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BIOLOGICAL EFFECTS OF RADIATION AND RELATED BIOCHEMICAL
AND PHYSICAL STUDIES

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In addition to the essential support by the AEC, Institute funds and NCI institutional project support have been employed. All publications and communications have identified both AEC and NCI support. We will seek for continued NCI or other support in addition to the requested AEC support in this proposal, in order that the total program described here can be carried out.

TABLE OF CONTENTS

PART A.	<u>INSTRUMENTATION AND DATA HANDLING</u>	<u>PAGE</u>
	1. Methodology of Absolute Whole Body Scanning	4
	2. Instrumentation Research and Data Analysis	17
	3. Neutron Activation Instrumentation	20
	4. Dual Photon Absorptiometry	30
	5. Total Organ Kinetic Imaging Monitor (TOKIM)	31
PART B.	<u>METABOLIC AND IMPROVED ORGAN SCAN STUDIES</u>	
	1. Regional Function Studies with Oxygen-15 at the Steady-State	33
	2. The Use of Carbon-11 Cysteine for Improved Pancreatic Imaging	46
	3. The Development of Isotopically Labeled Secretin and Pancreozymin as a Radio-Pharmaceutical Which Will Selectively Image the Pancreas	48
	4. ¹¹ C-Diphenyl Hydantoin and ¹¹ C-Hydroxyphenyl-phenyl Hydantoin for Brain and Brain Tumor Localization	51
	5. Nitrogen-13 Labeled Compounds for Soft Tissue Tumors	59
	6. Studies of Metabolism of ¹³ NH ₃ in Normal Dogs	62
	7. Nitrogen-13 Labeled Ammonium Chloride for Patient Studies	63
	8. Quantitative Evaluation of Radiation Therapy to Osseous Manifestations of β-Thalassemia Using ⁵² Fe and ^{99m} Tc	66
	9. Neutron Activation of Calcium and Other Elements	69

	<u>PAGE</u>
10. The Use of Bismuth-206 for Soft Tissue Tumor Localization	83
11. Kinetics of ⁴⁷ Sc Generated by Decay of ⁴⁷ Ca <u>In-Vivo</u>	92
12. Bone Mineralization Studies	96
13. Clinical Applications of Absolute Quantitative Organ Scanning Regarding Comparison of Hematopoietic and Phagocytic Function in Man	97
14. Treatment of Chondrosarcoma and Chordoma with ³⁵ S Sodium Sulfate	106
15. Evaluation of ¹⁸ F-Fluoride and ^{99m} Tc Labeled Diphosphonate and Polyphosphate as Bone Scanning Agents	108
16. Studies of Tumor Localizing Properties of ¹¹¹ In-Chloride and ¹¹¹ In-Labeled Bleomycin	109
17. Studies of ⁶⁷ Gallium Citrate for Soft Tissue Tumor Localization in Patients	112
18. Localization of Tumors with Radioactive Growth Hormone	114
19. Iodine-123 Labeled Hippuran	115
PART C. <u>FEASIBILITY OF CHEMICAL BONDING STUDIES WITH X-RAY SPECTRA</u>	117
<u>PUBLICATIONS</u>	118

PART A. INSTRUMENTATION AND DATA HANDLING

A-1. METHODOLOGY OF ABSOLUTE WHOLE BODY SCANNING

OBJECTIVE:

To develop scanning methods utilizing the High Energy Gamma Ray (HEG) scanner for absolute measurement of organ function in-vivo by determining the percent dose of radio-nuclide accumulation in an organ. The project includes the design of 'constant resolution' collimators and a scan data analysis procedure which relates organ radioactivity to the counts within its digital scan image subsequent to correction for surrounding radioactivity.

MATERIALS AND METHODS:

The dual detector High Energy Gamma (HEG) rectilinear scanner contains heavily shielded 4x4 in. NaI (Tl) crystals mounted on an Ohio Nuclear frame. The design of 'constant resolution' collimators for the energies of ^{51}Cr (320 keV) and ^{52}Fe (511 keV) has been completed. The scan program has been extensively modified to handle absolute and serial organ uptake calculations. Clinical applications of these scanning techniques for spleen function studies are discussed in section B-13.

Two modes of detection were investigated for the absolute measurement of the short-lived positron emitters ^{13}N , ^{11}C , and ^{15}O , in-vivo. Figure 1 shows a schematic diagram of the HEG system and interface to magnetic tape for the positron mode. Pulses from the opposing detectors were tested for coincidences with a fast coincidence circuit (FCC), with a resolving time of 30 nsecs. A real to random ratio of 50:1 was observed for all data acquisition. Limiting total singles rate, with constant fraction timing (CFT), of 40,000 cps was not exceeded in this study. Coincidence pulses for the full photopeak (ΔE - 100 keV) were detected for each scan increment and dumped on magnetic tape. Scan data were then replayed and processed on an IBM 1800 computer to obtain (a) point spread function data, (b) line printer images of phantom scans and (c) integral counts within phantom source image contours in 10% increments from 10-50%.

A series of straight hole collimators 4" long with diameters from (1.5 - 4 in.) were employed to restrict the coincidence response volume to within a reasonable (FWHM) for imaging large organs.

FIGURE 1

POSITRON MODE OF HEG SCANNER

To determine the best compromise between constant resolution and sensitivity, point spread functions were taken at different depths in a 20 cm lucite medium for each collimator. A 2 mm diameter point source of ^{68}Ge was scanned using a small scan increment of 0.1 in. x 0.1 in.

Operating the HEG scanner in the singles mode required the construction of 'constant resolution' collimators for 511 keV (Fig. 2). The design specifications for these collimators are listed in Table I. The inner ring of 8 trapezoidal apertures has a focal length of 14 cm while the outer ring of 16 apertures has an 18 cm focal length. Aperture size for each ring was reduced in area along the collimator radial axis. Focal lengths, collimator aperture areas, and separation were optimized to yield 'constant resolution' (FWHM) with depth using a collimator response simulation program. Design specifications were chosen to achieve sufficient spatial resolution for imaging large organs. Very thick septa were incorporated as necessary to reduce the septal penetration for 511 keV.

RESULTS:

For the coincidence mode, the best compromise between sensitivity and uniformity in the point spread function with depth was obtained with the 2 in. straight hole collimator at a detector separation of 40 cm. Figure 3 and Table II show the point spread functions obtained for the HEG system in the positron mode. For the 2 in. collimator, resolution (FWHM) was $3.0 \text{ cm} \pm 15\%$ throughout the absorbing medium with the point source response falling sharply to zero within 1.5 resolution diameters (FWHM), of the axis of the system.

Figure 4 shows the response data for the singles mode. Resolution (FWHM) was $2.5 \text{ cm} \pm 10\%$ over the absorbing medium. The point source response for the 511 keV collimators again decreased sharply along the radial axis falling to less than 1% within 2 resolution diameters beyond the collimator dual axis.

Similar resolution of source size and activity content for both radioactive and non-radioactive media was achieved for both modes of detection. Since the detector off-axis response was small for both the positron and singles mode, the source image contours (10-50%), remained close to the actual source boundary. Figure 5 shows how the 30% contour area (cm^2) closely correlated with the source cross-sectional area (cm^2) for each mode. It also illustrates how the response dependence (cts/ μCi) on phantom size was significant

FIGURE 2

Constant Resolution Collimators for 511 KeV.

TABLE I

Dimensions of the 25 Hole F(14 cm, 18 cm) Collimators
 Designed for 511 keV

25 Hole F(14 cm, 18 cm)	Focal Length (cm)	Aperture area crystal face (cm ²)	Ring Diameter (cm)	
			Inner	Outer
F ₀ (center hole)	14	2.54	-	1.8
F ₁ (inner ring)	14	.94	3.3	5.7
F ₂ (outer ring)	18	.83	6.9	8.7

Collimator Length = 12.5 cm

Collimator Diameter = 11.8 cm

FIGURE 3

TABLE II

Spatial Resolution and Response Characteristics for the Range
of Cylindrical Collimators Employed with the Positron Mode
Detector separation was 40 cm

<u>Collimator Bone Dia. (in)</u>	<u>Resolution (F.W.H.M.) Over 20 cm Lucite (cm)</u>	<u>Relative Sensitivity</u>
4"	5.5 $\pm$ 12%	100%
3"	4.7 $\pm$ 14%	95%
2"	3.0 $\pm$ 15%	52%
1-1/2"	2.5 $\pm$ 11%	30%

FIGURE 4

POINT SOURCE RESPONSE FUNCTIONS FOR
25 HOLE F (14 cm, 18 cm) COLLIMATORS USING 511kev

FIGURE 5

Source Resolution and Response
Characteristics of HEG System

only for the smaller sources scanned using the singles mode. When the total area scanned (T.S.A.) was integrated no significant response dependence on source size was found. Good resolution of source activity was achieved. By integrating the 30% contour area, approximately 75% of the total response to each source was achieved for the positron mode with a 65% response in the singles mode.

Even though thick septa collimators were used for singles detection, this mode proved to be the most sensitive, i.e. under conditions where similar 'constant resolution' characteristics are required. The relative sensitivities for the phantom arrangements in the 20 cm tank in Figure 5, were approximately 300 cts/ μ Ci for the singles mode and 60 cts/ μ Ci for the positron mode. This factor of five advantage in sensitivity is further improved when thicker subjects are scanned since the coincidence mode depends on the total subject thickness in contrast to the singles mode which depends on the relative source depths seen by each detector.

A series of whole body dog scans were performed to determine the distribution of ^{13}N -ammonium chloride (10 min. half-life) in normal dogs at various times after injection. Singles mode provided shorter scanning intervals. Figure 6 illustrates the organ resolution achieved for a lateral whole body scan of a normal dog 10 min. after injection of 10 mCi of ^{13}N -ammonium chloride. After intravenous injection, dynamic studies showed that ammonia was almost immediately taken up in the heart and liver. Approximately 5-10% of the injected dose was quickly removed from the blood stream by the kidneys and collected in the urinary bladder with a mean clearance half time of less than 10 min. Isotope equilibrium was essentially reached at 10 min. after injection. About 60% of the injected dose was distributed throughout the body, i.e. muscle, etc. Therefore, organ radioactivity had to be resolved from surrounding active tissues.

The calculated percent dose in the brain, heart, liver and bladder for various scan times after injection (10-15 min.) tabulated in Table III, showed remarkably consistent results, considering the biological variation expected. The percent uptake in the heart was in excellent agreement with data for the alkaline metals, potassium, rubidium and cesium using invasive methods. These isotopes are currently used as myocardial scanning agents and as indicators for the measurement of myocardial blood flow.

FIGURE 6

Whole body scan of a normal dog 10 minutes after
injection of 10 mCi of $^{13}\text{NH}_3$.

TABLE III

Organ radionuclide uptake in normal dogs derived from quantitative scans (10-50 min) after injection of ^{13}N ammonia. Results are shown for 15 scans of 5 normal dogs.

	<u>% Organ Uptake In-Vivo</u>	<u>% Tissue Background Correction</u>
Brain	0.46 $\pm$ 0.18 s.d.	75
Heart	3.62 $\pm$ 0.45 s.d.	40
Liver	11.96 $\pm$ 1.7 s.d.	40
Bladder	5.57 $\pm$ 2.0 s.d.	30
Blood	9.4 $\pm$ 0.9 (30 min. A.I.)	

CONCLUSION:

The advantage in sensitivity for the singles detection was the deciding factor for the implementation of this mode into clinical studies. This quantitative scanning technique has been employed for the measurement of (1) extramedullary erythropoiesis in the spleen with ^{52}Fe -ferrous citrate and (2) myocardial blood flow with ^{13}N -ammonium chloride in normal mongrel dogs and (3) organ distribution studies of ^{13}N -labeled amino acids.

A-2. INSTRUMENTATION RESEARCH AND DATA ANALYSIS

OBJECTIVE:

To design and implement an advanced software system, which incorporates all previously developed technical features, for the interpretation and analysis of rectilinear scanner data. This scan data package plus an existing display and analysis package for gamma-camera data would form a complete scanner/gamma-camera data handling system.

MATERIALS AND METHODS:

It was desired that a new scan package have the following attributes: versatility, modular design for ease of expansion, efficient in its utilization of computer time and input/output (I/O) handling, and ease of execution.

The IBM 1800 computer, with 32 K two-byte words of core, running under the Multiprogramming Executive Operating System, was the vehicle of implementation. High level software consisted of the IBM 1800 Fortran language and a collection of supporting system subroutines. Relevant peripherals consisted of two IBM 2401 tape drives, three IBM 1810 disk drives, an IBM 1443 line printer, an IBM 1816 typewriter/keyboard and a Tektronix 611A storage oscilloscope connected to the analog output of the IBM 1856 digital/analog converter.

Programming methods included two-way interleaving of magnetic tape I/O so that tape I/O and processing overlapped. A series of indexed files defining the relationship between count rate and a given standard deviation character representation for that count was also defined and generated. A third method consisted of the use of the operating system's overlay facility to construct a system which otherwise could not fit in the machine. This was accomplished by having a main control program which was overlaid by some functional program, which in turn is overlaid by the control program, and so on. Each main program, whether it be a functional program, a control program or an initialization program is considered to be an overlayable module. The COMMON area, included in all modules and containing the control and data regions, is never overlaid.

RESULTS:

A new scan package was written and implemented. This system replaces or amends existing systems and procedures. The design of the system conforms to the design criteria discussed above and improves considerably on the old scan package as evidenced by system performance.

Once the program is entered, it is controlled by various inputs to perform given functions. Only two card formats are required. Although the card format must be strictly adhered to in order to perform the desired functions, the program has been designed so that it does not abort in the case of an incorrect card but instead asks the user to resubmit that card. This is a significant improvement over the old scan package where a mispunched card could cause a job of several hours to abort and be lost.

The new scan package provides for a quick turn-around time for a scan output: an average of seven minutes per printed total body scan or a three-fold improvement in turn-around time. This is in part due to the fact that at the time of processing all of the decay corrected data is in core. The data is defined in COMMON as a linear matrix of values, MATRX(N), which can be reconstructed into a rectangular scan matrix given the number of rows, NR, and the number of columns, NC, in the scan. The maximum scan size is limited only by the size of addressable memory available, N, after taking into account the operating system and the size of the largest module. This scan package has been made available under two operating systems: a day shift real time operating version and a night shift batch processing operating system, whose respective linear matrix sizes are 8,000 and 15,500 addressable locations. The larger number represents a scan size of at least 100" x 24" at a 0.4" X and Y increment, or a scan size of 34" x 18" at a 0.2" X and Y increment.

The new scan package has several unique processing options, such as nine point and twenty-five point smoothing. The scans may be printed out as a one to five standard deviation character representation output. The output character set may be changed at will. A set of increasingly dense characters may be chosen for example. Thus, the same scan, on consecutive runs, could be displayed in a qualitative manner or a quantitative manner. Another means of qualitatively displaying the scan is through the storage oscilloscope option with dot-density output. This has already been found to be quite useful for visualizing tumor

uptake or whole-body distributions of radiopharmaceuticals. Other options provided are line overflow control, automatic over-skipping of scans, decay corrections for any one of 22 isotopes, half and quarter scale reductions, axis rotation and scaler summation and subtraction.

CONCLUSIONS:

The new scan package has proven itself in both the Hospital and the Institute. It is currently being used on a daily basis by the Nuclear Medicine Service for total body scans and liver scans on any one of three scanners. The Biophysics Laboratory of the Institute has been extensively using the scope output option of the new scan package for data generated by the High Energy Gamma scanner, in both patient and animal studies.

Because of the basic design of this package additional modules may be easily added. Such future processing might include: 1) image correction due to finite resolution of the detection system, 2) processing to enhance defects in areas of relative maxima and minima, and 3) scan comparison between diseased organ and the standard normal organ as an aid in clinical diagnosis.

The new scan package has been demonstrated to be a popular improvement at the Center with features not currently available in any other single system.

A-3. NEUTRON ACTIVATION INSTRUMENTATION

OBJECTIVE:

A. To study our present instrumentation and methodology for measuring patient expired breath samples with special attention to the total system efficiency, the volume of expired gas requiring analysis, and the uniformity of fast neutron exposure throughout a patient's body. To achieve thereby a viable low dose technique for quantitatively measuring the whole body stores of calcium.

B. To design a system capable of performing collimated field, fast neutron partial body studies in-vivo of calcium and other elements using a compact cyclotron. Such a system shows promise for wide application for the evaluation of all therapeutic methods attempting to cure local bone involved cancers noninvasively, i.e. radiation therapy, chemotherapy, immunotherapy, etc.

MATERIALS AND METHODS:

A. Whole body in-vivo calcium assay instrumentation.

A detailed study of the argon recovery efficiency of the breath collection and extraction system, described in detail in last year's Progress Report (1972-73), p.75-90, has been carried out in collaboration with Drs. Raymond Davis, Jr. and John C. Evans, Chemistry Division of Brookhaven National Laboratory (BNL). A known volume of ^{36}Ar was injected into the breathing gas supplied to the human subject. A second known volume of another isotope of argon, ^{38}Ar , was injected into the respiratory gas sample at the point where chemical processing began. At various stages of chemical processing a mass spectrographic analysis of the gas was performed. The measured isotopic abundance of $^{38}\text{Ar}/^{40}\text{Ar}$ and $^{36}\text{Ar}/^{40}\text{Ar}$ and a volumetric measurement of the argon sample gave sufficient information to fix the recovery efficiency at that point.

The uniformity of production of ^{37}Ar with depth in a water tank has been determined directly using the $^{40}\text{Ca}(n,\alpha)^{37}\text{Ar}$ reaction. This information was needed to verify that the $^{27}\text{Al}(n,\alpha)^{24}\text{Na}$ reaction can be used to map the ^{37}Ar production distribution in more realistic phantoms of the human body. Absolute quantitative calcium measurements obtained from in-vivo human exposures depend upon our knowledge of this

production efficiency throughout the body for all possible variations in human anatomy. Aluminum activation foils 1/2" in diameter weighing 0.25 gm represent a very minor perturbation to the neutron field and are convenient to assay in a NaI(Tl) well crystal.

Each calcium target was in the form of calcium acetate powder, sealed in a helium atmosphere in a pyrex bulb. Eight samples weighing approximately 2 gm each were suspended at 5.7 cm depth intervals in a 30x30x35 cm water tank. The ^{37}Ar , produced by reaction of the ^{40}Ca with neutrons from 23 MeV helium-3 bombardment of beryllium, was quantitatively removed by evacuation and flushing with helium. Collection was done on a liquid nitrogen cooled charcoal trap. The samples were then transferred to gas proportional counters for assay.

An experiment was performed to determine the ^{37}Ar production efficiency per gram per rad of radiation dose in a phantom of a human calf, placed at the usual tibia position during a human exposure, and, simultaneously, at an equivalent position without moderator. Bulbs containing about 15 gm of calcium nitrate in solution were utilized. A third bulb containing calcium acetate powder was also included in the same exposure. Previous experience at BNL had established that argon could be quantitatively removed from the solution. Extraction efficiency from the calcium acetate powder had not been measured. All of these bulbs were processed in a similar manner to those described above.

B. Local in-vivo calcium and other element assay instrumentation.

No other laboratory has investigated the study in-vivo of a portion of the human body irradiated by a collimated fast neutron cyclotron source. Every component of the instrumentation has been designed to achieve optimum results in such a study. The chief criteria were to measure calcium quantitatively at selected sites and to minimize the radiation dose required.

A unique NaI(Tl) counting facility has been designed especially for counting local portions of the human body with high sensitivity and low background. The equipment has been purchased and its installation is expected within approximately three months. Much effort has gone into the design of this facility as well as in the examination of components available from various suppliers, in order to design a state-of-the-art system, optimized for its size and cost, capable of

performing significant studies.

Two 9" diameter by 5" thick NaI(Tl) crystals each backed by four 3" photomultiplier tubes form the high sensitivity gamma ray detectors for the facility. The crystal mounting fixture is portable and allows the two crystals to be rotated 360° and vertically separated from contact to 36". Each detector is surrounded, except for the front face, by a 3" thickness of lead of high radiochemical purity. Shielding of the open detector faces, at all detector separations and with a patient in counting position, will be accomplished by placing the patient and detector fixture within a 4" thick walled steel counting room.

Cosmic ray showers provide a component of background which cannot be effectively attenuated with bulk shielding except by placing the counters deep in the earth. An inexpensive and practical method of reducing this component is provided by a fast plastic scintillation detector similar in configuration to an umbrella. The plastic detector generates a veto pulse whenever a cosmic ray shower occurs, thereby canceling any pulses occurring simultaneously in either NaI(Tl) detector. A 1/4" thick plastic phosphor cylinder and end plate are incorporated into a steel jacket surrounding the upper detector lead shield. They are each viewed by four 1-1/2" XP1010 low noise photomultiplier tubes with low background tube base assemblies. This cosmic shield provides a unique addition to a body counting facility, which should provide uncomparable low background quality.

The electronics package for signal processing, besides providing simple singles counting, allows sorting into coincidence and anti-coincidence events occurring between the two NaI(Tl) detectors with guaranteed 25 μ sec full width at one tenth maximum (FWLM) timing resolution. Coincidence and anti-coincidence events are stored in separate halves of an analyzer memory. The S12 channel analyzer includes sufficient flexibility to allow in-analyzer peak integration, peak stripping, storage and retrieval of desired spectra and transfer capability to the Sloan-Kettering Institute IBM-1800 computer for more sophisticated data analysis.

The neutron source provided by the SKI cyclotron must be collimated in order to irradiate a subject locally. A thick multi-layered shield has been designed to reduce the dose rate outside the useful beam to an acceptable level. The main function of each layer is as follows: a thick steel layer nearest the source attenuates fast neutrons by inelastic scattering, a polyethylene layer thermalizes and absorbs lower

energy neutrons, and a final lead layer reduces the dose due to capture gamma rays produced in the polyethylene layer. The region closely surrounding the beam axis is an exchangeable section (applicator). Different applicators of diverse aperture size and material will facilitate adjustments of beam size, uniformity and purity.

The steel required to construct the body counting facility was assayed at Brookhaven National Laboratory using their low background counting apparatus. Dr. Stanton H. Cohn and Dr. Kenneth Ellis were kind enough to perform these essential radiochemical assays for us. We are much indebted and appreciative for these efforts.

RESULTS:

A. Whole body in-vivo calcium assay instrumentation.

Argon recovery efficiency measurements applied to the argon collection and extraction system demonstrated nearly 100% efficiency for all components except the high pressure pump. Separate studies of the pump showed its approximately 30% losses to be reproducible. Losses of this size cannot be tolerated in routine use however, so a new considerably simpler system has been designed which eliminates the need for a high pressure pump. This system is currently under construction. All components of the gas extraction system performed well and no major modification in them is expected at this time.

The new gas collection system has three source gases, a 20% oxygen- 80% helium mixture, pure oxygen and pure helium. A patient mask with input and output regulators, designed to maintain a positive pressure differential, allows the human subject to breath normally without any respiratory strain. The mask is equipped with a microphone system to facilitate easy communication with the human subject at all stages of the procedure.

The system will function in the following manner. The subject will breath the 20% oxygen 80% helium mixture for approximately 15 minutes to flush his system and the collection apparatus of the majority of the cold argon and nitrogen dissolved in his body tissues. He will then be switched to a constant volume recirculating mode where pure oxygen is added and carbon dioxide is removed, similar in principle to the system utilized in routine respiratory function testing of

patients. The patient will be irradiated and remain in this mode of operation for a period of approximately one hour. He will then simultaneously be switched back to the gas mixture and into a non-circulating mode, where his expired respiratory gases will be vented through a liquid nitrogen cooled trap to the atmosphere. Finally, the mask will be by-passed and the system flushed with pure helium. The vent will be sealed and the gas processed according to our normal procedures.

As can be seen in Figure 7, the calcium bulb study of neutron fluence as a function of depth in a water tank was shown to agree as expected with the results of the aluminum and indium activation foil measurements. It is clear from this measurement that relative neutron flux results obtained from aluminum foil mappings in phantoms will not differ significantly from those obtained using calcium. Figure 8 shows the neutron flux uniformity expected from a bilateral exposure to a water target 10, 20 and 30 cm thick, respectively, to be ± 3.7 , ± 14 and ± 31 percent. These curves were obtained by fitting the tank data to a single exponential curve and then mathematically summing these functions for a bilateral exposure to the various thicknesses. The mean value of the response was determined for each case and then the results plotted as variations from the mean. The single exponential fits yielded half value attenuation layers of 7.9, 8.9, and 9.7 cm, respectively, for indium, calcium and aluminum assays. The functional relation for the curves is

$$A = 100 \exp \left(- \frac{\ln 2}{T_{1/2}} T \right)$$

where A is the percent neutron flux transmitted at a given depth T in water and $T_{1/2}$ is the depth at which the neutron flux dropped to 50% of its initial value.

Neutron flux variation measurements were also carried out for positions normal to the beam axis and at the patient irradiation exposure distance. These results and the experimental setup are shown in Figure 9 for both the aluminum and indium foil assays. The variations observed are due to the forward peaking of the $^9\text{Be}(^3\text{He},n)$ reaction. These measurements have given us the data required to design and fabricate a solid aluminum cone to correct this variation. This cone is positioned on axis 10 cm from the target surface to the base

Figure 7. Neutron flux measurements with depth in a water tank comparing aluminum, calcium and indium assay materials. Neutrons are derived from the $^9\text{Be}(^3\text{He},n)$ reaction.

Figure 8. Bilateral exposure neutron flux uniformity for 10, 20 and 30 cm depths in water.

Figure 9. Neutron flux measurements lateral to the neutron beam axis using aluminum and indium assay materials.

surface of the cone, apex toward the target and with a base incline of 35°. Testing of the flattening achieved and other beam modifying characteristics are under way and will proceed in a manner similar to those described for the unmodified beam studies.

An Alderson skeleton-containing phantom was fitted with aluminum activation foils at thirty-three different bone positions to determine the average relative neutron flux in twenty-two different body bone groups. Results of flux uniformity in those measurements will be included in Section B. 9 along with bone tissue distribution data.

The calcium bulb experiment, designed to determine the yield of ^{37}Ar at the calf position with and without moderator, showed 3.0 disintegrations per gm per rad in the moderated case which is 14% lower than for the unmoderated case. Comparison of the calcium nitrate solution and calcium acetate powder showed that the powder also releases its argon store quantitatively. The powder is more convenient to use for these purposes.

B. Local in-vivo calcium and other element assay instrumentation

The equipment design requirements needed to carry out partial body human studies in-vivo have been completed. Details of fabrication were worked out with the various vendors and installation is expected shortly. Radiochemical assays of the iron used to fabricate the counting enclosure have been completed. The gamma activity corresponds to 0.16 cts/hr/gm and no unsuspected peaks appeared in the multi-channel analyzer display.

CONCLUSION:

Instrumentation design requirements for both whole body and partial body in-vivo human studies have progressed significantly. Much of the essential equipment for the partial body studies has been purchased and is expected to be installed within approximately three months.

The equipment will then require thorough testing and calibration. We are confident we can develop methodology, based on this equipment, whereby studies of bone disease can be made with clinically useful precision and reproducibility, and with reasonable diagnostic dose requirements.

A number of areas requiring improvement have been identified in the whole body methodology. A gas processing system needs to be fabricated especially for this purpose, using design criteria data from our reported studies. The neutron source will be further optimized for uniformity and a new method of irradiation further investigated to increase depth uniformity. Because this method requires active exhalation of respiratory gas by a human, it is essential that reproducibility be tested using humans. The low dose requirements make the necessary repeat studies feasible. Clearly a number of parameters may control the rate of ^{37}Ar release from the body and these must be studied to determine methods to optimize reproducibility.

A-4. DUAL PHOTON ABSORPTIOMETRY

OBJECTIVE:

To interface the dual energy absorptiometric bone mineral analyzer to the IBM 1800 computer and to evaluate the dual energy system for the analysis of bone mineral content in human forearms.

MATERIALS AND METHODS:

A dual energy instrument was developed, using a dual isotope source consisting of a ^{241}Am pellet positioned immediately above a ^{125}I pellet in a shielded source holder. The instrument was interfaced with the digital input channels of our IBM 1800 computer. This permitted digitized transmission data, at two photon energies, to be sent directly to the computer for disk storage and subsequent analysis. At the completion of a scan, the transmission data also can be remotely retrieved and displayed graphically on an oscilloscope located adjacent to the bone mineral analyzer. The use of digital data from each channel (photon energy) allows a correction to be made for the escape peak from the ^{241}Am line (59.6 keV) which lies within the ^{125}I channel (at 27.4 keV). The computer program developed for this instrument permits the evaluation of bone mineral content (BMC) from information obtained for either photon energy or in the dual-energy mode.

RESULTS:

The dual energy method has been shown capable of correcting for the presence of fat in an artificially simulated arm consisting of paraffin (simulating fat) and a saturated water solution of K_2HPO_4 solution (simulating bone) in plexiglass (simulating soft tissue). Correction was possible for various severe fat configurations used which produced errors in the measured single energy BMC values ranging from 0 to about 30%. Difficulties were encountered in applying the dual energy approach to human arms where we have highly irregular (non-circular) cross sectional bone shapes and fat of unknown configuration.

CONCLUSIONS:

The dual energy system was found capable of correcting for various fat configurations in 3-component simulated arms where the bones are represented by symmetrical circular configurations. Evaluation of constants required for the equations used to solve for bone mineral content was found to be more difficult in the irregular configuration encountered in a human arm. A large number of dual energy scans should be carried out on both lean and obese individuals. From these data the scan coefficients required to determine the BMC of human forearm bones can be determined.

A-5. TOTAL ORGAN KINETIC IMAGING MONITOR (TOKIM)

OBJECTIVE:

To realize more fully the advantages of the Total Organ Kinetic Imaging Monitor (TOKIM) in the positron mode, particularly its advantageous spatial resolution, both laterally and in depth (axially), by minimizing the inherent limitation in its restricted field of view.

MATERIALS AND METHODS:

While the positron mode of TOKIM (1,2) operation has superior spatial resolution, both laterally and axially, a limitation to its usefulness is its restricted effective field of view. It was proposed to remove this limitation by using the TOKIM system, in the positron mode, as a scanning camera.

The scanning ability was provided by the use of a manually operated indexing table, to carry the subject or source distribution. The TOKIM has previously been interfaced with our IBM 1800 computer through which data are taken as 12 bit words and stored on magnetic tape for subsequent analysis. To obtain a tomographic view the data tape can be reread, and an image constructed for each desired plane. These planes are each processed as 64 x 64 computer word (4K) matrices. The processing of data for multiple positions will require the offset and overlap of these matrices to form the final image plane. Processing the scanning positron mode data for six positions will require a 128 x 196 word (24K) matrix. This would exceed the capacity of computer memory currently

available for matrix storage; therefore, each 24K image matrix will be stored in a disk file. Methods for constructing such a 24K matrix, handling only manageable portions of it at any one time, must be developed. The image matrix will then be displayed in either an alpha-numeric character line printer output, standard deviation format, or as a dot-density display on a storage oscilloscope.

RESULTS:

The capability of performing multiple positron imaging, in the positron mode of data taking, has been accomplished. Single tomographic images have been formed from these data using our computer hardware and software. However, the reconstruction of scanning or multiple position positron mode images has not been carried out since the required software has not yet been developed. This is due to a temporary shortage of computer personnel needed to design and implement these programs.

CONCLUSIONS:

The use of the TOKIM system in the positron camera mode has the following advantages: the ability to produce tomographic views of a source distribution, an order of magnitude greater sensitivity than a single detector camera with a multi-hole collimator, and the capability of making an absolute determination of source activity. By operating the TOKIM system in the positron mode as a scanning camera, one can in addition overcome the problem of the limited field of view of the positron camera.

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PART B - METABOLIC AND IMPROVED ORGAN SCAN STUDIES

B-1. REGIONAL FUNCTION STUDIES WITH OXYGEN-15 AT THE STEADY-STATE

OBJECTIVE:

To develop steady-state procedures for assessing regional function using oxygen and oxides labeled with ^{15}O .

MATERIALS AND METHODS:

Radioactive oxygen labeled with ^{15}O was produced in the SKI cyclotron by irradiating a flowing stream of nitrogen gas containing one percent oxygen with 7 MeV deuterons in an aluminum target chamber 60 cm long and 5 cm in internal diameter (ID). The flow of gas was adjusted to about 1 liter per minute and the deuteron beam current set at 1 μA . Oxygen-15 was produced by the (d,n) nuclear reaction of ^{14}N and the ^{15}O atoms formed reacted with O_2 in the carrier gas to form mainly $^{15}\text{O}:\text{O}$.

The gas was transported from the target chamber to a chemical processing unit in 1/4" (ID) polyethylene tubing. Radioactive impurities produced in the target chamber, ozone and oxides of nitrogen were removed by flowing the gas stream through activated charcoal at ambient temperatures. The gas was then dried over anhydrous calcium sulphate.

If carbon monoxide was being produced, the gas was further processed by flowing over charcoal at 1000°C . No oxygen, nitrous oxide or ozone was detected in the product.

To produce carbon dioxide labeled with ^{15}O the dried gas containing $^{15}\text{O}:\text{O}$ was passed first through a bed of charcoal at 500°C and then through a bed of cupric oxide at 500°C . Radioimpurities were assayed at less than 0.02%. No oxides of nitrogen or ozone could be detected in the product.

The labeled gas was mixed with an oxygen enriched air mixture to dilute the radioactive gas and to provide the flow and gas concentration required for the procedure.

The diluted gas was transported through 1/4" tubing from the processing area to a control laboratory. Levels of radioactivity were monitored continuously by flowing the gas stream through an ionization chamber and were recorded for the duration of the procedure.

Chemical and radiochemical analysis were performed by gas chromatography on a Hewlett-Packard Model 5740 gas chromatographic system equipped with a column packed with molecular sieve 5A. This separated oxygen, nitrogen and the oxides of nitrogen. The composition of a 1 ml aliquot of the dilute gas stream was estimated from the output of a thermal conducting detector. The eluted gases were passed by a NaI detector and the output allowed a correlation between the radioactive components of the gas stream and its composition.

In a typical procedure, gas was delivered at the rate of 4 liters/minute. The oxygen concentration was about 20% and the radiopurity was greater than 99%. Using a 1 μ Amp deuteron beam current on the target, the radioactivity in the diluted gas was about 3.0 mCi/liter.

The gas was transported in the polyethylene tubing to the area of the gamma detectors and administered to a large mongrel dog through an endotracheal tube. The continuously administered gases permitted the animal to ventilate under its own control. Expired gases were exhausted at a distant site.

Steady-state organ imaging or dynamic studies were performed on the SKI Total Organ Kinetic Imaging Monitor (TOKIM) gamma camera. For this study the TOKIM was operated in the singles mode with a non-focusing multi-hole collimator imaging an area in the animal approximately 30 cm in diameter. The data obtained were stored on magnetic tape for subsequent analysis. For dynamic studies, the retrieved TOKIM images were displayed on a storage oscilloscope. A program enabled arbitrarily shaped integration areas to be selected for the determination of integrated counts within these areas as a function of time.

Additional time dependent information was obtained by manually positioned probe detectors over designated areas of the body. Data obtained from the dynamic probes were stored on magnetic tape in digital form for later analysis.

Whole body imaging was performed on the High Energy Gamma (HEG) scanning system which consisted of a dual headed rectilinear scanner and associated electronics. The system was used to obtain static (steady-state) images. By use of appropriate multiple focal length collimators absolute quantitation of organ activities can be achieved.

RESULTS:

The labeled gases are taken up and approach the steady-state rapidly. Figure 10 shows the approach to the O_2 steady-state over the areas of the body as shown by the probe data. Steady-state is usually achieved in about 10 minutes for oxygen. Carbon monoxide and carbon dioxide steady states are achieved in about 300 seconds. A TOKIM image of the head (Fig. 11) clearly defines the region of the brain in addition to areas of the neck and jaw. A corresponding image produced with Cl^{50} , defining regions of blood pooling, fails to show these regions although the concentration of activity in the Cl^{50} image, is greater.

The thorax, viewed from the ventral aspect, reveals a large accumulation of activity in the region of the heart (Fig. 12), represented by the dark area and, to a lesser extent, by the lungs, represented by the surrounding light area.

Other TOKIM images show the kidneys as a well defined structure in the abdomen as viewed in the left lateral aspect (Fig. 13), and the testes, the dark spot in the center in the ventral pelvic image (Fig. 14).

Figure 15 shows a male dog scanned on the HEG scanner at the oxygen steady-state. The output on this and the following 2 standard deviation displays have been smoothed by nine point averaging. Elevated steady state levels are seen in the brain, in the heart and lungs, upper abdomen and kidney and in the testes.

A carbon monoxide steady state shown in Figure 16 is contrasted to the oxygen steady state, in that blood is presumed to be the principle labeled organ and that elevated steady state levels reflect regions of pooling and perfusion. This display is dominated by intense activity in the heart, lungs, the liver and kidney. The absence of activity in the region of the brain is also noteworthy.

Figure 17 shows the carbon dioxide steady state which represents a labeling of the water pools, as the carbonic

Figure 10. Uptake of $^{15}\text{O}_2$ in normal dog, not corrected for decay, using external probes over head and right rear leg.

Figure 11. TOKIM image of dog's head at $^{15}\text{O}_2$ steady state, viewed in left lateral aspect, shows localization of activity in region of the brain as well as areas of neck and frontal sinus.

Figure 12. Thoracic image, anterior view, of normal dog at $^{15}\text{O}_2$ steady state imaged with TOKIM. Dark areas in center of image are result of recycling the image and show myocardium as region of highest activity.

Figure 13. Left lateral abdominal image of normal dog at $^{15}\text{O}_2$ steady state. Areas of upper abdomen at left of image represent highest levels of activity. Light area in center is kidney.

Figure 14. Pelvic image, anterior view, of normal dog at $^{15}\text{O}_2$ steady state, imaged with TOKIM. Lower abdominal areas have been recycled several times to enhance image of testes at right.

Figure 15. Whole body scan, left lateral, of normal dog at $^{15}\text{O}_2$ steady state, performed on HEG scanner and displayed in 2 standard deviation summed output.

DOG M-97 σ
 $C^{15}O$ WHOLE BODY SCAN
STEADY STATE
SUMMED OUTPUT 2σ

Figure 16. Whole body scan, left lateral, of normal dog at $C^{15}O$ steady state, performed on HEG scanner and displayed in 2 standard deviation summed output.

DOG M-97 ♂
 $C^{15}O_2$ WHOLE BODY SCAN
STEADY STATE
SUMMED OUTPUT 2σ

Figure 17. Whole body scan, left lateral, of normal dog at $C^{15}O_2$ steady state, performed on HEG scanner and displayed in 2 standard deviation summed output.

anhydrase reaction will transfer most of the label to water. There are some apparent differences between the carbon dioxide steady state and the oxygen steady state; elevated activity in the kidney, diffuse elevated activity through the head, chest and abdomen and especially the complex activity contours around the heart and liver.

Figure 18 shows a regional scan of the oxygen steady state of a St. Bernard with an osteogenic sarcoma of the right forepaw. This image is from the dorsal aspect. In addition to the familiar landmarks, there are unusually high accumulations of activity in the area of the lesion.

A carbon monoxide steady state of the same animal fails to show accumulation of activity in the site.

CONCLUSIONS:

We have postulated that organ imaging at the steady state with oxygen-15 is a function of the metabolism of the organ. If, at the steady state, oxygen is metabolized rapidly and the net rate of diffusion of the resulting labeled water is small in relationship to the rate of physical decay, then regional steady state levels are functions of the rate of oxygen utilization.

Steady state images of $^{15}\text{O}_2$ provide a regional metabolic profile of the subject, silhouetting those organs which have the highest respiratory quotients.

The technique is being developed as a non-invasive in-vivo quantitative method for the recognition of normal, pathological and necrotic tissue, in diagnostic and screening procedures and in assessing regional response to therapy.

(a)

(b)

Figure 18. Large dog with osteogenic sarcoma of right forepaw, (a) in position for steady state scanning. (b) Displayed at $^{15}\text{O}_2$ steady state.

B-2. THE USE OF CARBON-11 CYSTEINE FOR IMPROVED PANCREATIC IMAGING

OBJECTIVE:

To develop a rapid and facile method for synthesis of ^{11}C -cysteine and to evaluate its potential as an agent for imaging the pancreas.

A progress note on the ^{11}C -valine study is included.

MATERIALS AND METHODS:

Because of the synthesis of ^{11}C -labeled cysteine with high specific activity was still being developed at the beginning of this study, organ distribution studies were performed using cysteine- $\text{U-}^{14}\text{C}$ purchased from New England Nuclear Corp., Boston, Mass. This was administered to a heterogeneous group of albino rats by injection into the peritoneum, two hours after feeding. The animals were sacrificed at designated intervals following administration and the pancreas was excised, along with blood, the liver, kidneys and spleen. Samples of each tissue were solubilized in NCS Solubilizer (Amersham-Searle Corporation, Arlington Heights, Illinois) and an aliquot was counted in a toluene-based cocktail in a liquid scintillation counter.

RESULTS:

The distribution of carbon-14 activity resulting from the administration of cysteine- $\text{U-}^{14}\text{C}$ is shown in Table IV. These results show that cysteine is well incorporated into the pancreas and maintains these high concentrations through the course of the experiment. By comparison the amounts incorporated by the liver and spleen are low. The kidney is about the same level as pancreas.

Since the Strecker synthesis method for preparing millicurie amounts of ^{11}C -valine was not successful, no animal or clinical work on the use of this compound as a pancreatic or soft tissue tumor scanning agent has been done during the past year. However we have previously reported in last year's progress report on the encouraging results in rats of the uptake of ^{14}C -valine in the pancreas, and we have been working on the development of another synthetic route to ^{11}C -valine using the lithioisocyanide intermediate. The success of this method is

imminent, and depends on the successful purification of $^{11}\text{CO}_2$ from non-radioactive oxides of nitrogen as discussed in Proposal 1 of this report. We would still like to evaluate ^{11}C -valine as a pancreatic scanning agent when it becomes available.

CONCLUSION:

The preliminary results are encouraging and suggest that further refinement would result in a significant improvement in localization over labeled methionine. On this basis, a full scale program to label cysteine with carbon-11 or selenium-73 as an imaging agent will be continued.

TABLE IV

Distribution of Activity in Various Organs Following
Injection of Cysteine- $\text{U-}^{14}\text{C}$

Time (min)	<u>Total Activity in Organ (cpm)</u>				
	Pancreas	Kidney	Liver	Spleen	Blood
11	950	3,600	5,000	1,600	700
27	35,000	26,000	6,700	4,800	180
47	11,000	14,500	4,100	4,500	540
48	8,700	---	6,700	5,600	--
57	19,500	17,000	6,000	2,750	800
72	12,500	15,000	5,900	4,000	380
81	28,500	19,000	--	--	280
112	22,000	19,000	5,200	6,900	510
124	4,650	6,800	1,900	--	180
160	22,000	16,000	8,100	5,200	700

B-3. THE DEVELOPMENT OF ISOTOPICALLY LABELED SECRETIN AND
PANCREOZYMIN AS A RADIOPHARMACEUTICAL WHICH WILL
SELECTIVELY IMAGE THE PANCREAS

OBJECTIVE:

To label two hormones secretin and pancreozymin, which normally target upon the pancreas and to test the extent of localization of the radio-labeled compound for the purpose of developing a pancreatic scanning agent.

MATERIALS AND METHODS:

Iodine-123 was produced in the SKI cyclotron by bombarding an enriched tellurium-123 target with 15 MeV protons as described previously in Report NYO 910-150. This was used to label porcine secretin (purchased from Sigma Chemical Co., St. Louis, Mo.) by treatment with chloramine-T under alkaline conditions. Inorganic iodide was removed by passing the iodinated secretin through a small column containing Dowex-11 ion retardation resin. Gel electrophoresis and TCA precipitation both showed that the ^{123}I activity was associated with the protein fraction.

The labeled metabolite (6000 cpm) was administered to a large female rat by ventricular injection and the animal was scanned on a single headed scanner (Picker Nuclear) equipped with a focusing collimator designed for thyroid scanning with $^{99\text{m}}\text{Tc}$. Scans were performed immediately following injection, at about 30 min. and about 1 hour. At the conclusion of the scans the animal was sacrificed and the following organs were excised and counted: liver, stomach, duodenum, jejunum, colon, pancreas, kidney, spleen, thyroid and ileum-caecum.

RESULTS:

The scans gave an indication of the dynamics of ^{123}I -secretin metabolism. It appears from these scans that the activity was accumulating in the gastric wall and traveling through the duodenum loop into the jejunum. It was not apparent whether there was any amount of activity in the pancreas.

The distribution of activity at the time of sacrifice is shown in Table V. The organs which were found to contain

TABLE V

Distribution of Activity in Various Organs Following
 Injection of ^{123}I -Labeled Secretin in the Rat

Organ	Counts Per Minute	
	Whole Organ	Per Gram Tissue
Liver	16,653	1,563
Kidney	10,369	4,599
Spleen	645	974
Pancreas	1,067	540
Thyroid	6,190	142,979
Bladder	12,678	7,241
Stomach and Contents	53,792	18,532
Stomach	19,849	12,725
Contents	21,996	23,739
Duodenum	1,740	2,347
Jejunum	26,330	5,092
Ileum-Caecum	6,739	752
Colon	1,526	497

the greatest amounts of activity following dissection were the stomach and its contents, portions of the small intestine, bladder, liver and kidney. Levels of activity in the pancreas were small.

CONCLUSIONS:

The results of a preliminary study were negative with respect to pancreatic localization. This is understandable in view of some of the difficulties which we had envisioned. By labeling the polypeptide externally we were perhaps altering its physiological properties so that it would not be recognized by its pancreatic target cells. The secretin molecule contains no tyrosine residues and only a single histidine residue at the N-terminal position. This limits the number of sites available for iodination and yields a product of questionable stability. The metabolism of secretin is not well established and it is not known how long it is bound in its target cells, if it is catabolized locally or if it is denatured and cleared. Secretin, in addition to its action in the pancreas, has been reported to have a hormonal action on the gastric mucosa. The commercial preparation was porcine in origin and contained about 20% pancreozymin. With these complicating factors, the negative results obtained do not rule out the possible use of ^{125}I -secretin (or pancreozymin) as a pancreatic imaging agent. However, this particular approach now has a lower priority in our search for pancreatic localizing agents.

B-4. ^{11}C -DIPHENYL HYDANTOIN AND ^{11}C -HYDROXYPHENYLPHENYL
HYDANTOIN FOR BRAIN AND BRAIN TUMOR LOCALIZATION

OBJECTIVE:

To evaluate localization of ^{11}C -diphenyl hydantoin (DPH- ^{11}C) and ^{11}C -hydroxyphenylphenyl hydantoin (HPPH- ^{11}C) in monkeys, as possible scanning agents for the brain, and primary or metastatic brain tumors.

MATERIALS AND METHODS:

DPH- ^{11}C or HPPH- ^{11}C was injected at a known rate into 5 male rhesus monkeys (5-7 kg) as summarized in Table VI. The injections were made through catheters using an infusion pump. The monkeys were scanned on the Total Organ Kinetic Imaging Camera (TOKIM) and the High Energy Gamma (HEG) scanner from 0 to 120 minutes post-injection. TOKIM data were collected and analyzed by computer. Areas over the brain, liver, heart and lungs, and forearm were selected and counts/sec in these areas were calculated for different elapsed times and the results plotted as a function of time. HEG scans were performed over the total body of the monkeys and activities in the area of the brain, heart and lungs, liver and whole body were calculated after tissue background activity had been subtracted. In this way it was possible to estimate the per cent of injected dose to each organ relative to whole body dose, at the time of the scan. These data were used to calculate radiation dose to the whole body as 0.011 rads/mCi, to the liver as 0.060 rads/mCi, and to the brain as 0.025 rads/mCi.

RESULTS:

TOKIM measurements over the head and trunk of the monkey were made for the first 20 minutes after infusion. The radioactivity in areas of the brain, the heart and lungs, the liver and the forearm were calculated at different time intervals and plotted in Figures 19, 20 and 21 for the three different injected materials. Striking differences are apparent in these three cases. The injection of 150 mg of HPPH at 30, 45 and 60 minutes prior to the injection of ^{11}C -DPH produced an increased ratio of brain to liver activity (0.34) compared with ^{11}C -DPH alone (0.23). HPPH is thought to be impermeable to the blood-brain barrier and the activity was seen to be more in the region of the mouth than of the brain. HPPH is known to be secreted in the saliva of humans. Furthermore the brain:liver ratio was only 1:0.16, when ^{11}C -HPPH alone was injected.

TABLE VI

^{11}C -DPH and ^{11}C -HPPH Experiments in Monkeys

Experiment No.	A	B	C	2A	2C
Compound Administered	^{11}C -DPH	^{11}C -DPH	^{11}C -DPH	^{11}C -HPPH	^{11}C -DPH + HPPH
Radioactivity administered (mCi)	9.15	7.87	9.02	6.9	4.17
Volume injected (ml)	3.4	3.05	3.08	1.74	3.02
Dose administered (mg)	33.4	88.6	75.7	32.2	75.5
Infusion time (min)	5.34	5.66	2.65	IV Bolus	2.6
Monkey weight (kg)	5.04	5.40	5.52	5.04	5.52
Radiochemical yield (%)	43.7	57.9	39.7	26.1	44.0
Site of injection	Right femoral	Intra-Muscular	Left Femoral	Left Femoral	Left Femoral

Fig 19. Relative counts/second in observed fields
 X1 = Brain, X2 = Lung-Heart, X3 = Liver, X4 = Forearm

I.V. INFUSION
MONKEY 2C
¹¹C-DPH + HPPH

Fig 20. Relative counts/second in observed fields.
X1 = Brain, X2 = Lung-Heart, X3 = Liver, X4 = Forearm.

Fig 21. Relative counts/second in observed fields.
 X1 = Mouth, X2 = Lung-Heart, X3 = Liver, X4 = Forearm

After the initial 20 minute period, when the distribution of radioactivity has stabilized, the monkeys were transferred to the HEG scanner. Three typical whole body scans for experiments No. C, 2C and 2A are shown in Figure 22. These scans illustrate the differences in distribution between ^{11}C -DPH, ^{11}C -DPH + HPPH and ^{11}C -HPPH. It was thought that there may be uptake of the metabolite HPPH in the pancreas, both from a report by Balachandran et al. (1), and from scans of the monkeys. Therefore 3 mCi of ^{11}C -HPPH were synthesized and injected intravenously into one rhesus monkey, which was sacrificed after 45 minutes. Samples of heart, liver, brain, colon and contents, and pancreas were taken and counted. The results, shown in Table VII indicate that no positive uptake occurred in the pancreas. Relative retention is defined as c/m/g of tissue divided by c/m/g of whole body.

CONCLUSIONS:

^{11}C -DPH definitely localizes in the brain and its uptake in the brain relative to the liver can be increased by prior administration of HPPH. ^{11}C -HPPH does not localize in the brain of the monkey. Rosenblum and Stein (2) have reported that grades III and IV astrocytomas (7 cases) had uptake of DPH in the tumor relative to normal brain of from 1.08 to 3.04 (mean of 2.13) and one case of meningioma had a ratio of 4.0. We have demonstrated that by using ^{11}C -DPH the monkey can be scanned satisfactorily one hour after administration of about 10 mCi of radioisotope, and we therefore believe that this labeled compound should be evaluated in patients with brain tumors as a possible new brain tumor scanning agent.

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Figure 22. Whole body scans of three rhesus monkeys injected into the left femoral veins with (A) ^{11}C -DPH 9.0 mCi, (B) ^{11}C -DPH 4.2 mCi plus non-radioactive HPPH, (C) ^{11}C -HPPH 6.9 mCi. Scans were started 49, 60 and 41 minutes respectively after injections. Scans are computer processed displays corrected for decay to time of injection and analysed into 16, 16 and 32 levels respectively.

TABLE VII

Distribution of ^{11}C -NPPH in the Monkey

	<u>Per Cent Injected Dose</u>	<u>Relative Retention x 100</u>
Heart	0.64	133.1
	0.64	131.8
	0.61	125.9
Liver	3.88	160.5
	4.22	174.7
	4.07	168.0
	4.01	165.3
Brain	0.70	41.5
	0.86	51.2
	0.78	46.8
Colon	0.41	103.3
	0.36	89.3
	0.36	89.4
Pancreas	0.28	40.4
	0.28	40.6
	0.29	42.1

B-5. NITROGEN-13 LABELED COMPOUNDS FOR SOFT TISSUE TUMORS

OBJECTIVE:

To investigate the potential usefulness of ^{13}N -ammonium chloride and other ^{13}N -labeled compounds as imaging agents for the localization of soft tissue tumors.

MATERIALS AND METHODS:

Approximately 30 dogs with a variety of spontaneous tumors and 5 normal dogs were used in this study. The animals with tumors were provided by and studied in cooperation with the Animal Medical Center (AMC). This fortuitous combination of the SKI cyclotron and radiopharmaceutical production facilities and the AMC animal facilities enabled the detailed comparison between imaging results, radiographic findings, and the determination of tumor type and extent of disease at surgery and/or postmortem examination.

The tumor imaging agents investigated in this work were ^{13}N -ammonium chloride and the ^{13}N -labeled amino acids, glutamine and glutamic acid. The nitrogen-13 label was produced in the form of $^{13}\text{NH}_3$ with the SKI cyclotron, using the $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ reaction with a water target and the subsequent reduction of the nitrites and nitrates thus produced. The ammonia, dissolved in the appropriate saline solution, was then ready for intravenous injection. The $^{13}\text{NH}_3$ was also used in the enzymatic synthesis of ^{13}N -glutamine and ^{13}N -glutamic acid (1).

Whole body distribution measurements and static imaging of tumor uptake of these three compounds were performed, 10 minutes after injection, with the Institute's dual-detector High Energy Gamma (HEG) scanner system (2). The use of specially designed "constant response" collimators (3) permitted the absolute quantitative determination of organ activity for these three agents, in terms of percent of injected dose. Scan data were stored on magnetic tape for subsequent display and analysis on our IBM 1800 computer. Display modes consisted of a line printer digital output with alphanumeric characters signifying count rate levels and a storage oscilloscope dot-density display. Both static imaging and dynamic uptake studies were also performed using the TOKIM (4) gamma-camera system.

RESULTS:

The whole body distributions of these ^{13}N -labeled compounds in normal dogs were found to differ significantly (1). ^{13}N -glutamine and glutamic acid both showed negligible uptake in the heart, while $^{13}\text{NH}_4\text{Cl}$ imaged the heart fairly well (uptake of ~4% of injected dose). In the liver, ^{13}N -glutamine was found to have approximately twice (~22%) the uptake of either $^{13}\text{NH}_4\text{Cl}$ or labeled glutamic acid. Uptake was also observed in brain, salivary glands, and bladder.

A positive correlation between tumor imaging with $^{13}\text{NH}_4\text{Cl}$ and postmortem findings was observed in 75% of the dogs studied (5). Poor correlation occurred in cases where uptake in the tumor was obscured by areas of high organ uptake (heart and liver). In one case involving tumor uptake near the myocardial region, ^{13}N -glutamine proved to be a superior imaging agent because of its low uptake in the heart. A positive correlation was also obtained using ^{13}N -glutamine as the imaging agent (5). This study was also extended to include tumors involving bone and the use of ^{13}N -glutamic acid as the imaging agent (6). Four dogs with tumors involving bone were scanned using ^{13}N -glutamic acid, and all were successfully imaged. In two of these four dogs $^{13}\text{NH}_4\text{Cl}$ and ^{13}N -glutamine were used as a comparison, yielding negative results in both cases for ammonium and in one case for the glutamine.

CONCLUSION:

Spontaneous canine and human cancers share many similarities; histological diagnosis, clinical course, and response to therapy are frequently comparable. This similarity, along with the prompt availability of thorough pathological evaluation, provided an excellent model for the study of these ^{13}N -labeled compounds as tumor imaging agents.

The random selection of tumor tissue types and anatomical region allowed the evaluation of a wide variety of neoplastic lesions. However, since few of each neoplastic tissue type could be acquired, definitive conclusions as to specificity of these agents in various diseases could not be made. Generalizations provide possible guidelines for further investigation of these agents. In general, enlarged lymph nodes and other organomegaly associated with lymphosarcoma were consistently well visualized with $^{13}\text{NH}_4\text{Cl}$ and ^{13}N -glutamine,

as were mammary adenocarcinomas and their metastases. Neoplasms involving bone and their metastases, however, were inconsistently visualized with these two agents, but were well demonstrated with ^{13}N -glutamic acid.

Normal regional distribution of the labeled compounds was also an important factor in tumor visualization. ^{13}N -glutamine and glutamic acid showed more potential for thoracic imaging, than $^{13}\text{NH}_4\text{Cl}$, because they exhibit low uptake in the heart. The extension of the ^{13}N label to other compounds, including other amino acids, may provide agents with similar regional advantages plus greater tissue specificity.

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B-6. STUDIES OF METABOLISM OF $^{13}\text{NH}_3$ IN NORMAL DOGS

OBJECTIVE:

To develop a metabolic basis for the localization of $^{13}\text{NH}_3$ and ^{13}N -labeled metabolites in mammalian systems.

MATERIALS AND METHODS:

Initial studies have centered about the development of a rapid assay for ^{13}N -labeled metabolites in the presence of $^{13}\text{NH}_3$. The procedure chosen involves an initial assay of the endogenous ammonia in the tissue sample, followed by conversion of the nitrogen function in the metabolite to ammonia and assay of the total ammonia in the sample. Ammonia was assayed by a modification of the Conway diffusion method. An aliquot containing $^{13}\text{NH}_3$ is pipetted into a small erlenmeyer flask which is sealed with a rubber cap. A well, containing 6N H_2SO_4 , is suspended from the cap and 10N NaOH is cautiously injected into the flask. The flask is then shaken gently for 5 minutes in a Dubnoff incubator shaker at 60° and the flask is opened. The well and the flask are counted separately. The percent of activity in the well represents the ammonia present in the sample. Urea is assayed in the sample, by treating initially with urease, incubating a few minutes and then assaying for ammonia. Glutamine, glutamic acid and asparagine require pre-incubation with glutaminase, glutamic dehydrogenase, and asparaginase respectively.

RESULTS:

The early results obtained indicated that only 50-58% of the ammonia was recovered in the well. The remainder was found to be in the flask. Efforts to improve the yield by increased agitation, higher temperatures, addition of carrier, steeper hydrogen ion gradients and longer incubation times were not successful.

CONCLUSIONS:

The study could not be continued until a reevaluation of the assay system could be made. Ammonia assay will be effected by performing the assay in the presence of ammonia carrier and the yield will be calculated by measuring the efficiency of the recovery system by semi-micro methods.

B-7. NITROGEN-13 LABELED AMMONIUM CHLORIDE FOR PATIENT STUDIES

OBJECTIVE:

To investigate the value of $^{13}\text{NH}_4\text{Cl}$ as an imaging agent for soft-tissue tumors in humans and to compare the results obtained using this agent with those obtained using ^{67}Ga .

MATERIALS AND METHODS:

In recent months, six patients were selected for this study with histologically proven evidence of malignancy at some time and with present clinical evidence of some active tumor. To reduce the number of variables affecting the study, the protocol required that patients not have had prior therapy except radiation and/or surgery at a site other than the one of current interest. The patients' tumor included epidermoid cancer, oat cell tumor, colon cancer and leiomyosarcoma.

The nitrogen-13 label was produced in our cyclotron facility, with the $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ reaction using a 14 MeV proton beam and a water target. The $^{13}\text{NH}_4\text{Cl}$ was then produced and processed in a sterile and apyrogenic form. Maximum dose, at time of injection, was 10 mCi of ^{13}N per 70 kg of body weight. The $^{13}\text{NH}_4\text{Cl}$ was administered intravenously, and tumor imaging was initiated zero to five minutes after injection. This choice of time to begin imaging was suggested by animal experiments (1,2) previously carried out here. These showed that clearance of activity from the blood was rapid for $^{13}\text{NH}_4\text{Cl}$, with organ "equilibrium" levels reached 5-10 minutes post injection. Tumor imaging was performed using the SKI dual-detector High Energy Gamma Ray (HEG) scanner system (3), using specially designed "constant response" collimators (4). Scan data were stored on magnetic tape for subsequent display and analysis on our IBM 1800 computer. Display modes were a line printer digital output, with alphanumeric characters signifying count rate levels, and a storage oscilloscope dot-density display. When possible, for the sake of comparison, scan images were also produced for these patients using ^{67}Ga -citrate as the tumor localizing agent. For these scans the ^{67}Ga was administered at a dose of 0.045 mCi/kg body weight, and tumor imaging performed approximately 48 hours after IV injection.

RESULTS:

In the first case studied (M.I.) with $^{13}\text{NH}_4\text{Cl}$, a case of leiomyosarcoma metastatic to the liver, a comparison scan was performed using $^{99\text{m}}\text{Tc}$ -sulfur colloid. Both agents showed multiple filling defects in the liver. Quantitative evaluation of the $^{13}\text{NH}_4\text{Cl}$ scans done pre- and post-hepatic artery ligation showed a drop from 25% to 16% of the injected dose present in the liver. Tumor areas contained less activity than normal liver in the images.

A 45 year old man (S.W.) with metastatic carcinoma of the colon was examined with ^{13}N -ammonium chloride and 3 weeks later with ^{67}Ga -citrate while receiving chemotherapy. The metastatic lesion took up less of both of these agents than did surrounding normal liver.

In the case of an oat cell cancer of the lung (C.H.), scans were performed with $^{13}\text{NH}_4\text{Cl}$ and ^{67}Ga -citrate, and in addition with ^{111}In -bleomycin. The gallium was found to be superior in this case, in that ^{67}Ga gave the highest ratios of activity in the tumor to normal lung, and to the liver. The ^{13}N -ammonium chloride scan showed the tumor region to have approximately 20% more activity than the normal lung. The liver region was more radioactive than the tumor, due to the high uptake ($\sim 10\%$) of the ^{13}N label in the liver. The ^{111}In -bleomycin results were intermediate, with tumor containing more ^{111}In than the liver.

The next case studied (C.M.) was an epidermoid cancer of the lung with a left supraclavicular mass. Studies were done with ^{13}N , ^{67}Ga , and ^{111}In -bleomycin. The tumor was better visualized with ^{67}Ga and ^{111}In -bleomycin and poorly seen with ^{13}N -ammonia.

A 48 year old woman (E.R.) with epidermoid carcinoma of the neck region, received ^{111}In -bleomycin, ^{13}N -ammonium chloride, and after bleomycin therapy a study with ^{67}Ga . The greatest tumor uptake was with ^{111}In -bleomycin, next ^{67}Ga , and then ^{13}N -ammonia which showed only slight differences from the contralateral side.

A man (J.P.) with recurrent leiomyosarcoma was examined with ^{67}Ga and ^{13}N -ammonia. The tumor was well visualized with both agents. Liver uptake was less than tumor uptake with ^{67}Ga but the opposite occurred with ^{13}N .

CONCLUSIONS:

Due to the small number of cases studied to date, and the fact that the number of each tumor type included is even smaller, it is impossible to draw any detailed conclusions about the usefulness of $^{13}\text{NH}_4\text{Cl}$ as an imaging agent for soft tissue tumors. So far, $^{13}\text{NH}_4\text{Cl}$ would appear to be less satisfactory than ^{67}Ga -citrate as an imaging agent in these cases.

Based on previous work done here (5,6) using animals with spontaneous tumors, it may be advantageous to extend the current study to include the use of ^{13}N -glutamine and ^{13}N -glutamic acid, at least for tumor types for which $^{13}\text{NH}_4\text{Cl}$ seems unsatisfactory. In animal studies, lymphosarcoma in nodes and other organs were consistently well visualized with both $^{13}\text{NH}_4\text{Cl}$ and ^{13}N -glutamine, as were mammary adenocarcinomas and their metastases. Neoplasms involving bone were inconsistently visualized with these two agents, but were well demonstrated with ^{13}N -glutamic acid. These observations suggest that there may be success in the application of ^{13}N -labeled organic compounds for tumor localization.

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B-8. QUANTITATIVE EVALUATION OF RADIATION THERAPY TO OSSEOUS
MANIFESTATIONS OF β -THALASSEMIA USING ^{52}Fe AND $^{99\text{m}}\text{Tc}$ SC

OBJECTIVE:

To ascertain the radiation dose required to interrupt the excessive bone marrow activity in the facies of β -Thalassemia patients by monitoring erythropoiesis with ^{52}Fe and $^{99\text{m}}\text{Tc}$ SC scans pre- and post-radiation therapy.

MATERIALS AND METHODS:

All Iron-52 scans were performed on the High Energy Gamma Ray (HEG) rectilinear scanner using the "constant resolution" collimators specifically designed for 511 KeV. The method of quantitation was analogous to that used for ^{51}Cr labeled acid citrate dextrose (ACD) damaged erythrocytes and ^{52}Fe labeled plasma. A head phantom was scanned in order to determine conversion factors to relate the counts within an organ's scan image to a known number of microcuries. For each patient the same type specific donor was used to obtain the necessary plasma. Repeat scans were performed until marrow activity in the irradiated bone was ablated.

Marrow activity was monitored by ^{52}Fe and $^{99\text{m}}\text{Tc}$ SC scans before radiation therapy was begun and at appropriate intervals afterwards. Depending on scan results, additional doses of 1000 rads were administered.

RESULTS:

A nine year old boy (R.C.) with homozygous β -Thalassemia (Cooley's Anemia) was the first to undergo this procedure. His severe anemia had caused an erythropoietin response which increased the mass of erythroid marrow. This widening of the marrow cavities of the frontal bone, orbits, and maxillae caused deformity and prominence of the facial bones. Skull x-rays showed a severe "hair-on-end" appearance of subperiosteal bone.

A plasma iron clearance study gave a half time of 5 hrs. and 18 min. at the time of the pre-radiation therapy scan. The first therapy consisted of five treatments of 200 rads each to the paranasal sinus using the 20 MeV Betatron with a field size of 9 x 13 cm calculated at 90% depth, with shielding of

both eyes. When the pre-radiation therapy (RT) scan is compared with the first post RT scan, a marked change in the irradiated area is evidenced with both isotopes. Results of the ^{52}Fe scans are shown in Table VIII. $^{99\text{m}}\text{Tc}$ SC scans were performed pre-radiation therapy and after the first 1000 rads. These were discontinued after the ^{52}Fe scans proved to be a much more useful monitor of the radiation effect.

Approximately 4 months after the end of the last therapy dose, and subsequent to normal growth, R.C.'s breathing was noted to be eased and slight facial improvement was observed.

CONCLUSION:

This procedure was designed to halt the distortion of the paranasal sinuses and consequently the deformity of the face. Bone improvement was already evidenced within a few months as normal skeletal growth proceeded. It is hoped to schedule a followup study in the near future. Additional patients will be actively sought to further evaluate the technique.

TABLE VIII

IRON-52 UPTAKE QUANTITATION

Scan and Therapy Sequence	<u>Percent Injected Dose in Head</u>	
	Upper Portion (non-irradiated)	Lower Portion (irradiated)
Pre Radiation Therapy (RT)	13%	12%
1000 Rads Administered		
6 Days Post End of 1st RT	19%	5%
41 Days Post End of 1st RT	12%	7%
Second 1000 rads given		
17 Days Post End of 2nd RT	19%	11%
Third 1000 rads given		
6 Days Post End of 3rd RT	19%	6%

B-9. NEUTRON ACTIVATION OF CALCIUM AND OTHER ELEMENTS

OBJECTIVE:

To determine the quantitative rate of release of ^{37}Ar by expiration and thereby the total ^{37}Ar expired following a fast neutron cyclotron irradiation of the whole body of a normal human subject in-vivo. To develop and implement methods to determine the total ^{37}Ar produced in the body during the irradiation. To attempt a physiological explanation of these data. In this explanation we assume:

- 1) The total ^{37}Ar is directly proportional to total body calcium, if a proper correction is made for mean bone crystal size.
- 2) Since the mean crystal size is smaller in regions of high metabolic activity than in more stable regions of bone, ^{37}Ar will move more rapidly from these active regions.

The first human fast neutron exposure in-vivo was carried out in this laboratory (Report 1972-73) to measure the amount and rate of release of ^{37}Ar by expiration. This followed a pioneering study by H.E. Palmer (1) in small animals. Our study was done with a very low radiation dose and thus demonstrated that assays of ^{37}Ar can be done in humans which permit further study of the above postulates. If predictable account can be made of the mechanisms responsible for ^{37}Ar expiration, this method will have potential for widespread application in the study of metabolic bone disease.

MATERIALS AND METHODS:

a. Study in-vivo

In last year's Progress Report 1972-73, we reported the results of the first human experiment in-vivo using the $^{40}\text{Ca}(n,\alpha)^{37}\text{Ar}$ reaction (2). This experiment was done in collaboration with scientists at Brookhaven National Laboratory. The experiment was qualitative. Sufficient ^{37}Ar activity was expired by the human subject in a reasonable period following a very low dose fast neutron exposure (0.8 mrad) from a Pu-Be neutron source, to provide a sound basis for the investigation of this method by quantitative methods. Studies by both in-vivo and in-vitro means have been carried out.

In common with other nondestructive quantitative activation analysis methods, uniformity of production throughout the target and equal efficiency for assay of all the radioactive products are essential. Neutron source investigations were directed toward maximizing production uniformity.

A nondestructive analysis of a living human being must be performed with acceptably low absorbed radiation dose. The radiation source must be capable of delivering the required dose quickly, so that patients can maintain a fixed position during exposure, and preferably, short enough to make a pulse dose approximation in the data analysis. Neutrons obtained from the Sloan-Kettering cyclotron by 23 MeV helium-3 bombardment of a beryllium target provide a reliable and adequate neutron source.

Obtaining uniform detection of the ^{37}Ar activity, generated throughout the bone tissue of the body, depends on the efficiency with which this activity is released from the body through the respiratory system. After leaving the body, the ^{37}Ar is separated from the other expired gases and assayed in a small, low background proportional counter with nearly 100% efficiency. This efficiency is chiefly responsible for the low radiation dose achieved by this procedure. Argon-37 decays 100% by electron capture with a disintegration energy of only 2.8 keV which cannot be detected externally. A nondestructive separation of the activity from the body (target) is therefore essential to this procedure.

Study of the excretion of an inert gas to ascertain its biological pathways, efficiency of release from the bone tissue production site, and time rate of release from the human body was necessary to establish further this method's feasibility for clinical use. Our quantitative human study was carried out to provide answers to these questions. The results were then compared with those available in the literature from other inert gas studies such as radon excretion by exhalation from bone tissue containing radium.

A normal human male subject was irradiated using fast neutrons produced in the $^9\text{Be}(^3\text{He},n)$ reaction. Low background counting techniques were applied to assay breath samples containing as little as 0.01 dpm corrected to end of irradiation (EOB). Six samples were taken in the 12.5 hr.

period following two one minute bilateral fast neutron exposures. Total neutron absorbed dose in this irradiation was limited to less than 2 mrad. These expired ^{37}Ar counting data were fitted by a two exponential component least square method. This data fit was then integrated to give the quantitative total ^{37}Ar activity expired as a result of this irradiation.

The total ^{37}Ar produced in the body was estimated as described below. The ratio of the total activity expired to the total activity produced is the fraction of ^{37}Ar removed from the body by way of expiration. If it is not quantitatively removed, the fate of the retained fraction must be determined. The retained fraction must be shown to be independent of physiological parameters, difficult if not impossible to control, which would make the expired fraction variable and thus not proportional to the calcium content of the body. The absolute production of ^{37}Ar per gram calcium was determined by irradiating calcium nitrate in water solution. This solution was sealed in a pyrex bulb and placed within a water moderated calf phantom. This phantom was then exposed in a position equivalent to that of the calf location. An Alderson phantom, containing a human skeleton, with access holes where aluminum activation foils could be placed, was then used to measure the average fast neutron flux relative to the tibia in a total of 22 bone subgroups. The phantom's outer plastic case allowed its body space, representing soft tissue, to be filled with tissue equivalent neutron moderator. The percent bone tissue in each of these bone compartments was determined by analyzing the bone tissue weights measured and tabulated by Mechanik in 1926 (3) for six total male human skeletons.

Weighting the percent bone tissue in each compartment by the relative neutron flux measured therein and summing the results was done to reduce flux non-uniformity errors expected from flux variation measurements elucidated in Section A.3 of this report.

Estimation of the subject's total body calcium mass was made from two independently determined algorithms for normal males published by Cohn et al. (4) and Nelp et al. (5). Multiplication of this calcium mass by the measured absolute ^{37}Ar production per gram calcium at the tibia position and by the weighted sum yielded the absolute production of ^{37}Ar resulted from this exposure.

b.. Bone tissue analysis in-vitro

Rowland et al. (6) showed that the radon produced in dog bones from internally deposited radium burdens exhibited identical fractional radon release in-vivo and in-vitro. In other words, acetone-fixed air-dried bone samples lost the same fraction of radon produced within them, as that lost by the body from these same bones in-vivo by way of the respiratory mechanism. Marinelli, L.D. et al. (7) showed fractional radon release from humans carrying long term radium burdens to exhibit a small standard deviation between individuals. Rowland et al. measured in-vitro the fractional release from one of these bones and found virtually identical results to Marinelli's in-vivo results. The small standard deviation seen by Marinelli is surprising since radioautography shows the radium to be very inhomogeneously distributed, even at these long burden times, and in areas of high concentration to show considerable evidence of local damage. A wide range of radium doses had been ingested by these individuals so that large variations in the amount of bone tissue damage might have been expected. Apparently the observed bone tissue radiation damage had little or no effect upon the fractional release of radon.

The fractional release of radon has been found to vary with age of the radium burden in a similar manner for rats, dogs and humans, but not to vary with age at injection (8). This was interpreted by Mays et al. (8) to mean that these species have uniformity in bone crystal sizes and in the rates at which their bone crystals grow.

The age of burden effect on the level of total fractional radon release is explained by the mean crystal size in the regions where radon is produced. Since argon is produced uniformly throughout bone its fractional release will depend upon the mean crystal size of the whole skeleton. Since there is evidence from electron micrographs (9) that senile bones exhibit larger average crystals than those in infant bones, an age correction will be required. This should not be large, however, especially in adults, because radon fractional release changes by only about 20% in the extreme case of a mean crystal size represented by a newly forming bone region (at close to time of radium injection) and that years later when crystal size in the radium containing regions are more representative of the mean in the individual.

Argon and radon are both inert gases. Radon's greater solubility in body tissues would be expected to lend greater difficulty to its escape from the body than for argon, once these radionuclides had entered the bone capillary system. Since radon is apparently not trapped by tissues other than bone, argon should behave similarly. In other words, either argon is trapped in bone tissue essentially permanently or it is evacuated from the lung by expiration. Clearly, according to the data of Rowland et al. (6) we expect that argon produced within bone in-vivo or in-vitro will exhibit identical fractional release. We now expect that any possible changes in fractional release, such as due to bone age, sex, location of bone, or disease invasion can be studied in-vitro and these results used to correct in-vivo results.

A section of normal human cortical bone was taken from the right fibula of a 18 year old man and studied to determine fractional argon release. Two portions, each about 5 grams, were fixed in acetone and dried at room temperature. One portion was not processed further. The other was ashed in a muffle furnace for 5 hours at 650°C. Both portions were placed in pyrex containers. The containers were evacuated and flushed three times with helium and then sealed in a helium atmosphere at 600 mm of mercury. Irradiation was carried out using neutrons produced by the $^9\text{Be}(^3\text{He},n)$ reaction. Activity in the container was removed by flowing helium through it until no more ^{37}Ar could be extracted, then admitting 1 molar HCl to dissolve the bone crystal and finally bubbling helium through the resulting solution until all crystal trapped ^{37}Ar was removed. The sum of these two quantities is the total ^{37}Ar produced and the ratio of the first fraction to the total equals the released fraction.

RESULTS:

The results of the in-vivo exhalation study are shown in Figure 23. Displayed is a plot of the absolute ^{37}Ar activity in disintegrations per minute of exhalation versus time following irradiation extended to 12.5 hr. The vertical bars are 69% confidence limits on each measurement. The horizontal bars correspond to the time period over which each breath sample was collected. A least square, two exponential component fit to the data satisfies the following

Figure 23. The absolute ^{37}Ar activity rate of release from a human subject's body by exhalation in disintegrations per minute versus elapsed time following irradiation.

relation:

$$A = 0.0468 \exp(-0.0177t) + 0.00197 \exp(-0.00339t),$$

where A is the activity in dpm per minute exhaled and t is the time in minutes following irradiation. The 40 and 200 minute half time components account, respectively, for 96 and 4% of the total exhaled ^{37}Ar activity. Integration of these results amounts to $3.2 \pm 0.5 \text{ dpm}_{\text{EOB}}$.

Table IX includes the results of the percent bone analysis, the neutron flux ratio to tibia, and the flux normalized percent bone. A weighting factor for the neutron flux and bone tissue distribution is obtained by summing the results in column 3 of this table, i.e.

$$\sum_i \left(b_i \frac{\phi_i}{\phi_{\text{Tibia}}} \right) = 1.27 \pm 3\%$$

where i = 22 bone compartments

b_i = fractional bone tissue (derived from Ref. 3)

$\frac{\phi_i}{\phi_{\text{Tibia}}}$ = neutron flux relative to the tibia position

The measured production rate at the tibia standard position (S_{Tibia}) for the in-vivo study was 3.8×10^{-5} dpm/gm calcium. This brings us to a whole body production sensitivity of 4.87 dpm/Kgm of calcium in the whole body.

The Cohn et al. (4) method of predicting whole body calcium content in normal males uses the following expression:

$$M_{\text{Ca}} (\text{gm}) = 54.6 H(K)^{1/2},$$

TABLE IX

Bone	Percent Bone	Neutron Flux Ratio Bone/Tibia	Flux Normalized % Bone
Humeri	7.0 ± 0.4	1.68 ± 0.03	11.8 ± 0.7
Ulnae	2.5 ± 0.3	1.32 ± 0.03	3.3 ± 0.4
Radii	2.0 ± 0.2	1.32 ± 0.03	2.7 ± 0.2
Hands and Wrists	2.8 ± 0.4	1.32 ± 0.03	3.7 ± 0.5
Upper Extremities	14.3 ± 0.9		21.5 ± 1.0
Femura	16.6 ± 1.0	1.14 ± 0.01	18.9 ± 1.3
Tibiae	9.5 ± 1.2	1.00 ± 0.01	9.5 ± 1.2
Fibulae	2.1 ± 0.4	1.00 ± 0.01	2.1 ± 0.4
Patellae	0.5 ± 0.1	1.16 ± 0.02	0.6 ± 0.1
Ankles and Feet	5.9 ± 0.4	0.91 ± 0.01	5.4 ± 0.4
Lower Extremities	34.6 ± 2.9		36.5 ± 1.8
Ribs 1-4	2.7 ± 0.7	1.32 ± 0.01	3.6 ± 0.9
Ribs 5-8	4.4 ± 0.9	1.38 ± 0.02	6.0 ± 1.2
Ribs 9-12	2.3 ± 0.4	1.29 ± 0.02	2.9 ± 0.5
Ribs 1-12	9.4 ± 1.8		12.6 ± 1.6
Cranium	10.9 ± 1.2	1.18 ± 0.02	12.8 ± 1.4
Mandible	2.26 ± 0.4	1.18 ± 0.02	2.7 ± 0.4
Head	13.15 ± 1.3		15.5 ± 1.5
Scapulae	3.62 ± 0.3	1.81 ± 0.03	6.6 ± 0.6
Clavicle	1.18 ± 0.1	1.81 ± 0.03	2.1 ± 0.2
Sternum	0.62 ± 0.1	1.33 ± 0.02	0.9 ± 0.1
Upper Girdle	5.42 ± 0.4		9.6 ± 0.7
Sacrum	2.23 ± 0.4	1.12 ± 0.02	3.9 ± 0.7
Innominate	10.08 ± 1.2	1.39 ± 0.01	8.1 ± 1.0
Lower Girdle	12.31 ± 1.3		11.9 ± 1.2
Cervical Vertebrae	1.94 ± .4	1.14 ± 0.02	3.9 ± 0.8
Dorsal Vertebrae	4.89 ± 1.0	0.95 ± 0.02	10.3 ± 2.0
Lumbar Vertebrae	3.99 ± 0.7	1.30 ± 0.02	5.1 ± 0.9
Spine	10.81 ± 1.5	1.13 ± .01	19.3 ± 2.5
Total Body	100 ± 3		127 ± 4

All indicated errors are ± 1 standard deviation and are considered independent.

where H (Meters) is body weight and K (gm) is total body potassium. The total body potassium measurement performed in the Brookhaven National Laboratory whole body counter facility gave 120 gm. A skeletal height measurement amounted to 1.74 meters. This gave 1090 ± 87 gm whole body calcium. The Nelp et al. (5) algorithm estimate yielded.

$$M_{Ca} \text{ (gm)} = 0.203(H)^3 \\
= 1069 \pm 59 \text{ gm}$$

Recently, Cohn, et al. (10) completed a study which included an analysis of the correlation between whole body calcium measurements by thermal neutron capture in ^{48}Ca with determinations of the bone mineral content of the radius. Correlation in this case was shown to be highly significant (0.973, $P < .001$). Dr. K. J. Ellis at Brookhaven National Laboratory kindly agreed to measure the bone mineral content of our subject and determine the predicted total body calcium based upon their correlation. The result was 968 gm. This result is approximately 10% lower than the result expected from the two prediction methods discussed above. A check of their data (10) on normal males revealed a percent standard deviation of 17% in the bone mineral measurements, whereas, it was only 4% in the total body calcium predicted values. The use of this standard deviation yields a 968 ± 164 gm result. The measurements are in agreement because their respective standard deviations overlap. The error in the calcium prediction is smaller, however, so we continue to use it for our total body calcium estimate.

The estimated total activity produced (R) is the product of the production sensitivity in the tibia (S_{Tibia}), the weighting factor sum derived above, and the calcium mass (M_{Ca}).

$$R = S_{\text{Tibia}} \sum_i \left(b_i \frac{\phi_i}{\phi_{\text{Tibia}}} \right) M_{\text{Ca}} \text{ (gm)}$$

$$= 3.8 \times 10^{-3} \text{ (dpm}_{\text{EOB}}/\text{gm Ca)} (1.27) (1069) \text{ (gm Ca)}$$

$$= 5.2 \pm 10\% \text{ dpm } ^{37}\text{Ar}$$

The ratio of total activity expired to total produced gives a fractional release of 0.6.

The in-vitro bone study gave 0.67 for the fractional release from the acetone fixed bone. On the other hand the ashed bone fractional release was only 0.17. This is further confirmation to the work of Rowland et al. (6) on radon that the inert gas fraction remaining in bone can be accounted for by essentially permanent trapping in individual hydroxyapatite crystals. Ashing causes the individual crystals to grow in size which would be expected to reduce the fraction of gas released, if crystal trapping is the mechanism responsible. Table X summarizes the comparative argon and radon in-vivo and in-vitro results. The agreement between the in-vivo and in-vitro results in both studies is excellent.

Figure 24 shows the integrated percent argon-37 released from the whole body as a function of time following irradiation. This curve was derived by integrating the rate of release fit. The arrows on the curve indicate the integrated fraction expired as a function of time if correction is not made for that retained by bone crystal.

CONCLUSIONS:

A single quantitative human body calcium measurement in-vivo has been carried out which has significantly added to our understanding of the mechanisms involved in the exhalation of ^{37}Ar produced in bone. Our results demonstrate a extremely low dose requirement for this assay. For example, a one hour exhaled gas collection and overnight activity assay would require a dose of 7 mrad with 1% statistical counting error. If collection were extended to four hours and one week analysis, the dose required would be lowered to 0.6 mrad.

The total fractional release behavior of radon and argon are remarkably similar. The radon data taken by itself indicates high confidence that fractional release in-vivo of an inert gas is stable and reproducible. The comparative total gas release figures in-vivo and in-vitro give us an accounting of all of the activity produced. Any dependence due to changes in mean bone crystal size in total fractional release in humans, such as those related to growth or disease processes, can be evaluated in-vitro with human bone samples obtained from autopsy cases. Algorithms can be derived in this manner for any corrections to in-vivo results that might be found necessary.

TABLE X
HUMAN RADON VERSUS ARGON FRACTIONAL EXCRETION

	RADON	ARGON
<u>IN-VIVO</u>	0.698 $\pm$ 0.027*	0.6
<u>IN-VITRO</u> AIR DRIED		
CORTICAL BONE	0.70**	0.67

*Long Term Radium Burden,
Marinelli, L.D. et al., 1962.

**Rowland, R.E., 1958

Figure 24. The percent ^{37}Ar activity released from a human subject's body by exhalation versus time following irradiation. Arrows indicate the percent of the total exhaled.

Such studies are currently underway in this laboratory. The equipment improvements discussed in the Neutron Activation Instrumentation Section of this report (A-3) will be implemented as soon as possible. Studies of the reproducibility of the rate and integral ^{37}Ar expired and their correlation with skeletal condition and total calcium will then begin.

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B-10. THE USE OF BISMUTH-206 FOR SOFT TISSUE TUMOR LOCALIZATION

OBJECTIVE:

1. To study the metabolism and distribution of radioisotopes of bismuth in normal and abnormal tissue.
2. To evaluate the potential of ^{206}Bi as a soft tissue tumor localizing agent.

MATERIALS AND METHODS:

Female rats of the CD strain, weighing about 350 grams each, were injected intraperitoneally with 180 μCi of ^{206}Bi -citrate or chloride. The animals were sacrificed by exsanguination from the heart at designated intervals following administration of the isotope. Samples were taken of eighteen organs and tissue. All samples were weighed in a tared vial and counted in a 3 inch sodium iodide well crystal or at a specified distance from the same crystal. The data were processed by correcting for background, normalizing for decay during the counting period, and correcting for system dead time and for physical decay to the time of injection. Volume corrections for samples of this size range were determined to be minimal and therefore were not made.

Retention in the whole body was measured by administration of an intraperitoneal dose of ^{206}Bi to sedated rats of the same strain. The animals were counted over the sodium iodide crystal within ten seconds following treatment and at designated intervals thereafter.

Whole body retention and excretion studies were performed by maintaining the subject animals in a metabolic cage. After administration of ^{206}Bi -citrate, the animals and accumulated excreta were counted at designated times over the sodium iodide crystal.

Scanning was performed on a single headed scanner (Picker Nuclear) equipped with a 19 hole focusing collimator designed for thyroid scanning with iodine-131.

RESULTS:

The retention of ^{206}Bi as the citrate, following a single intraperitoneal injection, is shown in Figure 25. The whole body clearance of bismuth can be represented as the sum of two exponential functions. One, a rapid compartment with a retention half time of 13 hours accounts for 43 per cent of the administered dose. A slower compartment, 26 per cent of the administered dose, is cleared with a half-time of 122 hours. The remainder of the dose is accounted for by a very rapidly clearing compartment, the half-time for which could not be assessed by this method.

Whole body retention of ^{206}Bi is compared to the cumulative activities collected in the urine and feces in Table XI. The early clearance of ^{206}Bi is almost entirely due to urinary excretion.

Following a single intraperitoneal injection, bismuth citrate clears rapidly from the blood and is taken up in significant amounts in several areas of the body. The distribution of bismuth citrate in the organs of the rat at various times following administration is shown in Table XII. Kidney is the major organ of accumulation. Bone takes up relatively high amounts of ^{206}Bi , but after 24 hours the level retained amounts to only about 1.0% of the injected dose.

The retention for several organs normalized to organ size and total body weight are shown in Figure 26. Highest concentrations of activity are in the kidneys. Relative retentions are also high in bone, spleen, gonads and liver. Muscle and brain seem to accumulate no bismuth. These studies indicate that since background levels are stable after 24 hours, this should be the optimal time after administration for imaging. A ventral whole body scan of the rat at 24 hours after injection of 180 μCi of ^{206}Bi -citrate is shown in Figure 27. The kidneys are shown clearly in the image. Unlike other scanning agents ^{206}Bi shows practically no background.

An autoradiograph of a transverse renal section is shown in Figure 28. This shows that the bismuth is concentrated in the renal cortex, probably in the epithelial cells of the proximal tubules.

Figure 25. Whole body retention of intraperitoneally administered ^{206}Bi -citrate in the rat, expressed as percent of administered dose retained. All values corrected for physical decay, curve fitted to data by method of least squares.

TABLE XI

Retention and Excretion of ^{206}Bi -Citrate in the Rat

	Average Percent of Injected Dose				
	<u>3 hr.</u>	<u>7 hr.</u>	<u>25 hr.</u>	<u>50 hr.</u>	<u>75 hr.</u>
Whole Body	83.5	81.7	78.5	61.5	59.7
Urine	16.4	16.6	20.1	25.5	25.1
Feces	0.3	0.3	0.9	13.1	14.0
Total	100.2	98.6	99.5	100.1	98.8

TABLE XII

Tissue Distribution of ^{206}Bi -Citrate in Rats

Time after Administration	Percent of Administered Dose Per Organ							Total Body
	Kidney	Bone	Liver	Muscle	Spleen	Gonads	Blood	
0.5 hr	36.6	6.87	0.40	21.7	0.09	0.042	1.17	--
	37.9	4.32	0.40	5.50	0.06	0.039	1.43	
6 hr	28.2	3.18	0.60	2.75	0.06	0.023	0.24	58.5*
	33.9	3.14	0.52	1.31	0.10	0.025	0.19	
12 hr	20.0	1.31	0.57	0.26	0.04	0.007	0.10	48.0*
	26.3	1.17	0.87	0.89	0.05	0.004	0.17	
18 hr	19.7	1.93	0.49	0.91	0.05	0.019	0.09	40.5*
	31.9	1.63	0.42	1.23	0.07	0.014	0.23	
24 hr	21.6	1.30	0.61	0.76	0.09	0.006	0.06	36.1
	40.3		0.99	0.41		0.008	0.07	
36 hr	11.7	0.62	0.32	0.52	0.04	0.009	0.05	29.7*
	11.8	0.79	0.25	0.43	0.03	0.004	0.05	
48 hr	14.2	0.78	0.43	0.43	0.03	0.008	0.02	25.4
	28.3		0.24	0.21	0.06	0.011	0.03	
72 hr	13.1	1.01	0.25	0.34	0.06	0.007	0.08	17.8
	11.6	1.49	0.20	0.63				
96 hr	12.0	0.77	0.16	0.15	0.04	0.002	0.04	14.4
	11.5	1.15	0.21	0.13	0.03	0.006	0.06	
120 hr	6.6	0.98	0.20	0.11	0.04	0.005	0.03	12.3
	12.5		0.22	0.11	0.03	0.004	0.03	
144 hr	11.9	0.81	0.17	0.14	0.03	0.005	0.06	
	12.3	1.06	0.15	0.23	0.02	0.003	0.03	

*Interpolated Points.

Figure 26. Retention of intraperitoneally administered ^{206}Bi -citrate in the organs of the rat expressed in relative retention. All values corrected for physical decay, curve fitted to data by method of least squares.

Figure 27. Whole body scan of rat at 24 hours following administration of ^{206}Bi -citrate.

Figure 28. Autoradiograph of transverse renal section
at 24 hours following administration of ^{206}Bi -citrate.

CONCLUSIONS:

It has been calculated from the results that bismuth citrate has a renal extraction ratio of about 92%. As much as 25% of the total injected dose is deposited into a slowly clearing compartment in the renal tubules in the first ten hours. It is thus apparent that any clinical procedures involving the utilization of ^{206}Bi would have to be performed with the recognition of the very high uptake and long retention times for ^{206}Bi in the kidney and the resulting radiation exposure to this organ. Continuing studies are directed toward reduction of the radiation dose by either diminishing tubular secretion of bismuth or by efficiently relieving tissue burdens following the diagnostic procedures.

B-11. KINETICS OF ^{47}Sc GENERATED BY DECAY OF ^{47}Ca IN-VIVO

INTRODUCTION:

The gamma-emitting radionuclide ^{47}Ca has been used extensively for the study of calcium metabolism, in man and in animals. Calcium-47 decays to a radioactive daughter, ^{47}Sc . Although the distribution of injected radioisotopes of scandium has been studied, little is known of the metabolic fate of scandium arising from the decay of ^{47}Ca in the body. It is desirable to examine the distribution of the generated scandium, both from the point of view of increasing our understanding of the movements of mineral in bone, as well as more accurately defining the radiation dose to the patient in radiocalcium metabolic studies.

MATERIALS AND METHODS:

A simple technique was developed for separating the parent and daughter nuclides, so that solutions of ^{47}Ca practically free of ^{47}Sc contamination could be prepared. Reactor-produced ^{47}Ca as received from Oak Ridge in 1 N HCl was evaporated to dryness in a clean glass beaker. After cooling, the residue was dissolved in distilled water. Almost all of the ^{47}Ca was taken up in the water, while 80 to 90% of the ^{47}Sc remained on the glass. Two or three repetitions yielded a solution of nearly pure ^{47}Ca .

Adult female mice were injected intraperitoneally with about 2 μCi of ^{47}Ca and sacrificed at 17 intervals from one to 42 days after injection, in groups of four. In a second series, mice were sacrificed at 0.05, 0.1, 0.25, 0.5 and 1 day. Specimens of blood, muscle, skin, liver, spleen, kidney, tibia, femur and calvarium were assayed for ^{47}Ca and ^{47}Sc content. Scandium-47 activity in tissue was expressed as a fraction of the total ^{47}Sc existing in an aliquot of the injection solution at the time of sacrifice. A computer program involving solutions of the maximum likelihood equations for proper weighting of count data and growth-decay corrections had been developed previously.

RESULTS:

The principal result was that ^{47}Sc generated in bone by decay of ^{47}Ca in bone was retained, in the three bones studied, at a level equal to or greater than the retention of the parent ^{47}Ca . In calvarium, where the ^{47}Ca concentration (% dose) did not change significantly from one to 42 days after injection, the ratio of $^{47}\text{Sc}/^{47}\text{Ca}$ activity in the bone, divided by that in the injection aliquot at time of sacrifice (the relative concentration, R) was $1.00 \pm .03$ (standard error of the mean) for all 68 specimens taken in this period. In tibia and femur, ^{47}Ca concentration reached a maximum at about 0.25 days, and declined to about 63% of this value at 42 days. R increased from $0.34 \pm .05$ and $0.47 \pm .05$ at 0.05 days to $0.98 \pm .02$ and $1.01 \pm .03$ at one day, to maximum values of $1.10 \pm .01$ and $1.08 \pm .01$ at 11 days, declining to $1.06 \pm .07$ and $1.06 \pm .01$ at 42 days for tibia and femur, respectively.

In soft tissue, relative concentrations of ^{47}Sc to ^{47}Ca at one day were: 4.9 in blood, 1.8 in muscle, 5.6 in skin, 13 in liver, 12 in spleen and 9.6 in kidney. At 11 days after injection, the values were: 2.3 in blood, 3.0 in muscle, 4.9 in skin, 23 in liver and 11 in kidney. Although subsequent measurement of ^{47}Ca in these tissues were hampered by the low levels of activity, ^{47}Sc content could be measured with reasonable precision for the full 42 day period.

From nine to 42 days, the ^{47}Sc content of liver, spleen, kidney and skin remained in roughly constant proportion to the ^{47}Sc activity in the injection aliquot, despite the very low levels of ^{47}Ca present in those tissues. In blood, the relative concentration, R, peaked at one day or less and declined to a steady level of about 2, from 2 to 16 days. In muscle, R reached a maximum of about 3.5 at 4 days, falling to about 1.5 at 24 days.

An estimate of the ^{47}Sc tissue content arising from generation (decay of ^{47}Ca) in situ was made from the appropriate time integrals of computer-fitted 3 or 4 component exponentials to the measured ^{47}Ca content, assuming no loss of ^{47}Sc except by decay. In liver, spleen, kidney and skin, measured ^{47}Sc was well in excess of that generated in situ through most of the period of study, reaching 4 to 14 times the latter at 42 days. Blood and muscle showed a consistent deficit of ^{47}Sc , starting at one day in blood, and at 0.05 days in muscle. In the plateau region between 9 and 42 days, the average ^{47}Sc deficit

in muscle was about equal to the combined ^{47}Sc excess in liver, spleen, kidney and skin (about 0.4% dose). The total soft tissue ^{47}Sc burden, in this period, averaged about 1.7% dose as against 0.8% dose for ^{47}Ca .

In bone, estimates of ^{47}Sc generated in situ agreed with measured values from 0.05 to 11 days, with the suggestion of some loss of ^{47}Sc at short times after injection. After 11 days, the above method increasingly overestimated the bone content.

CONCLUSIONS:

Recirculation of ^{47}Sc activity represents a large part of the observed pattern of distribution in all the soft tissues studied. Liver, spleen, kidney and skin, in that order, showed the greatest affinity for this recirculated ^{47}Sc , while muscle, the largest soft tissue store of calcium, steadily loses generated ^{47}Sc . Bone, however, accounts for the bulk of parent and daughter activity. Up to 11 days after injection, ^{47}Sc content in tibia and femur was consistent with the assumption of little if any loss of generated activity, although ^{47}Ca content is steadily falling after the first day, presumably due to surface exchange. Thereafter, rate of loss of ^{47}Sc content from these bones begins to approach that of the ^{47}Ca , suggesting that active resorption becomes the dominant mechanism of removal. In calvarium, which showed no significant loss of ^{47}Ca after the first day, the $^{47}\text{Sc}/^{47}\text{Ca}$ ratio remains the same as that in the injection solution, indicating no leakage of generated ^{47}Sc from that bone.

RELATED RESEARCH PROJECTS

These are projects underway here which initially rested on innovative developments but which are now in an essentially clinical research stage. They are largely supported by other funds and AEC support has been appropriately reduced to a minimal or zero level.

BR-12. BONE MINERALIZATION STUDIES

OBJECTIVES:

To continue the studies of forearm bone mineral content of patients in various stages of renal failure and after different lengths of time on maintenance hemodialysis. To obtain correlations of bone mineral measurements with the following obtained at the Bronx Veterans Administration Hospital, (a) radiographs of forearm and (b) serum CO_2 , calcium, phosphate and CaXPO_4 .

MATERIALS AND METHODS:

Bone mineral content (BMC) was determined in 57 patients on maintenance hemodialysis (MHD) by measurement of the mid-shaft radius and ulna with a single energy absorptiometric instrument. All patients received 70 g protein, 900 mg Ca diet and 6 gr $\text{Al}(\text{OH})_3$ weekly and were hemodialyzed 3 times weekly against a dialysate Ca concentration of 5 mg %. After control observations, up to 18 months, 8 patients received dihydrotachysterol (DHT) 0.2 mg/day, 6 received DHT 0.4-0.8 mg/day, and 11 received calcium carbonate, 9.6 g/day for 6-12 months. Two other patients underwent parathyroidectomy.

RESULTS:

During the control period, there was a progressive decrease in BMC of 7.3% per year ($P < 0.001$). Subsequently, neither the administration of DHT (low or high dose) nor $\text{Ca}(\text{CO}_3)_2$ treatment altered the downward trend of BMC. After parathyroidectomy BMC rose progressively in two patients. There was no significant correlation between BMC and serum CO_2 , calcium, phosphate and CaXPO_4 contents. In patients started on MHD, no significant difference could be found in the mean initial BMC of those with, and those without, radiographic evidence of osteitis fibrosa cystica.

CONCLUSIONS:

Under the conditions of the present study BMC falls progressively in all patients on MHD and is not reversed by the administration of DHT or calcium carbonate supplements. Parathyroidectomy appears to restore BMC toward normal in patients on MHD.

2

BR-13. CLINICAL APPLICATIONS OF ABSOLUTE QUANTITATIVE ORGAN
SCANNING REGARDING COMPARISON OF HEMATOPOIETIC AND
PHAGOCYTIC FUNCTION IN MAN

OBJECTIVE:

To evaluate splenic sequestration and hematopoietic function in patients with hematologic dyscrasias by quantitative scanning methods using ^{51}Cr -labeled acid-citrate-dextrose (ACD) damaged or undamaged erythrocytes and ^{52}Fe or ^{59}Fe -ferrous citrate labeled plasma.

MATERIALS AND METHODS:

The dual detector High Energy Gamma Ray Scanner (HEG), containing heavily shielded 4 x 4 in NaI (Tl) crystals and the collimators designed for constant resolution, was used for all patients studied. All data for both serial and absolute quantitative measurements were processed on the IBM 1800 computer using the programs that were developed for area integration and the ensuing organ uptake calculations. The data from each rectilinear scan are dumped on magnetic tape and computer processed to obtain a line printer image. Scan data are displayed as a raw data matrix with the counts per element represented by alphanumeric characters, with 2 standard deviations between adjacent count levels.

Calibration of the HEG scanner was achieved by scanning phantom sources of known activity to simulate the geometries of the liver and spleen in-vivo over a patient thickness range from 20 to 30 cm. Conversion factors were derived which relate the integrated counts within the organ's scan image to the organ's activity, as a function of size. From the patients computer scan image, the limits of the spleen, liver and background integration areas were chosen. The data analysis program calculated splenic or liver area and then selected the appropriate conversion factors to determine organ uptake as percent of injected dose.

All patients on the undamaged red cell protocol were injected with approximately 300 μCi of ^{51}Cr -labeled autologous red cells and received their first "zero time" scan beginning 20 minutes post injection. Scans were also performed on following days until the radioactivity remaining in the whole blood had dropped to 10% of the injected dose or the patient

was removed from the study. Blood samples were taken during each scan for use as the "Whole Blood Factor" correction in the organ uptake calculations.

The ^{52}Fe -ferrous citrate labeled transferrin procedure consists of incubating the patient's plasma with a known amount of ^{52}Fe for 20 minutes at room temperature. Patients are scanned 12-20 hours after receiving the ^{52}Fe -labeled transferrin. Plasma from a type specific donor is used for patients with known or suspected insufficient latent iron binding capacity. In some cases plasma iron clearance studies (necessitating blood samples 15 min., 1/2 hr., 1 hr. and 2 hrs. post injection and at time of scan) are performed. All patients have blood drawn at time of scan to determine residual activity in whole blood.

Approximately 50 μCi of ^{59}Fe labeled transferrin is given to each patient undergoing a long term ferrokinetic workup. The labeling procedure for ^{59}Fe is analogous to that of ^{52}Fe . Patients are scanned 1,2,3 and 4 days post injection, when feasible, and 2 or 3 times per week for the duration of the study. Blood samples are taken 15 min., 1/2 hr., 1 hr., 2 hrs. and 3 hrs. post injection on Monday, Wednesday, and Friday and/or at time of scan thereafter.

RESULTS:

Under the continuing project of absolute organ quantitation we have studied, during the past year, one additional patient with the ACD damaged ^{51}Cr -labeled erythrocyte protocol. This patient was scanned approximately 18 hours post injection. Scan results in-vivo indicated a 21% uptake by the spleen. This compared very well with the in-vitro results of 23% injected dose determined a few hours later on the extirpated organ. The dimensions of the 165 gram spleen were 13.5 x 9.7 x 4.5 cm.

Having previously established that we are able to determine quantitatively the chromium-51 radioactivity in the spleen, we proceeded to study a selected group of patients who were clinically thought to have an anemia whose etiology, at least in part, was hemolytic. The patients also were under consideration for possible splenectomy to alleviate this complication of their basic disease.

Chromium survival studies with spleen scans have been performed on 18 patients. At the time when half the circulating activity had cleared from the peripheral blood, splenic sequestration was determined to be from 2 to 42% of injected tagged cells.

Determination of sequestration was based on the assumption that activity over the spleen area at 1 hour post injection represented activity solely within circulating blood and not sequestered erythrocytes. Therefore, by integrating the counts over the splenic area on the following days and subtracting the circulating blood background (scan at "zero time" post injection) the organ uptake, day by day, can be ascertained. The formula below illustrates the method used to correct splenic sequestration for activity due to the circulating blood in the spleen itself. This was accomplished by subtracting from the organ activity on any day "n", the product of the organ activity on day "0" and the ratio of blood activity on day "n" to that of day "0."

$$\text{Sequestration} = S_n - S_0 \times \frac{B_n}{B_0}$$

(Day n)

S_n - Integrated organ activity on Day n

S_0 - Integrated organ activity on Day 0

B_n - Blood activity on Day n

B_0 - Blood activity on Day 0

{all radioactivity corrected for decay}

A graphical representation of chromium-51 RBC survival and splenic uptake in 5 typical patients is plotted against time in Figure 29. The patient's diagnoses included chronic granulocytic leukemia, chronic lymphocytic leukemia, Hodgkin's Disease, Hemoglobin K δ 1n, Waldenstrom's Macroglobulinemia, lymphosarcoma and melanoma. All except M.L. had increased survival. Their splenic uptakes were determined quantitatively by the method described.

Another way of depicting the data is to determine splenic sequestration of destroyed cells. Figure 30 depicts splenic uptake divided by cells destroyed (1 - whole blood factor (FWB)) plotted against time in 7 typical patients. The variation in splenic uptake is clear.

To properly interpret these data we quickly found that the splenic sequestration must be viewed in the light of the proportion of cells destroyed. We therefore developed what we call the sequestration index (SQI). It is an expression of the proportion of cells sequestered to cells destroyed, i.e.,

$$SQI = \frac{\text{Quantitative Uptake in Spleen}}{\text{1-Whole Blood Level (FWB)}}$$

Such data is generated for patients considered for splenectomy and is correlated with the clinical course of those patients chosen for splenectomy.

We were able to obtain the spleen of three of the four patients who were splenectomized. Data taken in-vivo compared favorably with that determined from the homogenized spleen, in-vitro.

<u>Patient</u>	<u>Disease</u>	<u>Percent Uptake</u>	
		<u>In-Vivo</u>	<u>In-Vitro</u>
RS	CML	43	40
EW	CLL	13	10
EK	Macroglobulinemia	15	13

R.S. died within a month; however, his transfusion requirement was clearly reduced. E.W. is a patient with Hairy Cell Leukemia. His hemoglobin ranged between 5 and 7 gm% and increased to levels of 11-12 gm% after splenectomy. R.M., a patient with Hemoglobin K⁸ln, was greatly benefited by splenectomy. His red cell survival was severely compromised with a striking uptake in the spleen. The half time of red cell survival occurred at 8 days. At that time, 26% of the injected radioactivity could be accounted for in the spleen. On the eleventh day, when only 35% of the injected dose was circulating, splenic sequestration was 32%.

FIGURE 30-- Range of Sequestration Indices for 7
Typical Patients

During the past year 7 patients have been serially studied with ^{59}Fe . Data were processed and integrated counts over liver, spleen and pelvis were automatically plotted using a modified computer plotter program.

We have now added nineteen patients to the continuing project of assessment of organ erythropoiesis with ^{52}Fe . We were able to obtain only one additional patient who underwent splenectomy for in-vivo and in-vitro comparison. The results appear in Table XIII.

CONCLUSION:

Quantitation of ^{52}Fe and ^{51}Cr radioactivity in liver and spleen is feasible. There was good agreement between values determined in-vitro and those obtained by the technique described. The accumulation of iron in the spleen does not necessarily mean that this iron is only there for incorporation in hemoglobin or is necessarily an absolute indication of erythropoiesis in that organ.

There may be deposition in storage depots or secondary sequestration of red cells freshly released from the bone marrow. Similarly, the presence of ^{51}Cr derived from tagged red cells in the spleen is not necessarily an absolute quantitation of splenic sequestration of these cells. Some chromate may elute from cells to remain in the spleen with continued survival of the cell. The retention of chromate by the spleen after cell destruction is, at this time, not fully understood or known.

There is good evidence of antibody production in the spleen which may contribute to the autoimmune process without direct effect on sequestration. The decision to remove the spleen may, therefore, also rest on other indications than those of sequestration, destruction or cell production. However, the quantitation of splenic radioactivity interpreted in terms of cells destroyed permits a more refined judgment of the spleen's actual contribution to hemolysis.

TABLE XIII

IN-VIVO IRON-52 UPTAKE BY LIVER, SPLEEN AND HEAD

<u>Patient</u>	<u>Diagnosis</u>	<u>Organ</u>	<u>% Uptake In-Vivo</u>	<u>Organ Activity (μCi)</u>	<u>Non-Organ Tissue Activity NOA (μCi)</u>
CE	CML*	Spleen	41	17	9
		Liver	11	5	6
DC	CML	Spleen	8	4	3
		Liver	89	48	15
GK	Myelofibrosis	Spleen	5	4	9
		Liver	9	7	9
GS	Myelofibrosis	Spleen	54	18	8
		Liver	15	5	6
WL	Myelofibrosis	Spleen	5	1	2
		Liver	4	1	2
JP	Myelofibrosis	Spleen	80	(Splenectomy)	18
		Liver		30	
SK	HD**	Spleen	15	7	4
		Liver			
FS	HD	Spleen	4	2	2
		Siver	5	3	3
EMc	HD	Spleen (235g)	3 (2% <u>in-vitro</u>)	1	3
		Liver	3	1	1
AS	Aplastic Anemia	Spleen	5	1	2
		Liver	20	6	3
EK	Aplastic Anemia	Spleen	5	3	3
		Liver	14	8	9

Patient	Diagnosis	Organ	% Uptake In-Vivo	Organ Activity (μ Ci)	Non-Organ Tissue Activity NAO (μ Ci)
JB	Erythro- leukemia	Spleen	8	4	3
		Liver	8	3	5
RK	Polycythemia Vera	Spleen	10	4	4
		Liver	13	5	4
ML	Polycythemia Vera	Spleen	1	2	8
		Liver	1	1	4
FR	Autoimmune hemolytic anemia	Spleen	4	1	1
		Liver	67	19	6
AG	RCS***	Spleen	12	7	9
		Liver	4	3	6
		Spleen	12	2	2
		Liver	6	1	2
		Spleen	14	12	17
		Liver	7	6	14
JS	Cooley's Anemia	Spleen	3	1	1
		Liver	6	2	2
		Spleen	2	1	1
		Liver	3	1	1
RC	Cooley's Anemia	Head:			
		Upper	13	Pre-Radiation Therapy (RT)	
		Lower	12		
		Upper	19	6 Days post RT (1000 rads)	
		Lower	5		
		Upper	12	41 Days post RT	
		Lower	7		
		Upper	19	17 Days post end of second RT (1000 rads)	
		Lower	11		
		Upper	19	6 Days post end of third RT (1000 rads)	
		Lower	6		

*CML - Chronic Myelogenous Leukemia
 **HD - Hodgkin's Disease
 ***RCS - Reticulum Cell Sarcoma

BR-14. TREATMENT OF CHONDROSARCOMA AND CHORDOMA WITH
³⁵S SODIUM SULFATE

OBJECTIVE:

To evaluate the effectiveness of inorganic ³⁵S-sulfate in controlling malignant tumors of cartilaginous origin. The high uptake of ³⁵S-sulfate by chondrosarcoma has been known for many years: a high uptake by chordoma was demonstrated in this work.

MATERIALS AND METHODS:

Patients with previously proved chondrosarcoma or chordoma were given test doses of 0.2 mCi/kg body weight of nearly carrier-free ³⁵S-Na₂SO₄ in physiological saline by i.v. injection. A few days later tumor tissue was obtained by biopsy and assayed for ³⁵S activity. If uptake was significantly above the body average, the patients were given one or more therapeutic doses of 4 to 7 mCi/kg as indicated clinically over periods up to 20 months. The retention of ³⁵S was followed by serial biopsies and measurement of activities in the tissues obtained.

RESULTS:

A total of 11 patients with chondrosarcoma and 10 patients with chordoma were studied. The clinical results were given in the previous Progress Report. Significant control of tumor was obtained in 3 patients with chondrosarcoma but in only one with chordoma. There was evidence of marked bone marrow depression in all patients who received full therapeutic doses and problems of pancytopenia were so severe that no new cases were started on this regimen during the past year. Additional data on ³⁵S in tissue have been obtained during this period.

It was confirmed that initial uptakes in chondrosarcoma and chordoma tissues were high and about equal, but that subsequent loss from chordoma tissue was so rapid that the accumulated radiation dose was much less than in chondrosarcoma. Loss of ³⁵S from red bone marrow was slower than initial results indicated, and radiation dose was correspondingly higher. On the basis of these findings in tissue specimens

the accumulated radiation doses which may be expected from administration of 30 mCi/kg body weight in one year are as follows:

Chondrosarcoma	4650 rads
Chordoma	1470 rads
Normal cartilage	4050 rads
Red bone marrow	990 rads

These findings were reported at the Fifth International Congress of Radiation Research, Seattle, Washington, July, 1974.

CONCLUSIONS:

It is possible to control the growth of many chondrosarcomas and an occasional chordoma by i.v. injections of $^{35}\text{S Na}_2\text{SO}_4$, but the use of this modality is severely limited by associated bone marrow depression.

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BR-15. EVALUATION OF ^{18}F -FLUORIDE AND $^{99\text{m}}\text{Tc}$ LABELED
DIPHOSPHONATE AND POLYPHOSPHATE AS BONE SCANNING AGENTS

OBJECTIVE:

Intercomparison of three radiopharmaceuticals for bone imaging was desired.

MATERIALS AND METHODS:

The SKI cyclotron produced the ^{18}F -sodium fluoride used. Diphosphonate was obtained from Proctor and Gamble (trade name Osteoscan) and labeled with both generator and instant technetium- $^{99\text{m}}$ from several suppliers. The polyphosphate, obtained from Diagnostic Isotopes, was of moderate chain length.

Patients were referred for bone scans. In the period from January 1973 to August 1974 we have performed rectilinear bone scans utilizing 1,235 injections of ^{18}F , 302 of $^{99\text{m}}\text{Tc}$ -diphosphonate and 10 of $^{99\text{m}}\text{Tc}$ -polyphosphate. In 26 patients repeat scans were performed within a few days utilizing two different radiopharmaceuticals for comparison purposes.

RESULTS:

Only a few scans were performed with $^{99\text{m}}\text{Tc}$ -polyphosphate because of high soft tissue uptake persisting 3 hours after injection. With ^{18}F there was low soft tissue uptake and high contrast of the lesion with normal bone 2 hours after injection. Diphosphonate initially gave much less non-osseous uptake than polyphosphate, although kidney uptake has always been greater than with ^{18}F . Recently, diphosphonate bone scans are frequently accompanied by high gastric uptake, indicating poor binding of the pertechnetate. Diphosphonate has the advantage of lower energy, permitting the use of a collimator with a FWHM of 0.8 mm, compared with 1.5 cm for ^{18}F . This permits scans with finer resolution so that individual ribs and vertebrae are seen in many instances. $^{99\text{m}}\text{Tc}$ has also permitted us to make a few spot views with the gamma camera to better define the exact location of the area of increased uptake.

An exhibit of comparisons of these two agents, together with the computer analysis of results was made at the 1974

Annual Meeting of the Society of Nuclear Medicine. In 13 patients ^{18}F showed a greater difference from the contralateral side than $^{99\text{m}}\text{Tc}$ -diphosphonate, equal in 3 and less difference in 10.

CONCLUSION:

We continue to use both ^{18}F -sodium fluoride and $^{99\text{m}}\text{Tc}$ -diphosphonate for bone scans at present.

BR-16. STUDIES OF TUMOR LOCALIZING PROPERTIES OF ^{111}In -CHLORIDE AND ^{111}In -LABELED BLEOMYCIN

OBJECTIVE:

To determine the usefulness of $^{111}\text{InCl}_3$ or ^{111}In -labeled bleomycin in detecting various tumors and to compare their sensitivity and specificity with other available tumor localizing agents.

MATERIALS AND METHODS:

Tumor bearing mice with Lewis lung or Ridgeway osteogenic sarcoma and rats with experimental abscesses produced by intramuscular injection of turpentine or Freund adjuvant were used to study the metabolism and tumor or abscess to soft tissue ratio with ^{111}In -chloride, bleomycin, ^{67}Ga -citrate or ^{75}Se -methionine. In rats, urinary excretion of ^{111}In -bleomycin was 65% in the first day and very small on the second day. Increased $^{111}\text{InCl}_3$ and ^{111}In -bleomycin uptakes were found in tumors as well as abscesses. However, the target to soft tissue ratio was higher in the gallium and ^{57}Co -bleomycin studies.

One hundred and thirty-one patients with various malignancies were given 3-5 mCi of ^{111}In -bleomycin intravenously with a maximal amount of carrier of 1 mg. Blood and urinary activities were measured in some patients. The total body scanning was usually at 48 hours after injection. Comparison with ^{67}Ga scans was made within two weeks in 43 cases. In this part of our study, only two patients were evaluated with $^{111}\text{InCl}_3$. Both of them failed to localize the known tumor.

RESULTS:

Our clinical results of indium bleomycin scans are summarized in Table XIV. The tumor detectability of carcinoma of the lung, regardless of histological type, was about 50%. Eleven of 12 patients with reticulum cell sarcoma and other types of sarcoma had positive scans. All 13 patients with Hodgkin's disease, 22 of 23 cases of malignant melanoma, all three patients with hepatoma and all five patients with known carcinoma of the breast had positive scans. However, the quality of bleomycin scans was rather poor and the tumor to soft tissue ratio was very low. The high liver and kidney uptakes often obscure tumor uptake in adjacent areas. Comparison of computer data in bleomycin and gallium scans was possible in 27 pairs or a total of 91 lesions. In Hodgkin's disease, the tumor to soft tissue ratio was 3.60 ± 0.58 standard deviations above the surrounding "normal" tissue in bleomycin studies and 10.37 ± 1.87 standard deviations in gallium studies. In the non-Hodgkin's disease cases, the ratios were 4.59 ± 0.38 and 8.7 ± 0.78 respectively.

No adverse effect was noted in any of the 131 patients. Several of them had two studies. Patients with previous reactions to bleomycin did not show any side effects.

Similar to our animal studies, bleomycin is not tumor specific. False positive results were found in the patient's with chronic osteomyelitis, stitch abscess or recent surgery.

CONCLUSION:

This study should be continued to include more varieties of malignancies. The relatively low ^{111}In -bleomycin radioactivity in the gastrointestinal tract makes bowel preparation unnecessary. The possibility of tumor detectability in some gastrointestinal tumors should be expanded. More tissue analysis from surgical or necropsy specimens will be carried out. We also wish to extend our work to bleomycin with other radionuclides. Merits of ^{111}In -bleomycin will be compared with those from $^{111}\text{InCl}_3$.

TABLE XIV

CLINICAL RESULTS OF INDIUM BLEOMYCIN SCANS

<u>Diagnosis</u>	<u>Positive Scans</u>		<u>Negative Scans</u>	
	<u>True</u>	<u>False</u>	<u>True</u>	<u>False</u>
Carcinoma of head and neck	4	0	0	0
Lung tumors	16	0	0	8
RCS, sarcoma	11	0	1	0
Lymphoma	1	0	0	1
Osteogenic sarcoma	0	0	0	1
Hodgkin's disease	13	0	0	0
Carcinoma of adrenal	0	0	0	1
Carcinoma of breast	5	0	3	0
Carcinoma of cervix, vagina	16	0	0	0
Carcinoma of bladder	2	0	0	0
Carcinoma of penis, prostate	3	0	0	0
Carcinoma of esophagus	3	0	0	2
Carcinoma of pancreas	0	0	0	1
Hepatoma	3	0	0	0
Colon Ca and liver mets	1	0	0	3
Malignant melanoma	22	3	1	0
Leukemia	0	0	0	2
Osteomyelitis	1	0	0	0
Cirrhosis of liver	0	0	1	0
Choriocarcinoma	1	0	0	0
Neuroblastoma	1	0	0	0
Adeno Ca (unknown primary)	1	0	0	0
Total	104	3	6	19
Brain Lesion	13	0	13	0

BR-17. STUDIES OF ⁶⁷GALLIUM CITRATE FOR SOFT TISSUE
TUMOR LOCALIZATION IN PATIENTS

OBJECTIVE:

To evaluate the usefulness of ⁶⁷gallium citrate in the staging of malignant disease.

MATERIALS AND METHODS:

⁶⁷Gallium citrate was obtained from Oak Ridge Associated Universities (ORAU) until 31 January 1974, and since then from commercial suppliers (New England Nuclear and Medi-Physics). Patients with malignancy received 0.045 mCi/kg and were examined between 48 and 72 hours post-injection usually with total body scanning, and with computer analysis when possible. Up to 31 August 1974, we have injected 568 doses of ⁶⁷gallium citrate for tumor localization, with some serial studies performed during and after treatment.

RESULTS:

Coding of data from patients receiving ⁶⁷Ga-citrate furnished by ORAU is now complete. Preliminary results in untreated patients have been published (1,2,3) and show that ⁶⁷Ga-citrate is useful in Hodgkin's disease, non-Hodgkin's lymphoma and lung cancer. The non-specificity of ⁶⁷Ga-citrate uptake reported by others (4) has been confirmed. Analysis of the response of these diseases to treatment, and a type by type examination of true positive, true negative, false positive and false negative scans in other types of malignancy is underway at ORAU. Our results show ⁶⁷Ga-citrate to be most useful in hepatoma, malignant melanoma and sarcomas. Percentage results await computer runs on the ORAU pool of information from the 16 centers in the Cooperative Group to study Localization of Radiopharmaceuticals.

Since the ORAU radiopharmaceutical supply has ended we have been employing ⁶⁷Ga-citrate as a relatively well established (but still research protocol) method for staging lymphoma. We are also making comparative studies of tumor uptake of ⁶⁷Ga-citrate, ¹¹¹In-bleomycin, ¹¹¹In-chloride and ¹⁸F-sodium fluoride.

CONCLUSIONS:

This material is useful in staging Hodgkin's disease, other lymphomas and in selected non-lymphomatous malignancies, especially hepatoma.

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BR-18. LOCALIZATION OF TUMORS WITH RADIOACTIVE GROWTH HORMONE

OBJECTIVE:

- 1) To evaluate the use of ^{131}I labeled human growth hormone in the localization of human tumors.
- 2) To determine the metabolic clearance rate of human growth hormone.

MATERIALS AND METHODS:

Routine labeling techniques of Human Growth Hormone (HGH) with high specific activity ^{131}I have been developed in the Clinical Isotope Laboratory of the Center. The kinetics of organ uptake were measured by a gamma camera that was interfaced to a computer. Hormone localization was studied with a rectilinear scanner.

RESULTS:

Ten studies have been done on nine patients with the following diseases: metastatic breast cancer (3), malignant thymoma (1), lymphosarcoma (1), medullary carcinoma thyroid (1), hepatoma (1), eosinophilic pituitary tumor (1), and Hodgkin's disease (1).

Uptake of labeled hormone was demonstrated in the malignant thymoma. The hepatoma failed to bind ^{131}I -HGH in the same manner as normal liver. HGH localization was not demonstrated in the other tumors studied.

The biologic half-life of labeled HGH in blood was approximately 30 minutes and normal binding of HGH was demonstrated in the liver, spleen and kidneys by rectilinear imaging techniques. Computer techniques have allowed us to quantitate the above binding. Flow study techniques have shown that maximal binding in the liver occurs at about 30 minutes. Of interest is the fact that the label can be demonstrated in the gall bladder of some patients between 12 and 24 hours after administration, thus suggesting a pathway of degradation.

CONCLUSION:

These studies have demonstrated the feasibility of routinely using labeled hormones for kinetic and localization studies utilizing radionuclide imaging and quantitation techniques.

BR-19. IODINE-123 LABELED HIPPURAN

OBJECTIVE:

Iodine-123 is recognized to have physical characteristics which are superior to those of ^{131}I . Calculations showed that if ^{123}I instead of ^{131}I were used as a label on Iodohippurate when doing renograms with a gamma camera, it should be possible to obtain 10 times the count rate with no increase in radiation dose to the kidney. For this reason it was decided to label Sodium Ortho-Iodohippurate with ^{123}I .

MATERIALS AND METHODS:

A modification of the procedure outlined by Short, et al. (1) was used. The following reagents were added to a 25 ml pear-shaped boiling flask: 1 mCi of ^{123}I in a volume of 1 ml, 0.1 ml of saturated iodine solution, 0.1 ml of 10N HCl, 0.1 ml of a 50% solution of diethanolamine and 200 mg of Hippuran. The flask is heated under reflux for 2 hours and then placed in an ice bath where the Hippuran is precipitated with 10N HCl. The supernatant is removed and the Hippuran dissolved using 0.2N NaOH. The pH is adjusted to 7 and the product is autoclaved.

RESULTS AND CONCLUSIONS:

The labeling yield was 60%. Renograms performed on a dog with both a single probe and a gamma camera gave typical curves with the maximum occurring at 4 minutes and decreasing to 40% of maximum at 20 minutes. Thin layer chromatography on both a commercial preparation using ^{131}I and the ^{123}I

preparation gave an Rf value of 0.9 in a butanol, acetic acid solvent. Sterility and pyrogen testing is being carried out. The procedure takes 3 hours; it therefore seems like a procedure which could reasonably be performed with good results.

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PART C. FEASIBILITY OF CHEMICAL BONDING STUDIES WITH
X-RAY SPECTRA

OBJECTIVE:

To compare the sensitivity for the detection of the K-alpha lines of the lighter elements ($Z < 23$), by means of an x-ray crystal spectrometer, using a beam of cyclotron accelerated α -particles in comparison to electron (25 KeV) and x-ray excitation.

MATERIALS AND METHODS:

Ion optical focusing of the α -particle beam made it possible to focus down to our required dimension ($\leq 1/4''$) without use of physical collimation close to the target. This eliminated much of the extraneous background produced in the physical collimation previously used.

RESULTS:

Even with the improved system, where background from the physical collimators was greatly diminished, the extraneous background still remains very high and is the factor limiting the sensitivity that can be obtained. It is estimated that the sensitivity of our present α -excitation system, with considerable shielding added, would be no better for the element Ti ($Z = 22$) than our x-ray emission instrument which employs x-ray excitation.

CONCLUSION:

The extraneous background still remains the factor which severely limits the sensitivity attainable with x-ray spectrometry where the spectral excitation is obtained by cyclotron produced α -particles. A further decrease in the background requires complicated absorption shielding and/or coincidence shielding. Because of these complicated procedures, it was recommended that this program be terminated.

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NOTICE OF RESEARCH PROJECT

TITLE OF PROJECT: Biological Effects of Radiation and Related
Biochemical and Physical Studies

Results to Date:

Results to date have included the development of the method for quantitative determination of the amount of radioactivity in a given organ based entirely on external scanning and applicable to different energies of radionuclides, the design of a low level counting facility designed for use with neutron activation of partial body irradiation; further development of a sophisticated scan package for use with both rectilinear scanners and gamma cameras; the further development of a dual energy photon in-vivo bone scanning apparatus and the refinement of the method of using the dual gamma camera system (TOKIM) for three-dimensional localization.

Other results include the development of a method for regional function studies with short-lived nuclides administered over equilibrium periods, demonstration of pancreatic concentration of cysteine labeled with ^{11}C , the study of the localization of ^{11}C -diphenyl hydantoin and ^{11}C -hydroxyphenylphenyl hydantoin in monkeys in connection with their possible use as scanning agents for brain tumors, the demonstration of the superior myocardial localization of ^{13}N -labeled asparagine as well as metabolic results with other ^{13}N -labeled compounds, and clinical results of studies of localization of other cyclotron produced compounds.