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Nuclear Medicine Instrumentation Development: DOE Program Study Group Report

February 1979

U.S. Department of Energy
Assistant Secretary for Environment
William W. Burr, Jr., M.D.
Office of Health and Environmental Research

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PREFACE

In 1975-1976, a comprehensive review of the entire DOE (then ERDA) nuclear medicine research program was conducted by a Special Task Force appointed by the Director of the Division of Biomedical and Environmental Research. The final report of the Task Force, Nuclear Medicine Research: An Evaluation of the ERDA Program, ERDA-76 135, was published in August 1976. In that report it was recommended that "Support for instrumentation research and development should be increased substantially to take advantage of the unique opportunities for technology transfer made available by close relationships existing between the ERDA nuclear medicine, physics and engineering programs." As a result, the Office of Health and Environmental Research requested that a study group, chaired by Dr. Gale I. Harris, Michigan State University, conduct a more specific and detailed evaluation of the DOE nuclear medicine instrumentation efforts to provide better perspective on the current status and future needs for such instrumentation. The report of that study group is presented here. Any questions or comments with respect to the report should be addressed to Dr. Gerald Goldstein, Office of Health and Environmental Research.

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ABSTRACT

This report presents observations and recommendations of a study group which was formed to consider the status and future directions of instrumentation research as applied to nuclear medicine clinical applications and biomedical research being pursued under the aegis of the U.S. Department of Energy (DOE). The study was conducted for a more specific and detailed evaluation of nuclear medicine instrumentation development as a means to extend and to aid implementation of recommendations made by a special ERDA/HEW Task Force which completed a comprehensive evaluation of the entire DOE nuclear medicine research program in August 1976. For this purpose, the study group was constituted of individuals generally having long experience and detailed knowledge related to instrumentation for clinical nuclear medicine and biomedical research application. The report summarizes the historical evolution and present status of the DOE sponsorship of this research, and it presents technical data regarding needs and appropriateness for emphasis on nuclear medicine instrumentation research and development. It also presents views and recommendations concerning the relative roles in this field of the DOE laboratories and extra-mural research programs, of other Federal agencies, and of the commercial sector. Future directions for instrumentation research are defined in relation to their potential benefits for the study and diagnosis of major disease problems and in conjunction with new radiopharmaceutical agents becoming available. The specific observations and recommendations are separated into two general categories; i.e., those which relate to general support and conduct of the work by DOE and industry or academic sectors, and those which are more related to technical direction for instrumentation research and development for clinical and biomedical applications.

Generally, it is concluded that the role of governmental support remains of great (perhaps increasing) importance and should be concentrated on concept generation and development through proof of technical feasibility of systems employing substantially novel technology not currently in use in the field. This development may be carried out with close cooperation and partial support by industry to enhance the probability of transfer of technology to industry, and finally, to implementation in health care.

I. INTRODUCTION AND BACKGROUND

This report presents the results of a special study group evaluation of instrumentation research as applied to nuclear medicine for clinical applications and biological research being pursued under the aegis of the U.S. Department of Energy. The report summarizes the historical evolution of the Department of Energy's sponsorship of this research and presents technical data regarding needs and appropriateness for emphasis on nuclear instrumentation research and development.

The use of radioisotopes for the detection of disease processes and the study of basic biological mechanisms had its major stimulus after World War II, when a concerted effort was made by the Atomic Energy Commission in the peaceful uses of atomic radiation. Radionuclides provide methods of diagnosis and research not otherwise available and can be used without harm to patients because extremely low radiation doses are involved. Essential to the development of methods using radiotracers is the instrumentation required for detection of radiation. It is in this area that the Department of Energy (DOE) and its predecessors, the Atomic Energy Commission (AEC) and, subsequently, the Energy Research and Development Administration (ERDA), have made valuable contributions to medicine and science, because the basic nuclear physics supported by these agencies could be, and was, applied to radionuclide detection of tracers in the body. In contrast to X-ray diagnostic techniques, radiotracer methods involve diagnosis

and research aimed at understanding the physiological and mechanistic properties of the body. The specialty field of medicine and biology for which this instrumentation development has had the greatest application for disease detection and treatment is known as nuclear medicine.

In the legislation which established ERDA in January 1975, it was stipulated that the new agency should be responsible for all activities previously within the AEC and not specifically assigned to other agencies. A similar policy has been followed since the more recent (1977) creation of the DOE, with administrative responsibility for nuclear medicine research programs remaining in the Division of Biomedical and Environmental Research (DBER), formerly the Division of Biology and Medicine and now the Office of Health and Environmental Research.

Upon the creation of ERDA in 1975, need for a comprehensive evaluation of federally-supported nuclear medicine research programs was expressed by several Federal groups interacting with these programs in various ways. These groups included the Congressional Office of Science and Technology, the Office of the Secretary of Health, Education and Welfare (HEW), and the Office of Management and Budget. Subjects in need of evaluation, in light of ERDA's newly-expanded role in energy-related matters, ranged from the appropriateness of continued support by ERDA of the AEC nuclear medicine research programs to a critical evaluation of the scope of nuclear medicine, its content, and its impact on national health care. In response to these queries, a Task Force was appointed in January 1975 to conduct a comprehensive review of these issues, with an added specific charge to evaluate in historical perspective the productivity of the nuclear medicine program

of DBER and to recommend future directions and opportunities.

The Task Force was constituted with the understanding that the latitude of its basic recommendations might vary from elimination of the program on the one extreme, or transfer to another agency, to increased support through ERDA on the other extreme. The Task Force was soon combined with a study group convened for a similar purpose by HEW. Because of the scope of the required evaluation and latitude of possible recommendations, individuals engaged in the study were selected from various fields related to the issues involved, and thus did not necessarily have vested career interests in nuclear medicine. This group consisted of knowledgeable individuals from many disciplines, including economics of health care delivery, management of technology, engineering, physics, anatomy, pharmacology, radiology, cell biology and nuclear medicine.

The observations and recommendations of the Task Force, based on the work conducted over the 18-month period starting in January 1975, were reported in 1976.¹ While details of these recommendations relevant to the present report are given in a following section, the Task Force generally concluded that continuation of support of nuclear medicine-related research by ERDA was not only appropriate but also critical to the continued viability of nuclear medicine and related biomedical research. A major reason for this overall conclusion was that no other Federal agency or private industry has the needed combination of capital equipment (e.g., isotope production facilities

¹Nuclear Medicine Research: An Evaluation of the ERDA Program, ERDA-76/135, August 1976.

and specialized laboratories), experienced intramural or extramural research teams, and opportunities for synergistic technology transfer from basic physics and engineering research programs. Thus a significant transfer of responsibility to another agency was not a reasonable option. Also, the Task Force identified specific areas needing increased emphasis and support, some of which were more appropriate for support by other agencies, and others which had been receiving disproportionate emphasis.

In particular, the first of four recommendations, related to modifications in emphasis of specific programs, contained the statement:

Support for instrumentation research and development should be increased substantially to take advantage of the unique opportunities for technology transfer made available by close relationships existing between the ERDA (now DOE) nuclear medicine, physics and engineering programs.

In its elaboration on this recommendation, the Task Force noted that "a major contribution of the DOE laboratories has been the genesis and development of instruments which, typically, are brought into use for biomedical research and clinical medicine through marketing programs of the private sector," and that "of the areas that have been identified by the Task Force, instrumentation development may well hold the most promise for providing, in the near future, a more effective and efficient biomedical research program and improved diagnosis of disease."

(Emphasis added.) However, other than cite some examples which had become evident during their general review of the overall nuclear medicine related programs, the Task Force did not deal with more specific observations or recommendations, directed to identification of needs, degrees of emphasis, or the relative roles of Federal agencies,

academic and research institutions, and the industrial sector, in the instrumentation development process.

As the Task Force completed its study, and during deliberations related to implementation, it was apparent that more specific and detailed attention needed to be given to instrumentation development, by a different study group, more intimately involved and knowledgeable in this area. Through ensuing correspondence and discussion between the DBER director, representatives of its Physical and Technological Programs office and the Task Force Chairman, a study group effort was initiated to respond to the more specifically circumscribed questions related to instrumentation.

It was understood that this study group would concentrate primarily on identifying the needs for nuclear medicine instrumentation in relation to clinical application and biomedical research, the areas in current academic, industrial and/or governmental research which require focus for meeting these needs, and the relative priorities for program emphasis. For these purposes, the study group was comprised mainly of individuals (principal participants are identified in Appendix I), with long and recognized experience in actual instrumentation development and application to nuclear medicine needs, generally based in the academic or industrial sector, many of whom have extensive insight into the DOE programs through long working relationships. This report summarizes the findings of the study group.

II. NUCLEAR MEDICINE AND INSTRUMENTATION

A. Definition and Evolving Role of Nuclear Medicine

Nuclear medicine is that branch of medicine which involves the application of nuclear science and related technology to the study, diagnosis and treatment of disease. While the term is often used in the more restrictive sense to refer to that area of medical practice in which radioactive materials are used in diagnostic tests for certain diseases, the broader interpretation is used here to better represent the additional inherent potentials, both realized and projected, for better determination of basic biological and disease mechanisms. The treatment of certain specific diseases by internal administration of radionuclides is also an integral part of nuclear medicine practice, but the development of this form of therapy has not been a major focus of the DOE or its predecessors' programs and will not be considered specifically here.

Some statistics related to the effect that nuclear medicine has had on the practice of medicine and health care delivery were presented in the 1976 report of the ERDA/HEW Task Force. At that time, based on the latest figures then available, approximately one in vitro nuclear medicine procedure was being performed in the U.S. for every four hospital admissions, and these procedures were being done in 3000 hospitals and 2000 independent clinical laboratories. The industry supporting these applications was growing at a rate of at least 20% per year. These in vitro procedures, first important in endocrinology for their ability to measure peptide hormones in plasma, now are applied to a wide variety of biological substances and serve many medical

subspecialties.² In biomedical research, the application of radio-nuclides and tracer methods has had a profound impact on the understanding of normal biologic processes and the pathophysiology of disease. Applications range from studies, concerning the nature of the genetic material and the immunoassay of trace organic materials, to more recent developments, using stable isotopes to determine metabolic pathways in both health and disease states. Much of the current research in such fields as cancer biology and cardiovascular physiology depends on techniques developed through the application of radio-nuclides and tracer methods. In all of these areas, the DOE laboratories and extramural research programs have played a crucial role through development and distribution of isotopes (both radioactive and stable), investigations of basic chemistry and biological processes, and development of appropriate detection methods and devices.

A similar rate of growth was evident in the clinical application of diagnostic imaging and scanning procedures, although some uncertainty in projection of future growth and the use of some specific imaging procedures was being introduced by the emergence of X-ray computerized tomography (CT) scanning in 1972, with its subsequent rapid commercial development.³ While it can be argued that CT scanner technology has been derived in several respects from a base in nuclear science in common with nuclear medicine imaging procedures (e.g., reconstruction tomography, radiation detectors and rapid data processing methods),

²Tiersten, S. Radioimmunoassay: State of the Art. *Applied Radiology* 7:125, 1978.

³Hounsfield, G. Computerized Transverse Axial Scanning: Description of the System. *British Journal of Radiology* 46:1016, 1973.

which were developed primarily under the AEC-DOE sponsorship, this transmission CT method has not been considered a part of nuclear medicine practice.⁴ Thus CT scanning with X-rays is a competitive alternative to some clinical nuclear medicine diagnostic procedures, and its effect on nuclear medicine applications and instrumentation development will be determined as the CT innovation continues to evolve in medical practice.

In some areas of application, the impact of CT imaging on nuclear medicine practice is becoming somewhat more clear. For example, the radionuclide (pertechnetate) brain scan (RBS), previously the most common examination in nuclear medicine, has been evaluated by Evans and Jost for its clinical efficacy and economic cost relative to the CT alternative, in four major intracranial diseases: mass lesions, metastatic lesions, cerebral infarction and intracerebral hemorrhage.⁵ While these researchers show that for these specific situations the cost per correct CT diagnosis is double that of the RBS, they conclude that the improvement in diagnostic ability, accuracy and other factors favors CT, and therefore predict that this method will compete with the RBS, except for certain mass lesions or vascular abnormalities. Less information is available on the relative merits of CT and radionuclide

⁴It is appropriate to note in this context that in 1963, D. Kuhl and R. Edwards described a nuclear medicine tomographic imaging method (Image Separation Radioisotope Scanning. *Radiology* 80:653, 1963), developed with AEC support, having conceptual similarity to the present X-ray transmission CT, but which applied to emissions from radionuclides. Later modifications enabling this system to provide quantitative data led to nuclear medicine systems conceptually identical to the X-ray CT system.

⁵Evans, R. and Jost, R. The Clinical Efficacy and Cost Analysis of Cranial Computed Tomography and the Radionuclide Brain Scan. *Seminars in Nuclear Medicine* 7:124-136, 1977.

studies in their application to body imaging. These authors also point out that radionuclide studies will continue to be less expensive and thus probably remain the preferred choice unless CT demonstrates significant advantages. They conclude that "CT does not (now) compete with bone, lung, renal or myocardial radionuclide studies."

Actual experience related to replacement of RBS procedures by CT imaging seems to still vary at different institutions, and the long-term effect is not entirely clear. While cases of significant reduction in utilization of RBS have been described, there are other cases in which an initial reduction occurred with the advent of CT only to rebound as the applicability of CT became better understood, and the complementary role of CT and RBS became more widely recognized. An exposition of the complementary roles of CT and RBS in cases of suspected central nervous system diseases has been given by Fordham, who upon detailing the relative advantages and disadvantages of each, concludes generally that patients suspected of having such disorders should have access to both.⁶ Thus it may be that the longer-term effect will be a reduced rate-of-growth of RBS rather than an absolute reduction. Few clear trends have developed in other body organ imaging applications of X-ray CT versus radionuclide procedures.

In summary, the advent of CT does not invalidate the more specific recommendations or observations concerning instrumentation development made in 1976 by the ERDA/HEW Task Force. However, there is a need for more attention to priorities and emphasis on lines of development of instrumentation which stand in a complementary or enhancing relationship to CT imaging.

⁶Fordham, E. The Complementary Role of Computerized Axial Transmission Tomography and Radionuclide Imaging of the Brain. *Seminars in Nuclear Medicine* 7:137-159, 1977.

B. Instrumentation: History, DOE and Industry Roles

In its 1976 report the ERDA/HEW Task Force observed that the "AEC-supported laboratories have been responsible for the research leading to almost all of the instrumentation now in use in clinical nuclear medicine. Examples range from the initial development of thallium-activated sodium iodide [NaI(Tl)] crystals for detection of gamma rays (1948) and the application of pulse-height analyzers (1954) through the implementation of the collimated scintiscanner to the development of gamma camera systems (1957)." In Appendix II are listed some of the more commonly cited innovations in nuclear medicine instruments with dates of introduction or publication. While this list is considered more as representative of significant developmental ideas than as an exhaustive review, and not all instruments have had the same degree of acceptance in practice, it is found that most were supported by the AEC, and the work performed in connection with an AEC intramural or extramural project, which in some cases was jointly funded by the NIH or the USPHS.

The report of the ERDA/HEW Task Force identified several factors which have fostered the continuing evolution of technology and associated clinical and biomedical research applications. The two most significant of these factors appear to be:

- a) Relatively stable, long-term continuity of support for established, experienced research groups.
- b) Effective means of technology transfer through overlap of the nuclear medicine program with [DOE] basic and applied physics, chemistry and engineering programs, and with NIH programs which emphasize the study of disease processes.

The Task Force pointed out that "long-term continuity of support has allowed for stable, long-term research efforts, which have been important

to the application of nuclear technology to both basic biomedical research and clinical nuclear medicine," and gave as an illustrative example an instrument now basic to clinical nuclear medicine, the scintillation camera, the development of which was started in 1956 by H.O. Anger at Berkeley. The long-term effort required to bring the instrument into commercial production and clinical application in 1964 would not have been possible through short-term programmatic funding. It was also stressed that the programmatic relationship between nuclear medicine research program and both technologically-oriented and disease-oriented programs has been beneficial to medical research and consequently to health care. Several advantageous features include the strength of personnel experience and knowledge in the [DOE] technological programs, and the opportunity for utilization of major resource investments in facilities and personnel in basic physical research and engineering fields, allowing for efficient technology transfer at relatively low incremental costs.

In regard to the role of industry in instrumentation development, the Task Force generally observed that while industry has made significant contributions to the development, trial and implementation of new products, it has had little involvement in those phases of the technology transfer process identified as "theory building, speculative research, or feasibility studies." Their report also points out that while recently industry has taken a greater role in the end-development stages of instruments which originated in AEC laboratories, this sector "has not generally been responsible for the major innovations which have received widespread application in nuclear medicine." For example, the autofluoroscope was primarily developed by private industry, but

it has not received widespread clinical application. More typical is the example cited above, the scintillation camera, which, after a long development process under AEC support, was finally and successfully picked up by industry for manufacture, clinical introduction and distribution. Another example is the scanning tomographic camera, also developed by H. Anger. Additionally, practically all research instrumentation was first developed outside industry, in particular, the positron camera developed by G. Brownell, currently being marketed by the Cyclotron Corporation, the single photon ECT developed by D. Kuhl, now marketed by several companies, and the positron ECT developed by M. Ter-Pogossian and M. Phelps, marketed by the Ortec Corporation and the Cyclotron Corporation.

In its considerations, the current study group has examined the view that nuclear medicine may now be reaching a stage in which, as a market for new instruments and devices, it has matured so that innovation and product improvement can be expected to come entirely from the industrial sector. It is concluded that, in the specific area of instrumentation development, the role of industry may be even more restricted to the end-stage (i.e., "implementation") of the research and development process than is generally the case. The effect is to highlight even more the importance of continued Federal support in this specific area to assure adequate response to public need; and in particular, to bring focus on the DOE role because of its unique capabilities, experience and technology transfer mechanisms not available in other Federal agencies. The reasons for these views are as follows.

For example, it is certainly true that the scintillation camera is far from the original model designed and built by Anger. Over the

years most of its performance parameters such as intrinsic resolution, collimator performance, uniformity and count rate capability have been improved significantly, and there is no reason to believe that further improvements in these areas will not be forthcoming. However, it is observed that attempts by industry at major innovative instrumentation have often met with limited success or failure, and it is expected that the trend in number of future attempts along these lines will be downward.

A major factor now expected to reinforce this trend is recent device legislation which requires extensive clinical trials and proof of efficacy before new instrumentation can be introduced and marketed for diagnostic nuclear medicine. One effect of this legislation will almost certainly be an increase in length of the development cycle with a rise in risk and expense sufficient to shift corporate decisions away from commitments of resources to such development efforts. Often in the past, this risk and expense has been borne by the public through premature introduction of a product. Only after clinical trials performed by early purchasers of the newly-introduced equipment did it become known that it was of no significant benefit to the patient. Thus, it is expected that industry will increasingly seek assurance of technical feasibility and clinical efficacy before undertaking a commercial development, since demonstration and proof of these requirements will be expected to be part of the development process.

From these considerations, it is reasonable to expect that industry will invest significant resources only in the development of imaging instruments that appear to have a substantial market, with already proven clinical efficacy and technical feasibility, i.e.,

instruments that have high probability of wide acceptance in routine clinical nuclear medicine. Clearly not included in this category are instruments optimally designed, specifically for biomedical research utilizing radioactive tracers.

In its review of the ERDA budget for the nuclear medicine research program, the ERDA/HEW Task Force could identify approximately only \$900K in FY 1977 specifically designated for nuclear medicine instrumentation research. While they recognized that this figure did not include indirect support through other ERDA activities, such as in physics research and related instrumentation development, which contributes substantially to the medically-targeted programs, they also clearly recognized that this budget was quite small in relation to opportunities perceived and potential benefit to improved health care and understanding of disease. In their consideration of appropriate modifications in level of support for the four principal budget categories;

- a) Instrumentation Research and Development,
- b) Isotope Production Techniques,
- c) Radiopharmaceuticals and Labeling Techniques,
- d) Clinical Nuclear Medicine Research,

the first of these was given highest priority for increased support, with the specific recommendation that "support (for this category) should be increased substantially..." (Emphasis added.) Recommendations for the other categories varied between maintenance of support to moderate increase. A review of the latest budget data available to us shows the above recommendation has not yet been fully implemented. The current budget (FY 1978) of approximately \$1.1 M for development of advanced instrumentation represents at best a very modest increase in view of inflationary effects. Although it is appropriate to stress again that this figure reflects only a directly identifiable portion

of the funding which impacts on medically-targeted instrumentation development, the study group believes this level of funding is even more inadequate today than the Task Force believed it was two years ago.

Outlined in the following section are identified areas of opportunity and need for future instrumentation development support along with some of the parallel developments in radiopharmaceutical applications to clinical medicine and research, which provide a basis for useful instrumentation. Pursuit of these opportunities through continued Federal support should be considered in light of the disturbing escalation of medical care costs which have been associated in some discussions with the increasing use of certain high technologies such as the transmission X-ray CT scanner. Whatever the merits of this view, it does not appear reasonable to attempt to contain this escalation by suppressing further development of improved diagnostic imaging devices. On the contrary, it appears more reasonable to base cost containment on more rational and efficient use of existing and projected diagnostic tests, reduction of average hospitalization time with increased patient throughput, and better understanding of diagnostic decision-making and the patient management processes.

Specifically, there are significant features of the health-care delivery system which reinforce a tendency to do all available relevant tests on each patient. For example, in many cases the motivating factor is protection of the physician against the real or perceived threat of malpractice charges. To reverse this trend, research is needed to determine optimal sequences of diagnostic tests which might become accepted as the basis of good medical practice and thus protect the physician. Such a sequence might be terminated at any point where

additional tests would provide only redundant information or not affect the course of patient management. Thus as an integral and responsible part of its instrument development program, the DOE should provide support to develop the methodology for research based on signal detection theory (characterization of observer performance), on decision theory, and on the advancing techniques such as multivariate analysis and pattern recognition. Development of such methodology may be considered as an extension of the basic theoretical work, currently supported by DOE, on criteria for comparing and evaluating diagnostic imaging devices and on optimal design of such devices for specific applications. Primary support for the clinical research utilizing these methods appropriately would be derived from non-DOE sources such as the NIH or NCI.

III. OPPORTUNITIES AND DIRECTIONS FOR INSTRUMENTATION DEVELOPMENT

A. Nature of Applications, Disease Problems and Program Emphasis

The basic assumption is that the future contribution of nuclear medicine will be dependent on its successful application to studies of function and metabolism. Its past strengths in clinical medicine have been principally in the areas of morphology and function and to a lesser extent in therapy. There is little question that its utility in relation to morphology is now being seriously challenged by CT scanning, as discussed previously, and also to some extent by ultrasound techniques. As already noted, in some instances these new modalities replace nuclear medicine procedures, and in others they complement them.

The active current interest in developing better methods for study of function and metabolism is due primarily to a fortunate confluence of recently available emission tomographic instruments, greater sophistication in radionuclide production, and in radiopharmaceutical research and preparation. It is expected that the conceptual basis and design of future instruments will be highly influenced by function and metabolism study goals, and thus will necessarily proceed hand-in-hand with the development of appropriate radionuclide production techniques and radiopharmaceuticals.

On another level, some of the specific disease problems for which nuclear medicine techniques offer the potential for a better understanding include:

- a) Detection of occult coronary artery disease,
- b) Detection of and research on the etiology of cerebral disorders such as schizophrenia and epilepsy,
- c) Early detection and staging of cancer for effective treatment,
- d) Detection of pulmonary embolism,
- e) Evaluation of renal disorders.

Each of these selected areas presents major problems of health care and cost to society. Of these disease problem areas, perhaps the two most significant in terms of the incremental gains to be made through improved instruments and methods are heart disease and mental disorders.

Two major concepts in the evolution of imaging instruments, coupled with radiopharmaceutical developments, are emerging which show increasing promise for providing improved knowledge and diagnostic approaches for these disease problems. Both are adaptations of the computed tomography principle based on image reconstruction using radiation emitted from radionuclides, or Emission Computed Tomography (ECT), as opposed to the computed tomography (CT) based on transmitted X-rays, which is now in widespread use. While the latter yields morphological images based on relative density (or X-ray absorption) of different body tissues or organs, the former yields images showing the concentration of appropriately labeled radiopharmaceuticals, which can be tailored for specific organ systems and physiological processes. The two emission computed tomography concepts are:

- 1) Single-photon ECT, and
- 2) Positron ECT.

While the different technical design considerations of these two ECT approaches are intimately connected with different physical nuclear emission processes involved (i.e., single-photon gamma-ray emission in (1) versus simultaneous emission of two 0.51-MeV gamma photons in opposing directions from a positron annihilation event in (2)), and the different types, availability and production modes of the radionuclides involved, the major difference between these concepts lies in the medical problem being addressed and the class of radionuclides

dictated by the biological or clinical aspects of the problem. For example, in a research project directed at mapping the distribution of dopamine receptor sites in the brain in three dimensions, a single-photon ^{123}I labeled phenylethylamine derivative might be chosen as appropriate in the analysis of mental disorders such as schizophrenia. On the other hand, brain blood flow might best be evaluated using ^{77}Kr and a positron ECT system. Evaluation of myocardial perfusion is perhaps most efficiently accomplished with the positron emitters ^{82}Rb , ^{38}K or $^{13}\text{NH}_4$ and a positron ECT; however, a high sensitivity single photon ECT system with $^{99\text{m}}\text{Tc}$ -diphosphate might yield the best post-infarction sizing information.

The relative applicability of these two conceptual developments in imaging is also closely related to differences in ability to accurately determine radionuclide activity per unit volume (quantitative ability) and whether the needed radionuclide and pharmaceutical can be made available conveniently and cost effectively. The short half-life (typically a few minutes) of the most important positron-emitting radionuclides generally requires on-site cyclotron production and rapid radiopharmaceutical preparation methods, while the longer-lived, single-photon emitting radionuclides generally allow for production and distribution from a remote facility. In view of these factors, and the fact that most clinical nuclear medicine can be done successfully with less accurate quantitative measures of the radionuclide activity distribution (as compared with biomedical research), the use of tomographic imaging methods utilizing single-photon ECT may well provide adequate clinical results without the added complexities and

cost of on-site production and preparation. On the other hand, the needs of biomedical research requiring quantitative measures of activity per unit volume may best be met by improved positron ECT systems, at least for study of the heart.

Nevertheless, the research importance of the single-photon ECT lies in the fact that for metabolism studies, a number of biologically useful tags, such as ^{123}I or organically bound ligands labeled with ^{67}Ga or $^{99\text{m}}\text{Tc}$, which might not alter the biochemistry of biologically active compounds or at worst alter them in a predictable way, could be used in settings remote from the production site. Further, the types of compounds which could be studied present less of a problem in labeling than do many of the compounds labeled with positron emitters. However, this role for single-photon ECT is not as well developed as that for positron ECT, and present systems are too slow to follow rapid changes in biochemistry or physiology.

An important reason for the currently greater activity in positron ECT system development is related to the fact that the relevant positron-emitting radionuclides are isotopes of those elements which make up the substance of living systems, i.e., carbon (^{11}C), nitrogen (^{13}N) and oxygen (^{14}O and ^{15}O). In addition, fluorine (^{18}F) is an important label for many of the compounds being studied today. Other important positron emitters include potassium (^{38}K), bromine (^{77}Br) and gallium (^{68}Ga). Not only are a wide variety of compounds available but their biochemistry and pharmacology are often well understood or accessible for study.

Radiopharmaceuticals labeled with positron emitters exist which can act as probes for such diverse functions as regional glucose metabolism and receptor site evaluation in vivo. Indeed the combination of

positron ECT and ^{18}F -2-fluoro-2-deoxy-D-glucose has already been demonstrated to be capable of allowing the measurement of regional brain glucose metabolism. These developments in radiopharmaceuticals and work with other positron emitters such as ^{11}CO , $^{11}\text{CO}_2$, H_2^{15}O , $^{15}\text{O}-\text{O}$, ^{82}Rb , etc. are providing a stronger rationale for related instrument development.

Including the two principal ECT image system concepts referred to, the Study Group identifies need for research and development support in the following listed areas, each of which has significant potential for positive contribution to both the unique and complementary roles of radionuclide-based procedures in clinical and/or biomedical research approaches to major disease management problems:

1. Single-photon ECT imaging systems,
2. Positron ECT imaging systems,
3. Detector materials and devices,
4. Radiopharmaceutical preparation devices,
5. Small animal ECT systems,
6. Radionuclide assay systems,
7. Data handling and display systems.

Although these areas are singled out for emphasis and priority, they are not intended to be exclusive. For example, continuing developmental and research emphasis is advised for other complementary and innovative approaches, including direct delivery of positron emitters to the body by cyclotron injection at high energies, and collimator studies to utilize recent parameter optimization analyses, which indicate the feasibility of improving detector sensitivity and spatial resolution by using different fabrication materials and techniques. Other investigations needing further support include, for example, coded and time varying aperture systems, fluorescence imaging methods, and image processing device concepts derived from studies of observer performance to demonstrate improvements in diagnostic image quality.

In the following section, we review some of the specific needs, current limitations, and directions for further development of the above systems or devices. Where it is appropriate, system performance goals are stated, based on current perceptions of medical or biomedical research need and achievable state-of-the art.

B. Instrumentation Needs, Limitations and Directions

The importance of the role of the emission computed tomographic imaging systems will be best understood and their potential best realized in advances keyed to the advantages presented by parallel developments in new radiopharmaceuticals. For optimal exploitation of their potential applications, improvements are needed to give more rapid sensing, e.g., good statistics with acceptable patient dose in scans taking less than a minute, to yield resolution under normal operating conditions of under 5 mm, and to provide quantitative capability for volume activity measurement. Concomitant with this approach is a need for imaginative programs of radiopharmaceutical research to prepare compounds specifically tailored for use with these instruments.

Biomedical research utilizing radionuclides frequently calls for repeated studies on the same individual; in addition, the use of normal volunteer subjects is sometimes required to establish a reference base. In order to keep the radiation exposure to the subject within reasonable limits, it is essential to conduct such research with instruments having the highest possible sensitivity. In general, increased sensitivity provides the possibility not only of dose reduction but also of increased data acquisition rates for improved dynamic function studies (e.g., heart studies), improved statistics or noise reduction, increased patient throughput, and/or a tradeoff for better spatial resolution.

In general, future needs for improved instrumentation include systems with quantitative three-dimensional imaging ability having high sensitivity and high resolution. Three-dimensional quantitative information is important in order to objectively measure the concentration of substances in the body. High resolution is important because regions of interest and centers of specialized activity in brain, heart, pancreas and other organs are usually less than 10 mm in diameter and often only a few millimeters. The number of events required to give specific quantitative accuracy increases with the third power of the resolution change for a transverse image section; thus, if the resolution element is decreased by a factor of two, then eight times more information is needed for the same data reliability. The ultimate limit in instrumentation development is the counting rate capability of the detectors. Present instruments are operating near the saturation limits of present crystal detectors.

Sensitivity is increased in proportion to the solid angle seen by the detectors. If the body is surrounded by the detector arrays, the sensitivity increases in direct proportion to the number of detectors which see the same volume of interest for single-photon detection schemes. For positron-annihilation photon detection systems, the sensitivity increases even more rapidly depending on the geometry. Methods of increasing the solid angle coverage without unduly multiplying the cost of phototubes and detector crystals are seen in the Burnham-Brownell camera, The Harper-Muehllehner camera, the Washington University PETT III system⁷, and the PETT IV⁸ and PETT V designs for

⁷Ter-Pogossian, M. et al. A Positron-Emission Transaxial Tomograph for Nuclear Imaging (PETT). *Radiology* 114:89-98, 1975.

⁸Ter-Pogossian, M. et al. A Multi-slice Positron Emission Computed Tomograph (PETT IV) Yielding Transverse and Longitudinal Images. *Radiology* 128:477-484, 1978.

positron annihilation systems. Dual scintillation camera rotating systems, the Kuhl Mark IV and the Union Carbide single section system for single photons all strive to increase sensitivity with economy in number of crystals and phototubes.

Continued research is needed to more fully develop the potential of both the single-photon and positron ECT systems. Many of the problems in instrument research for both types require experience and facilities rarely found outside DOE laboratories or academic centers which have been involved in nuclear instrumentation development for biomedical application for many years.

1. Single-Photon ECT System

While earliest applications were tumor surveys without quantification, single-photon ECT has provided the first quantitative tomographic measurements of local organ function in man; D. Kuhl's Mark IV was used to determine local cerebral blood volume and local cerebral glucose utilization in absolute units by scanning ^{99m}Tc red cells and ^{18}F -fluoro-deoxy-glucose, respectively. Further development of the method is warranted.

It has been shown recently that, in principle, the solid-angle advantage of positron ring-systems over single-photon systems is nearly compensated by the contribution from scattered radiation and the lower detector efficiency for positron annihilation photons in the positron ECT systems.⁹ These theoretical and simulation predictions have now been verified by the currently available clinical single-photon devices such as the Mark IV and Union Carbide systems. However, improvements

⁹Budinger, T. et al. Emission Computer Assisted Tomography With Single-Photon and Positron Annihilation Photon Emitters. *Journal of Computer Assisted Tomography* 1:131-145, 1977.

are needed to obtain better sensitivity to achieve images taking less than a minute with acceptable patient dose, to achieve spatial resolution of 5 mm or better, and above all, to develop quantitative measures of activity distribution.

For a variety of socio-economic reasons, industry in general has not responded adequately to the single-photon ECT approach; thus, DOE support is needed for development of more sensitive instruments for multiplane tomography to reduce patient dose and to increase patient throughput. Approaches holding promise for these purposes include the use of large arrays of discrete detectors or multiple Anger-type scintillation detectors surrounding the patient. In particular, there is much room for improvement in implementation of the latter principle through the use of larger detector crystals with more photomultiplier tubes to increase sensitivity, to reduce edge packing (and thereby increase image contrast), to improve the tomographic effect, etc. Such improvements would particularly enhance the application of single-photon tomography to whole-body imaging.

Industrial developments currently underway in the single-photon ECT area use both scintillation cameras and discrete detectors. However, the problems associated with this major innovative approach are numerous, and successful development efforts will be dependent on continued input from academic and DOE laboratory sources. Examples are investigations into novel and specific configurations such as cylindrical detectors, techniques for attenuation correction needed to achieve quantitative activity measurement objectives, and methods for display of volume activity when information is contained in a number of transverse or longitudinal tomographic sections.

2. Positron ECT Systems

Many of the positron-labeled compounds mentioned above under active study today would be of little use were it not for the fact that there are now some working positron tomographic image systems available, e.g., the Burnham-Brownell camera available from the Cyclotron Corporation, the Ter-Pogossian-Phelps PETT III system and the Ortec ECAT. Very recently the Budinger-Derenzo, 280-detector continuous ring system at Donner Laboratory has become operational and is showing exceptional results consistent with its predicted sensitivity and resolution. Generally, under operating conditions these tomographs have resolution in the 8-15 mm range, can gather statistically reliable data in meaningful experiments in 2 to 10 minutes and can provide absolute disintegration rates per unit volume, i.e., they are quantitative instruments. Two instrument versions now exist: whole body machines and head machines.

With these machines, we are currently at a stage where "slow" processes can be studied and biochemical pathways, e.g., regional glucose metabolism, can be studied using pseudo steady-state approaches. The state of the art allows no more. The advances being made in positron-labeled radiopharmaceuticals for these applications serve to highlight the needed advances in performance parameters of these machines. These include specifically:

- a) Higher resolution to take full advantage of the current state of radiopharmaceutical availability. For the brain, 2-4 mm spatial resolution is needed.
- b) Higher sensitivity so that, when combined with the above resolution, data collection times of under 30 seconds with good statistics can be obtained to take advantage of capabilities to assess dynamic processes such as metabolic changes, cellular growth rate and receptor site activity.

The resolution required is related to limits dictated by the positron annihilation process, i.e., the mean range of the positron from a specific radionuclide and the spatial environment of the process being studied. The sensitivity or collection time required to produce a statistically acceptable image is related to the biochemistry and physiology being probed.

Three lines of approach to these objectives are suggested by recent device developments. They are:

- a) Multisection positron devices composed of detector arrays based on the Burnham-Brownell or Ter-Pogossian-Phelps PETT III concept with wobble of the detector assembly to improve angular sampling,
- b) Large numbers of fixed crystals (up to 2000) in multiple layers with individual crystals-phototube coupling as being pursued at the Donner Laboratory, and
- c) Multiple Anger positron cameras surrounding the subject. This approach could provide a feasible instrument if the count-rate limitations of large single crystals can be overcome.

While the first approach may have the advantage of least cost, the others have advantages of no mechanical motion during the imaging process.

The ultimate choice between these approaches will depend on the relative technical success of the systems, as well as on considerations of what medical objectives are to be served. More study will be needed to sort out the medical or research advantages of the ultimately faster continuous ring systems over wobbling ring systems which might take 10 seconds to gather sufficient data for reliable quantitative assessments. For example, can one perform dynamic physiologic studies of the brain, heart and other organs on a second-to-second basis, and if so, with what resolution? Final answers to these questions will

involve considerations of the specific medical problem, the nature of radiopharmaceutical availability and behavior, and allowable doses to the patient.

As an example of some of the considerations involved, suppose it were decided specifically to build a head system with 5 mm spatial resolution in the image with accuracy in the reconstructed activity distribution of $\pm 10\%$. For a 30 cm port, collection of approximately 6×10^6 events for each tomographic section would then be required; and if information were desired on a second-by-second basis, a counting rate of 6×10^6 events per second would be involved. Since currently known systems do not have a sensitivity greater than 30 events/sec/ $\mu\text{Ci}/\text{axial cm}$, the size of the injected dose for a given imaging interval can be predicted. The result might lead to the conclusion that, for presently available technology and radiopharmaceuticals, the study could not be performed because the total injected dose is prohibitive. However, the result should not hinder instrument optimization development as animal studies are possible, and the parallel developments in radiopharmaceuticals may provide the appropriate agents with suitable characteristics for safe studies.

Resolution, sensitivity and accuracy objectives can only be met by intensive effort in instrumentation research, construction and evaluation. Choices, such as that between concentration of effort on head or whole body machines, need to be assessed in relation to ultimate impact on medical care needs and in relation to which approaches may result in immediate versus ultimate application. They can be made only as the performance evolution proceeds, the costs are more fully determined and the medical benefits of the combination of new radiopharmaceuticals and imaging systems are understood.

A specific objective believed to be realizable in the not too distant future is development of a positron ECT system which in combination with the germanium-gallium generator system can potentially have more desirable imaging characteristics than the Anger scintillation camera, now in wide use with the technetium generator. At this stage, it appears feasible to develop such a system having better than 8 mm system resolution, more than 10 times higher sensitivity than the Anger camera, and achievable count-rate capabilities in static studies exceeding 20,000 counts per second per transverse section, allowing imaging time less than one minute. The remote-site availability of a germanium-gallium generator system would make such a system particularly attractive. Needs include the joint development of the generator system, the necessary radiopharmaceuticals and preparation devices, and the basic detectors.

3. Detector Materials and Devices

In view of the situation that the major limiting factor in instrumentation development is the counting rate capabilities of radiation detectors which are now operating near their saturation limits, it is surprising that after all these years the major detector in nuclear medicine systems is still the sodium iodide crystal using photomultipliers for light detection and conversion. Both sodium iodide crystals and photomultipliers have not been changed significantly over the last twenty years, and indeed only minimal research has been conducted to find better detector materials specific to the needs of nuclear medicine.

Six parameters which are of special importance in selection or development of suitable detectors are:

- a) Photopeak conversion efficiency,
- b) Light output or quantum yield,
- c) Rise and decay time of the material or device,
- d) Uniformity and stability,
- e) Energy discrimination, and
- f) Production cost.

Areas of basic detector development which require continued support or new support are identified as follows.

Solid State Detectors. Examples are pure germanium and mercury iodide which can be expected to lead to better energy discrimination and higher count-rate capability through rejection of scattered radiation contributions to background. Disadvantages include the relatively low density of germanium and the slow rise and decay times of mercury iodide which limit their usefulness for positron annihilation systems; nevertheless, both have potential application to single-photon ECT systems.

Scintillator Materials. While thallium activated, sodium iodide crystals are currently the mainstay of nuclear medicine detectors, bismuth germanate (BGO) is superior primarily because of its density and stability. The recent adaptation of BGO detectors for use with some X-ray CT systems is providing experience and impetus for further use of this material. Although the light output (quantum yield) of BGO is low, ECT systems using these detectors would have a sensitivity triple that of systems using sodium iodide. Until recently, production costs have been prohibitively high for BGO systems involving large numbers of individual detectors, but their use in X-ray CT systems is reducing that cost constraint on development. Other needed areas of development include manipulation of crystals such as pure sodium iodide and BGO by cooling to increase light output, leading to improved system spatial resolution and count rate capability, and use of

liquified xenon or argon to provide improved sensitivity and time precision for crude time-of-light techniques. Also, improvements can be expected from further research on the coupling between crystal detectors and phototubes. Such work includes investigation of fundamental material surface properties and experimentation with graded index of refraction materials.

Conversion Devices. Phototube research is generally performed in industrial research laboratories; however, the DOE efforts related to imaging system development for nuclear medicine includes selection of optimum phototubes. If small parallelepiped phototubes could be developed to replace the conventional cylindrical devices, many of the coupling problems mentioned above would disappear. Also needed are large phototubes with their active surface modulated by a controllable electrostatic grid. Other directions needing DOE support include fluorescent screens and channel amplifiers. The latter has special merit for providing position information; disadvantages are high cost of production of large arrays and no current benefit in speed and stability over present phototubes.

Position Sensitive Detectors. In addition to the channel amplifier, position sensitive multiwire proportional chambers filled with gas or liquid as the active medium can potentially lead to lower cost and higher count-rate capability.

4. Radiopharmaceutical Preparation Devices

If accelerator products are to be used in daily patient care and full advantage to be taken of the emerging image systems, attention must be given to the design and construction of devices. In many cases the basis already exists for realizing such construction. For example, the preparation of $^{11}\text{CO}_2$, ^{11}CO , ^{11}CN , $^{15}\text{O-O}$, C^{15}O , C^{15}OH_2 , ^{15}O , $^{13}\text{NH}_3$,

$^{13}\text{N}\equiv\text{N}$ could be easily fully-automated today at modest cost. The delivery of H^{18}F , $^{18}\text{F}-\text{F}$, NO^{18}F , can also be fully automated. Preparation of compounds such as ^{18}F -fluorodeoxyglucose, ^{11}C -deoxyglucose, labeled catecholamines, amino acids, purines, pyrimidines, neuroleptics, etc., by automated devices are, of course, not pertinent until utility has first been demonstrated. In addition, "compound automation" will require different approaches and a greater degree of sophistication than is necessary for the simple precursor compounds listed above.

An investment in mechanical, electronic and chemical engineering skills is needed to solve these problems.

5. Small Animal ECT Systems

While positron tomography and new radiopharmaceuticals have developed rapidly, instrumentation allowing the dynamic study of these new materials in experimental animals has not kept pace. Monkeys, and to a lesser extent dogs (with the very obvious restriction imposed by the size and shape of dog brains), have been studied on existing tomographs but the situation is far from ideal. A device suitable for small animals would allow the pace of research in this area to accelerate materially. It would also help to ameliorate the need to perform human studies before a really thorough background study has been carried out in the smaller animal organs. The situation with neuroleptic studies and receptor site studies are cases in point. What is required is a small continuous ring and associated electronics to allow reconstruction and quantitation but without the extensive storage capability and high sensitivity necessary in machines designed for human use.

6. Radionuclide Assay Systems

In general, instrumentation needs for the assay of radionuclides by the conventional types of detectors and devices are more than adequately serviced by private industry. Many choices in equipment are available.

The area which is not likely to be addressed by private industry, because of the small market potential, involves dynamic assay equipment relative to gas delivery from accelerators directly to the patient, as with $^{15}\text{O}-\text{O}$, or to a synthesis facility, e.g., gases such as ^{11}CO , $^{11}\text{CO}_2$, $^{13}\text{N}=\text{N}$, $^{13}\text{NH}_3$, $^{18}\text{F}-\text{F}$, etc. Essentially, all of these assays are carried out by crude estimation based on beam exposure time or aliquoting and assaying in an ionization chamber. Direct assay of activity while it is being delivered will result in more accurate dosage of patients, will allow greater efficiency in synthetic procedures and is indeed essential to effecting the development of wholly automated synthesis devices which can be operated by technicians or by hospital nuclear pharmacies. In addition, these remote and continuous devices would aid in materially reducing exposure to technicians, chemists and physicians charged with preparing and using the labeled materials.

Such devices have been built based either on ionization chamber detection systems or flow-through proportional counter systems but essentially no effort has been directed toward design and construction of devices with broad capability and adaptable to routine operation.

The problems here are not as complex or as difficult as in the case of the emission tomographs. Solutions should be considerably less troublesome than those required in the emission tomograph area.

7. Data Handling and Display Systems

The DOE sponsored research on new instrumentation has already reached the stage where practical devices provide more image information than the present display and data manipulation systems can present for efficient assimilation by the viewer. Fully three-dimensional distributions are available for the brain, heart and other organs; yet we are at present limited by the ability to look at only two-dimensional slices through the object. Methods of using motion, color, and psuedo-focusing are approaches to this important problem.

IV. CONCLUSION

The DOE Medical Application Program in general and the supporting nuclear medicine instrumentation development efforts in particular have been a major factor in producing the presently productive role of radionuclide applications to health care and biomedical research. Principal reasons for this successful contribution have been an operating policy of relatively stable, long-term continuity of support for established, experienced research groups, and an effective means of technology transfer through an interdisciplinary approach involving DOE basic and applied physics, chemistry and engineering resources, and NIH programs which emphasize the study of disease processes.

The interrelated roles of academic research groups, DOE laboratories, and industrial development and product distribution mechanisms, on the whole, have been very successful in advancing new concepts through the various research, development, evaluation and implementation stages. The appropriate role of the commercial sector in the technology transfer process for instrumentation can be understood from the effect of economic and regulatory factors which together require industry to seek greater assurance of technical feasibility and final marketability before undertaking a commercial development program which must bear the cost of proof of clinical feasibility and efficacy. The role of governmental support thus remains of great (perhaps increasing) importance and should be concentrated on concept generation and development through proof of technical feasibility of systems employing substantially novel technology not currently in use in the field. This development may be carried out in close cooperation with and partial support by industry to enhance the probability of transfer

of the technology to industry, and finally, to implementation in health care.

Future directions for instrumentation research and development are defined in relation to their potential benefits in the study and diagnosis of major diseases and in conjunction with new radiopharmaceutical agents becoming available. The conceptual basis and design of future instruments will be particularly influenced by research goals related to body function and metabolism, and less by morphological imaging capabilities. The emergence of X-ray CT imaging is causing some shifts in use of certain clinical nuclear medicine procedures based on imaging of morphology. A complementary relationship between X-ray CT and single-photon or positron ECT diagnostic approaches is seen. The evolution of new higher resolution and higher speed ECT imaging systems, with improved accuracy and quantitative capability, and related developments in detector materials, radiopharmaceutical preparation and assay methods, combined with promising avenues of investigation of metabolism and function, will prove to be important contributors to solution of major disease problems in the future.

V. SUMMARY OF OBSERVATIONS AND RECOMMENDATIONS

For emphasis and convenience of reference, study group observations presented with their background and rationale in the previous sections are restated more concisely here along with specific recommendations. The observations and recommendations are keyed to the section of the report where the relevant discussion appears. They can be separated into two general categories; i.e., those which relate to general considerations of support and conduct of the work by DOE and industry or academic sectors, and those which are more related to technical direction for instrumentation research and development for biomedical application.

A. General Observations and Recommendations

1. Observation: Concurring with the 1976 ERDA/NIH Task Force, the study group believes that, of the areas of nuclear medicine related research supported by ERDA (now DOE), "instrumentation development may well hold the most promise for providing, in the near future, a more effective and efficient biomedical research program and improved diagnosis of disease," and endorses the associated Task Force recommendation which evidently has not yet been fully implemented; i.e.,

Recommendation: Support for instrumentation research and development should be increased substantially to take advantage of the unique opportunities for technology transfer made available by close relationships between the (DOE), nuclear medicine, physics and engineering programs." (Sec. I and II. B.)

2. Observation: Of the several factors identified by the ERDA/HEW Task Force as having major impact on providing a continuing evolu-

tion of technology and associated clinical and biomedical research application, the study group finds the most significant for instrumentation development to be:

- a) Relatively stable, long-term continuity of support for established, experienced research groups.
- b) Effective means of technology transfer through overlap of the nuclear medicine program with DOE basic and applied physics, chemistry and engineering programs, and with NIH programs which emphasize the study of disease processes.

Recommendation: To assure the achievement of important goals in major disease problems through opportunities presented by new radiopharmaceutical developments combined with new instrument systems concepts, it is essential that program management be guided and program policy continue to be formulated on the basis of the above factors. (Sec. II. B.)

3. Observation: The study group does not concur with the view that nuclear medicine may have reached a stage in which, as a market for new instruments, it has matured so that innovation and product improvement can be expected to come entirely from the commercial sector. Rather, economic and regulatory considerations suggest instead a trend toward increased need for assurance by industry of technical feasibility and clinical efficacy before undertaking a commercial development, since demonstration and proof of these requirements is expected as part of the development process. The effect is to highlight even more the importance of continued Federal support in this area to assure adequate response to public need; and in particular, to bring focus on the DOE role because of its unique capabilities, experience, and technology transfer mechanisms not available in other Federal agencies.

Recommendation: Program management should continue to foster a cooperative relationship between the DOE intramural and extramural instrument development efforts, and industrial laboratories so that effective technology transfer can be maintained. (Sec. II. B.)

4. Observation: While the advent of X-ray computerized tomography (CT) appears to be having some effect on the utilization of certain radionuclide diagnostic imaging procedures in clinical practice, principally the radionuclide (pertechnetate) brain scan, the longer-term effect is not yet entirely clear. It is clear that for many areas of biomedical research and for many clinical diagnostic imaging applications, X-ray CT and radionuclide imaging procedures will stand in a complementary relationship.

Recommendation: Research and development program concepts and priorities for nuclear medicine instrumentation should be structured so that emphasis is placed on lines of development of instrumentation which stand in a complementary or enhancing relationship to X-ray CT imaging. (Sec. II. A.)

5. Observation: DOE support of new, high-technology instrumentation for biomedical research and health care needs must be considered in light of the general escalation in the public cost of medical care associated in part with the increasing use of such technologies. Reasonable approaches to this problem appear not to be through suppression of further development of improved diagnostic imaging devices, but rather, through more rational and efficient use of existing and projected diagnostic tests, reduction of average hospitalization time with increased patient throughput and better understanding of diagnostic decision-making and the patient management processes. Research is needed to determine optimal sequences

of diagnostic tests which might become accepted as the basis of good medical practice.

Recommendation: As an integral and responsible part of its instrument development program, the DOE should continue to support methodology for research in areas such as signal detection theory, decision theory, multivariate analysis and pattern recognition. Primary support of the clinical research utilizing these methods appropriately would be derived from non-DOE sources such as the NIH or NCI. (Sec. II. B.)

B. Technical Program Observations and Recommendations

6. Observation: The future contribution of radionuclide procedures will be increasingly determined by successful application to studies of function and metabolism and, to a decreasing extent, to morphologically-based studies. Expanding opportunities for contribution to solution of significant problems in major disease areas are seen to lie in a fortunate confluence of recently available emission tomographic instruments, greater sophistication in radionuclide production, and in radiopharmaceutical research and preparation.

Recommendation: The conceptual basis and optimal design of future instruments should focus on function and metabolism study goals, and the development program should be coordinated with and supported by a vigorous effort in continued radionuclide production, research and radiopharmaceutical development. (Sec. III. A.)

7. Observation: The Study Group identified several areas of need for research and development support, which together have critical bearing on achievement of programs directed toward health-care

goals through focus on opportunities presented by function and metabolism studies. These areas are:

- 1) Single-photon ECT imaging systems,
- 2) Positron ECT imaging systems,
- 3) Detector materials and devices,
- 4) Radiopharmaceutical preparation devices,
- 5) Small animal ECT systems,
- 6) Radionuclide assay systems, and
- 7) Data handling and display systems.

Each of these areas can draw upon unique DOE capabilities and resources, which, if not made available, would have significant negative, long-term consequences on achievement of these goals. Needed work on other complementary and innovative approaches is also noted.

Recommendation: Although not to be viewed as exclusive, the above identified areas should be given particular emphasis in the DOE instrumentation development program to assure effective progress, made possible because of unique DOE capabilities, toward objectives having greatest marginal impact on solution of major disease problems. (Sec. III. A.)

8. Observation: Two major concepts, both based on the computed tomography principle using radiation emitted from radionuclides in vivo (ECT), are emerging in the evolution of imaging instruments, coupled with radiopharmaceutical developments, which show increasing promise for providing improved knowledge and diagnostic approaches in health care. They are the single-photon and the positron ECT systems. While considerable technical progress has been made with these instruments, design and performance have not yet achieved the full potential which could be realized through application of the experience and facilities available to DOE.

Recommendation: While commercial versions of these systems are now becoming available with design and performance based on recent state-of-the art capabilities, a concerted effort supported by DOE resources is required to achieve their full potential. General performance parameters which should be addressed include improved sensitivity, increased count-rate capability, spatial resolution, as well as capability and accuracy for three-dimensional quantitative volume activity measurement. (Sec. III. A. and B.)

9. Observation: For a variety of reasons, industry in general has not responded adequately to the single-photon ECT approach; thus, DOE support is needed for development of more sensitive instruments for multiplane tomography to reduce patient doses and to increase patient throughput.

Recommendation: Continued input from DOE laboratory and academic sources should be maintained to develop the use of large arrays of discrete detectors and multiple Anger-type scintillation detectors to surround the patient, as well as to investigate techniques such as those for attenuation correction and for display of volume activity when information is contained in a number of transverse or longitudinal tomography sections. (Sec. III. B. 1.)

10. Observation: With currently available positron ECT imaging systems, we are currently at a stage where "slow" processes can be studied and biochemical pathways can be investigated using pseudo steady-state approaches. The advances being made in positron-labeled radiopharmaceuticals for these applications highlight needed advances in performance parameters of these machines. Three approaches are suggested by recent device developments; i.e.,

- a) Multisection positron devices consisting of detector assemblies with wobble to improve angular sampling, and,
- b) Large numbers of fixed crystals in multiple rings with individual crystal-phototube coupling,
- c) Multiple Anger positron cameras surrounding the subject.

Recommendation A: For optimal development of the capabilities of positron ECT systems, approaches such as these should be pursued with resolution goals in the range of 4 mm and sensitivity goals corresponding to data collection times of under 30 seconds. Choice between approaches as they develop should be based on considerations of comparative performance, cost, and the biological or medical applications and benefits of the combination of new radiopharmaceuticals with these systems. (Sec. III. B. 2.)

Recommendation B: A more specific, shorter range objective should be considered to develop a positron ECT system with less than 8 mm system resolution with high sensitivity and image production time under one minute, which can be used with the germanium-gallium generator system. Necessary DOE-industry cooperation should be encouraged to develop the generator system, the necessary radiopharmaceuticals and basic detectors. (Sec. III. B. 2.)

11. Observation: A major limiting factor in the achievement of design goals for nuclear medicine instrumentation is the counting rate capabilities of radiation detectors now operating near their saturation limits. While the widely used combination of sodium iodide crystals and photomultiplier tubes has not changed significantly over the past twenty years, only minimal research has been conducted to find better detector materials or devices specific to the needs of nuclear medicine.

Recommendation: The four principal areas of detector development to which program emphasis should be directed are: Solid State Detectors, Scintillator Materials (e.g. BGO and detector cooling techniques), Conversion Devices, and Position Sensitive Detectors. (Sec. III. B. 3.)

12. Observation: To achieve full advantage of accelerator produced radionuclides, attention must be given to the design and construction of radiopharmaceutical preparation devices and radionuclide assay systems.

Recommendation: The necessary support and commitment of mechanical, electronic and chemical engineering skills should be provided for development of these systems (Sec. III. B. 4. and 6.)

13. Observation: While rapid strides have been made in positron tomography and new radiopharmaceuticals, instrumentation allowing the dynamic study of these new materials in experimental animals has not kept pace. Studies involving small animals, made with existing tomograph systems, are far from ideal because the animal organs are small relative to available ECT resolution. Small, high-resolution instruments would help to ameliorate the impetus for going into human studies before sufficient background study has been conducted.

Recommendation: Resources should be allocated to develop a small, continuous ring ECT system to allow reconstruction and quantitative capability, but without the expensive storage capability and high sensitivity required for human use. (Sec. III. B. 5.)

14. Observation: The DOE sponsored research on new instrumentation has already reached the stage where practical devices provide more image information than the present display and data manipulation

systems can present for efficient assimilation by the viewer.

Recommendation: Investigation of methods including motion, color and pseudo-focusing should be pursued to extend present two-dimensional viewing capabilities to three dimensions. (Sec. III.

B. 7.)

APPENDIX I

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APPENDIX II

Some Principal Innovations in Instrumentation for Nuclear Medicine

1948	Development of NaI (Tl) Detector: Hofstadter
1950	Rectilinear Scanner: Cassen
1952	Focused Multichannel Collimator: Newell et al.
1952	Commercial Production of NaI(Tl) Crystals: Harshaw Company
1953	Two Detector Positron Scanning System: Brownell and Sweet
1954	Pulse Height Analysis to improve signal-to-noise ratios: Allen et al.
1954-56	Photoscanning Technique - Prototype for Standard Clinical Scintiscanner: Kuhl et al.
1958	Scintillation Camera: H.O. Anger
1959	Twin Crystal Positron Camera: H.O. Anger
1962	Autofluoroscope: Bender and Blau
1963	Emission Tomography: Kuhl and Edwards
1968	Fluorescent Scanning: Hoffer et al.
1972	Fresnel Zone Plate Imaging: Rogers et al.
1973	Two Panel Detector Array for Positron Imaging: Brownell et al.
1975	Positron Emission Transaxial Tomographic System: Phelps, Ter-Pogossian et al.