information is needed on the nuclear medicine requisition form?

Should the type(s) of studies performed in a given patient be determined by the referring physician or by the nuclear medicine specialist?

How should the results of the examination be reported?

How can the quality of nuclear medicine procedures be maintained and improved?

What is the relation of nuclear medicine procedures to the diagnostic process in general?

In trying to answer these questions, it is helpful to answer the last question first since it is difficult, perhaps even impossible, to contribute significantly to the solution of a problem that we do not understand.

DIFFERENTIAL DIAGNOSIS

Implicit in the process of medical diagnosis is the assumption that it is possible and useful to classify patients into disease categories. Although each patient is in many respects unique, as a patient he is suffering from a disease process that has certain features in common with those of other patients. What we call diseases are not biological entities but categories in which we place patients because it helps us predict what is likely to happen to them (prognosis), decide what can be done (therapy), and at times help elucidate why the disease occurred (biomedical research). We decide in which category the patient should be placed (i.e., what disease he has) by analysis of manifestations of the disease derived from the patient's own words (history), the physical examination, and other ancillary procedures that extend the physical senses of the physician. These manifestations comprise what is referred to as the patient's syndrome, or collection of manifestations.

In essence, radioactive tracers permit us to measure body functions, which helps elucidate the nature of the patient's problems. The role of the physician can be looked at as defining the patient's problems with progressively increasing precision. For example, the patient complains of weakness and tiring easily. On examination, the physician observes that he is pale. Studies of his blood indicate that he is anemic. Measurement of the survival of the patient's red blood cells labeled with radioactive ^{51}Cr reveals that the anemia is the result of increased destruction of the patient's red blood cells. Measurement of the accumulation of the labeled cells by the spleen indicates that the spleen is the site of abnormal red-blood-cell destruction. The problem has been defined with progressively greater precision. Without the radioactive tracers it would be possible only to document that the patient's red blood cells were abnormally shaped and fragile and assume that they were probably being destroyed by the spleen.

Manifestations of disease are evaluated according to their reliability (reproducibility), sensitivity, specificity, and cost. Cost includes danger and discomfort to the patient and all other undesirable factors in addition to economic cost.

A major characteristic of the diagnostic process is its probabilistic nature.¹ Rarely can a medical diagnosis be made with absolute certainty. In caring for the patient, the physician reaches working diagnoses at several stages in the diagnostic process: after the patient describes his illness, after the physician has asked further questions, after the review of the past history and performance of the physical examination, and after additional special studies.

In making these working diagnoses, the physician will find it useful to estimate the probability of each disease under consideration. A four-category classification is useful: (1) high probability (this means that there is greater than a 67% probability that the specific disease is present), (2) moderate probability (between 33 and 67% probability), (3) suspicious (between 5 and 33% probability), and (4) no evidence (less than 5% probability).

The diagnostic process usually follows two major paths: (1) the physician progressively increases the probability that the patient's illness is a particular disease and (2) he decreases progressively the probability that the illness is due to other diseases. For example, a patient may be found to have a vague mass in the right upper quadrant of the abdomen and the spleen may be enlarged. The physician believes that cirrhosis of the liver is the most probable diagnosis in view of the patient's heavy consumption of alcohol. However, he is concerned that the patient might possibly have a tumor within the liver and therefore asks for a liver scan. The *a priori* diagnoses are: (1) cirrhosis of the liver, high probability; (2) tumor of the liver, suspicious. The liver scan performed after the administration of ^{99m}Tc -sulfur colloid indicates an area of decreased phagocytic activity that could be cirrhosis alone but increases the likelihood of a tumor. The probabilities of cirrhosis alone vs. cirrhosis plus hepatoma are approximately 50-50; so the nuclear medicine physician requests that an ionic ^{67}Ga scan be performed. This study indicates that the area of decreased colloid uptake accumulates ^{67}Ga avidly, which greatly increases the probability of its being a neoplasm. With the probability of neoplasm being 90%, a needle biopsy of the liver is performed, and the diagnosis of primary carcinoma of the liver is made with certainty. The scan aided in the selection of the proper biopsy site. A reasonable question is, Why not perform the biopsy immediately after the physical examination? This would be a little risky since the lesion may be missed. There is also the danger that a focal decrease in reticuloendothelial-system (RES) activity in the liver scan may have been produced by the needle. This might interfere with the interpretation of the liver scan which would follow the negative biopsy. Surgery or celiac arteriography would also have been approaches to the diagnosis but would be associated with increased cost in terms of morbidity etc.

How sure does the physician have to be of his diagnosis? This varies with the disease and can be expressed in terms of thresholds. The physician must make the diagnosis with a degree of certainty that exceeds a decision threshold value, which is a function of the losses that will result from diagnostic errors and the gains associated with a correct diagnosis. The decision threshold would be low for such diseases as pernicious anemia or subacute bacterial endocarditis, in which the losses associated with missing the diagnosis are exceedingly high whereas the costs of treatment are relatively low. Consequently a decision to treat for either disease may be reached if the probability of either is greater than, say, 10%. This means, of course, that the physician must be willing to treat a number of patients unnecessarily.

A second threshold is the probability below which the physician is willing to state that a disease is not present; it is a measure of how certain he must be before he is willing to accept the risk of making the decision that the patient is free of a given disease. This also varies with the disease under consideration. A patient could not be discharged, for example, if it remained a 20% probability that he had diabetes. On the other hand, if a 4-year-old child without focal

neurological signs has a generalized convulsion, the finding of a normal brain scan lowers the probability of the child's having a brain tumor below 5% or less. This will often obviate the need for hospitalization for further study, and the patient can be started immediately on anticonvulsant drugs.

Following the decision model formalized in 1947 by Wald,² the physician can at times wait to make a decision until sufficient information is available. At times he is forced to make decisions under conditions of uncertainty. For example, if he waits until he is absolutely certain a patient has appendicitis before operating, he will often delay surgery until complications, such as peritonitis, occur that could have been prevented by earlier surgery. On the other hand, if he operates with too little evidence, too many patients who do not have appendicitis will be subjected to unnecessary surgery.

Faced with this dilemma the physician can again be guided by Wald,² who in 1947 suggested that the relative costs of errors rather than simply the number of errors are the important considerations. His decision rule states that the total expected cost should be kept to a minimum. He defined total expected cost as follows:

$$\text{Total expected cost} = [(\text{probability of false positives}) \times (\text{cost of false positives})] \\ + [(\text{probability of false negatives}) \times (\text{cost of false negatives})]$$

Such a decision model is helpful in many problems in nuclear medicine, e.g., in the setting of the normal and abnormal ranges of quantitative data, such as the accumulation of radioiodine by the thyroid.

To cite another example, we state that pulmonary embolism is the most probable diagnosis if we observe perfusion defects that correspond to one or more segmental arteries in association with a clear chest radiograph or one showing changes seen in pulmonary infarction. These include linear streaks (atelectasis), small pleural effusions, elevated diaphragm, or peripheral hemispherical densities of the type described by Hampton and Castleman.³ We are cautious about diagnosing pulmonary embolism if the patient has obstructive lung disease, which produces perfusion defects similar at times to pulmonary embolism. If we interpreted all perfusion defects as pulmonary embolism, the number (and cost) of false positives would become exorbitant. This has, in fact, occurred in some hospitals.

To cite another example, the cost of calling normal a patient with pernicious anemia is quite high because of the serious consequences of leaving this disease untreated. We make every effort to avoid a false negative. We found that measuring plasma levels alone after the administration of ⁵⁷Co-vitamin B₁₂ yielded false-negative results in 7% of our patients with pernicious anemia. Therefore we returned to relying on the classical Schilling test, which tends toward false-positive rather than false-negative results in the diagnosis of pernicious anemia. If the patient loses urine, a false positive is obtained if the loss is not recognized.

In setting our normal values, we cannot restrict the limits of normality too much or the cost of the error or of calling many normal people abnormal will become exorbitant. Scheff⁴ has analyzed the possible consequences of this type of error. He points out that physicians usually assume that judging a sick person well is more to be avoided than judging a well person sick, that it is far more culpable to dismiss a sick patient than to retain a well one. This decision rule may often place patients in the sick role who could otherwise have continued in their normal pursuits. Undoubtedly the decision rule, "when in doubt diagnose illness," is frequently extremely helpful. One need only cite the occasional tragic occurrence of an undetected subdural hematoma to emphasize the point. Occasionally, however, this rule can lead to errors. Garland⁵ reported that in the examination of 14,867 chest X rays for signs of tuberculosis, there were 1216 positive readings that turned out to be clinically negative and only 24 negative readings that turned out to be clinically positive. This report provides objective evidence of the application of the decision rule, "better safe than sorry."

What is one to do when faced with the dilemma of where to set normal values for a laboratory procedure? We should consider carefully the costs of both types of error rather than only the number of possible errors. Then the levels of normality can be established which will minimize total expected costs.

THE NUCLEAR MEDICINE SPECIALIST

Fundamental to the successful operation of a nuclear medicine department is the establishment of a practical system of communication for use by referring physicians, nuclear medicine staff, trainees, and others concerned with the application of radioactive tracers to medical diagnosis.

Weed⁶ has suggested that medical records rarely qualify as dynamic, creative instruments for facilitating comprehensive, highly specialized medical care. He recommends that they be problem oriented, concise, cogent and complete, not diffuse, superficial, or fragmentary. Can we be satisfied with less in the nuclear medicine requisition and report?

From the requisition, an interview with the referring physician, or from the patient himself, the nuclear medicine specialist must be able to identify the patient's problems and relate them to the specific technology of nuclear medicine. He must define each problem, separate complex problems into their individual components, and organize them for possible solutions. He must assure proper performance of the tracer studies, record the data, and communicate the results clearly to the referring physician. He should state the results in a way that promotes objectivity and permits self-evaluation through follow-up. In this way he can continually sharpen his skills and develop order, logic, and consistency in his approach to the patient's problems and in his instruction of trainees.

If we fail to provide an orderly approach to the patient's problems, we should not be surprised if our students and trainees reveal anxiety and confusion in interpreting studies of patients with complicated problems.

At present I believe it is essential that the physician responsible for the patient's study in the nuclear medicine department be aware of the patient's problems and the key information available prior to the nuclear medicine procedure. We encourage the referring physician to list the working diagnoses and the probability of each. If he has not done so, the nuclear medicine physician must.

To avoid bias in the interpretation of the tracer procedures, we have at least one physician interpret and record the results without any a priori information. This helps establish the intrinsic value of the information provided by the study. We then combine the results of the study with a priori information to arrive at the final diagnosis. Again a probability statement is given for each diagnosis.

The report to the referring physician is given in three parts:

1. Description: This translates information from scanning or camera images into words; e.g., "There is an abnormal accumulation of radioactivity, spherical in shape and 2 cm in diameter, in the right frontal region in the anterior, right lateral, and vertex views."

2. Interpretation: This consists of disease categories and probability statements, with all other words eliminated; e.g., "High probability of neoplasm, most likely a meningioma although an astrocytoma is also possible. Less likely is a cerebral abscess."

3. Comment: This section is used primarily to keep the interpretation section as simple and as clear as possible. Qualifying expressions or recommendations are given in this section.

In nuclear medicine, as in much of life, a major problem is communication. It is exceedingly difficult, if not impossible, to solve a problem if we do not understand it. If we rely entirely on the information on the requisition, we frequently will not be able to fully understand the problem or the key findings. An example of a specific patient may illustrate this point.

A young man with known Hodgkin's disease thought to be in remission began to have abdominal pain that was aggravated by eating. The requisition stated "rule out Hodgkin's disease; probable gallbladder disease." The nuclear medicine physician examined the patient's abdomen prior to study and asked the patient to draw a line with a skin-marking pencil around the area of pain. He did so, encircling a space about the size of a golf ball. When the scan was performed, a filling defect in the hepatic distribution of ^{99}Tc -sulfur colloid corresponded exactly with the painful area. It could be stated that the pain came from the abnormal area in the liver scan.

With the increasing complexity of medicine, it is impossible for the referring physician to know as much about an area of disease as the specialist in that field. Similarly it is not possible for the specialist to know as much about a given patient as the referring physician. It behooves each to do everything possible to overcome communication barriers among the three concerned parties: the patient, the referring physician, and the nuclear medicine specialist. Communica-

tion among all three must be increased. This requires person-to-person contact with the possibility of back and forth exchange of information.

Another reason for the physician to see the patient prior to study is that in present-day nuclear medicine standardized procedures are less common than in the past. For example, in a brain scan we may or may not do a study of the cerebral blood flow. We may or may not do special flexion or extension views or pin-hole collimator views of the posterior fossa in light of the clinical problem.

In summary, I believe the nuclear medicine specialist should have the opportunity to speak with and examine every patient prior to study. He should know the patient's problems and the key findings. He should list the a priori diagnoses with the probability of each. He should plan the studies and instruct the technologists.

The patient should not leave the department until the results have been reviewed and a judgment made that nuclear medicine techniques have contributed all they can to the solution of the patient's problems.

The interpretation should be stated in the form of diagnoses and probabilities. Vague statements, such as "compatible" or "consistent with," should be avoided.

Follow-up of the patients should be carried out on a routine basis to ensure consistently adequate performance.

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QUANTITATIVE ASSESSMENT OF THE INDICATIONS FOR RADIOLOGIC EXAMINATIONS

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ABSTRACT

Widespread use of tested criteria for patient selection would increase the effective capacity of the nation's radiology departments. Studies should be undertaken to evaluate our clinical criteria and develop strategies for the optimal utilization of the examinations in diagnostic radiology.

Many physicians and medical economists concerned about the welfare of the nation have been convinced of two important propositions about diagnostic radiology: The first is that there are not enough radiologists and radiological facilities to meet the needs of our population.¹ The second is that the largest portion of the exposure to radiation experienced by the general population and the only readily reducible fraction comes from diagnostic radiology. Hospital administrators and directors of departments of public welfare often espouse the first cause, whereas publicists and physicists are most vocal about the second. Both problems are central concerns of the diagnostic radiologist, and he should assume a serious commitment to participate actively in solving them.

If medical practice is looked upon as a private occupation, the consultant physician or the consultant department does not tend to judge the criteria for referral used by referring physicians. However, if medical practice is looked upon as a public trust or a national resource, the effective demand for it is the same as the national need, and the effective limitations are the resources in educated individuals and specialized equipment.

Many approaches for overcoming these limitations have been suggested.^{1,2} Our technology could be improved. Automated machinery, remote transmission of images, and mechanized film handling are potential labor-saving devices. They must be tested in practice, however, to determine whether the radiologist's time is truly conserved. Another method is the use of paramedical personnel. This approach is likely to make important inroads on the problem, but it is limited by

the availability of persons of adequate ability willing to enter a nonprofessional occupation as well as by the ability of the physician to supervise a number of paramedical technicians. Increasing the number of diagnostic radiologists is a direct approach. Certainly, the number of residents entering diagnostic radiology is now the third largest in the country, behind internal medicine and general surgery. Despite the rising number of medical-school graduates entering radiology, this has only limited possibilities because the need for physicians of all types is such that radiology cannot expect a disproportionate rise in its numbers.

Widespread use of tested criteria for the selection of patients would be one of the best methods of increasing the effective capacity of the nation's radiologic departments. Studies should be undertaken to evaluate our criteria and develop operating models for optimal utilization of the examinations in diagnostic radiology. For each of the radiologic investigations currently in use, the commonly used indications should be evaluated and the percentage yield of significant diagnostic information determined. Since the operational concepts involved in (1) the treatment of illness, (2) the prevention of illness, and (3) public health case finding are different, three different levels of yield may be anticipated. From the analysis of this information, it could be possible to develop an effective strategy for the optimal utilization of radiological investigations.

If the reason the physician requests a specific type of radiologic examination answers the question, What clinical findings lead you to think the patient may have a disease demonstrable on this examination? the validity of those findings as indications for radiologic examination will be shown by the results of the examination (within the limits of error of the examination method). The findings can be designated as having a high or a low yield. All patients showing the same low-yield finding can be considered to represent a group. The important question that could then be answered is, How many cases of disease will be missed if all the patients in each low-yield group are not examined radiologically? This is the crucial information needed to rationalize any effort to decrease unnecessary utilization of diagnostic radiology. A retrospective study based on a review of clinical charts would be burdened by a major disadvantage. Clinical records often do not reveal the actual indications that motivated the referring physician to request the examination. Well-designed prospective investigations are needed. Few such studies exist in the literature, and these are of limited scope. The time has come when the quality of research into how medical care is provided must be equal to the quality of research that provides the scientific basis for that medical care. Saenger³ appropriately observed: "in diagnostic radiology at present, there are no systems to determine whether a diagnostic procedure has been of clinical value in each or any given case, nor is there an impartial method for determining that a given examination is truly indicated."³

Data collection for an effective prospective study might be organized so that we can record any indication that might induce a physician to request the examination in question. It is critical that the list of indications be entirely realistic. The incidence of positive examinations could then be determined in relation to the specific indications for the study. The likelihood that a specific indication would be associated with a relevant positive finding on the X-ray examination could be numerically derived. A statement of results in terms of likelihood criteria would permit the widest use of the data derived. In all positive examinations with low-yield indications, the clinical course could be analyzed to determine whether the management of the patient was altered by the positive finding. The risk of eliminating the diagnostic procedure on patients with low-yield indications would then be calculated on the basis of the "likelihood" data and the established effect on patient management.

Over-utilization or unnecessary utilization has been considered by many to be a heavy burden in the field of diagnostic radiology. The recent study by Bell and Loop⁴ of the utility of the radiologic examination of the skull in skull trauma indicates that almost 30% of a series of 1500 examinations studied consecutively could have been eliminated with no detectable deterioration of patient care. Whether we view these statistics in terms of the dollars and cents that can be saved by a nation that must consider its economic priorities or in terms of the number of patients who are now denied necessary radiologic examinations because of limitations in facilities and medical manpower, the fact remains that funds and personnel for health care are not unlimited. The general welfare requires that quantitative scientific studies of utilization be conducted so that the output of the radiologic facilities and manpower, either at present or as expanded in the future, will be maximal.

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