COO/2777-04

EVALUATIVE STUDIES IN NUCLEAR MEDICINE RESEARCH

Progress Report

for Period October 1, 1979 - June 30, 1980

E.J. Potchen, M.D.

Michigan Research Center, Inc.

Okemos, MI, 48864

July 1980

Prepared For

THE U.S. DEPARTMENT OF ENERGY

UNDER CONTRACT NO. EY-76-S-02-2777.A002

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1. INTRODUCTION

Effort under this contract since the last progress report (September 1979) has been directed toward assessing the potential short and long term benefits of continued development and application and medical research of emission computed tomography (ECT). This report summarizes results of that work to date.

Section 2 contains a review of existing ECT technology, including functional descriptions of current and proposed image systems, for both single-photon ECT (SPECT) and positron ECT (PECT) approaches. Medical research and clinical topics to which ECT has been, or may be, applied are presented in Section 3. One such area of investigation involves the effects of stroke. The application of ECT to laboratory research, and to clinical diagnosis and prognosis, of stroke may result in improved management of the disease. An illustration of the potential savings in the cost of management of stroke due to the effects of applied ECT research is the subject of Section 4.

The results presented in Sections 2 and 3 represent a compilation of data collected from conversations with, and conference presentations by, ECT users, researchers and image system designers, and from a review of the literature (Appendix I). Data on the epidemiology and cost of management of stroke were obtained from published results of the National Survey of Stroke performed by the National Institute for Neurological and Communicative Disorders and Stroke.

2. SINGLE-PHOTON AND POSITRON EMISSION TOMOGRAPHY:

CONSIDERATIONS OF CURRENT STATUS OF IMAGE SYSTEMS

Computed tomographic techniques based on external detection of photons emitted from internally administered, radiolabeled phamaceuticals is currently achieving promising status as a biomedical research tool, and indications are that a longer-term potential exists for significant application to diagnosis and to evaluation of treatment for disease. Today, most of the activity associated with these techniques appears to be directed to studies of function and metabolism of the brain and heart. While the development of imaging systems is still rapidly evolving along several lines of approach, it has been observed that the imaging technology is reaching a stage where the primary limitation on further application to biomedical problems may now lie in the development of appropriate radiopharmaceuticals and a more detailed knowledge of metabolic processes. The purpose of this section is to review and summarize in a general way some of the operating principles and limitations of current emission tomographic imaging systems.

Emission tomographic systems for formation of images based on external detection of photons emitted from within a subject have been under development for several years. System development has proceeded primarily along the two following lines:

1) Single Photon Emission Computed Tomography (SPECT)
2) Positron Emission Computed Tomography (PECT)

General characteristics and examples of these systems are briefly reviewed in the following. However, both depend on the computer assisted technology for transaxial image reconstruction introduced in nuclear medicine before 1960 by Kuhl and colleagues, but adopted and intensively developed by Hounsfield in the early 1970's for x-ray computed tomography. The formulation

of the reconstruction problem is the same for x-ray computed tomography and emission tomography. A variety of reconstruction algorithms have been developed which generally can be classified in two categories: algebraic techniques which usually involve successive iterative steps to approach an "acceptable" image reconstruction, and convolution or Fourier transform techniques most commonly appearing in the form of the linear superposition of filtered back projections. A significant difference (and an additional complication for emission computed tomography) in the application of these algorithms to transmission and emission reconstruction is that they neglect the effect of attenuation by the surrounding material of emitted photons from activity distributed within the object. Thus another set of unknowns must be introduced and solved for to represent attenuation in order to reconstruct the image accurately in the emission case. Much of the recent development activity associated with these systems has been devoted to satisfactory resolution and understanding of this "attenuation problem". The inaccuracy inherent in the corrections for attenuation propogate through the reconstruction process leading to inaccuracies in the final images. This major source of inaccuracy is present in all emission computed tomography systems; however, at present the problem is less severe in the PECT systems than in the SPECT systems.

2.1 SPECT Systems

These systems can be separated into two general types: scanner based and camera based. Both employ detection of gamma-ray photons by scintillation detectors suitably positioned in the plane of the cross-section to be imaged in the patient. The photons are emitted from internally administered radio-pharmaceuticals containing generally the radionuclides commonly used in

nuclear medicine such as ^{99m}Tc, ^{131}I, ^{201}Tl, etc., which ideally decay by gamma emission with photon energies optimal for efficient detection and with half-lifes appropriate to the procedures performed. The required single-photon gamma emitters are typically commercially available at reasonable cost as reactor-produced nuclides and are often provided in generator form for convenient local use (e.g., ^{99m}Tc). For these reasons SPECT systems may have greater near-term potential in clinical applications than do the PECT systems.

The scanner based systems employ an array of NaI(Tl) detectors situated around the patient in the image plane. The detector array is designed to translate and/or rotate in this plane to provide the required interval sampling of the image field. Two examples of existing systems of this type are as follows:

MARK IV This head scanning system, now at UCLA, but developed by David Kuhl and coworkers at The University of Pennsylvania as one in a sequence of designs in the Mark I, II, III, and IV series, consists of 32 NaI(Tl) detectors mounted in banks of 8 detectors each, forming a square array in the reconstruction plane. The array continuously rotates in this plane in a complete 360^{o} scan requiring 50 sec during which photon detection events are recorded and binned into angular projections. From the accumulated, binned data, image reconstruction using an algebraic iterative algorithm is accomplished in about 30 sec. Progressive development of the image can be monitored as the array is allowed to continuously rotate. In practice, a five-revolution scan is used in most clinical studies. Converging collimators are mounted on each of the 32 detectors. Recent applications of this system include evaluation of head injury and stroke.

Union Carbide Twelve Sided System. This system, installed at St. Elizabeth Hospital, Brighton Mass., consists of a twelve-sided array of NaI(Tl) detectors with converging collimators. Also constructed as a head unit, the detectors in this system scan in a rectilinear fashion with a 21 cm field of view. Simultaneous data accumulation and image reconstruction can be performed with the aid of a Data General Eclipse S-220 minicomputer with scan times available between 2-5 minutes.

The camera-based systems utilize versions of the gamma camera developed originally by Hal Anger which singly, or in combination, are mounted to view the cross sectional image field from different directions in the image plane. Systems of this type have now been designed in such a way that up to 64 simultaneous cross-sectional images can be reconstructed from data accumulated in a single revolution of a camera system about the patient (Searle/Duke collaboration at Duke University). Examples of existing camera-based SPECT systems include the following:

University of Michigan Single Head Camera ("Humongotron")

This system, developed by Keyes et al., uses a scintillation camera mounted on a rotating, cantilevered arm with provisions for radial adjustments of the distance of the camera from the patient. The arm/camera assembly rotates through 360^{o} about the patient with adjustable speed. Provisions are available for both conventional and transaxial tomographic imaging. In typical operation in the tomographic mode, eight 1.5 cm thick cross-sections of the head are obtained in 20-30 minutes with a single rotation of the camera and spatial resolution of about 1.5-1.8 cm. Usually, data are accumulated from 30 angular projections taken at 12^{o} intervals which requires about 30 sec for the reconstruction of each cross sectional image. Most applications have been to patients with focal cerebral disease using ^{99m}Tc-pertechnetate.

Searl/Duke SPECT System With this camera-based system, a single revolution of the camera gantry about the patient provides up to 64 cross-sectional images with spatial resolution of slightly over 5 mm FWHM achieved by modifications which include replacement of the standard 1/2" thick Nai(Tl) crystals with 3/8" crystals. Recent clinical applications of this system have been to kidneys, lungs, myocardial infarct and heart wall motion studies.

2.2 PECT Systems

Positron emission computed tomographic systems are based on coincidence detection of the simultaneously emitted 511-keV photons arising from the annihilation of a positron-electron pair in the tomographic section to be imaged. Coincidence detection is performed by oppositely mounted scintillation detectors electronically connected pairwise to record the two annihilation photons. Since physical momentum and energy conservation laws require emission of the two photons at 180^{o} relative to one another (in the center-of-mass system of the annihilating pair), a coincidence detection event fixes the emission point in the spatial region subtended by the faces of the opposing detectors.

This physical constrainingon the emission region "viewed" by the paired detector is frequently cited as the major advantage of PECT systems over single photon emission systems. In the latter, extensive collimation must be used to achieve a similar result, with the effect that the sensitivity of PECT systems is inherently higher. A given detector in these systems can be coupled electronically to record the events in coincidence with several opposing detectors in the ring. This fan-beam geometry provides a great increase in detection efficiency of PECT over SPECT systems. The theoretical limiting sensitivity for PECT systems is approximately 5×10^{7} counts per second per microcurie per cc concentration. Current single-ring PECT systems

operate at about 1% of this positron limit.

The non-negligible range in tissue of the positron and center-of-mass motion of the annihilating positron-electron pair limit the achievable spatial resolution of PECT systems to approximately 5-7 mm depending on details of the situation. Some current systems appear to be approaching this expected performance.

Although errors are introduced into the reconstruction image by methods used to correct for photon attenuation in all emission computed tomographic systems, the methods now available produce less error and provide more accurate corrections in PECT systems than in single photon systems. Quantitative image analysis is thus at a more advanced state in PECT systems.

While several versions of PECT systems have been constructed using opposing linear arrays of detectors, the trend appears to be toward complete rings of detectors. Two-ring systems exist which incorporate cross-over counting between rings to improve sensitivity and produce simultaneous imaging of more than one tomographic cross section. Multiple ring systems are under consideration with the potential existing for development of actual 3-D imaging with such systems. Progress with these systems has been very rapid and advanced stages of development are being achieved.

Set against the several technical advantages mentioned of PECT over SPECT systems is the circumstance that the positron emitting radionuclides required for PECT are for the most part short lived and require on-site production. As proton-rich nuclides, their production generally requires a cyclotron or other positive-ion accelerator to initiate the production reaction. For example, much interest has been shown the application of ^{11}C, ^{13}N, and ^{15}O positron emitters to studies of various metabolic processes because of the importance of these elements and their compounds in biological systems. Their few-minute half lives, however, require that accelerator

production and the necessary chemistry be performed locally; a situation which mitigates againsttheir use in many clinical and research settings because of the cost and required technical personnel. Some longer lived, generator produced positron emitters do exist however. For example, ^{68}Ga ($T_{1/2}$=68m) is available in generator form as a daughter product of ^{82}Sr ($T_{1/2}$=25d) which has been used for example in heart imaging. Also ^{18}F ($T_{1/2}$=110m) is available and frequently used in bone studies.

In large part because of this radionuclide cost and availability problem, PECT systems are currently seen as having their greatest potential in research investigations rather than in clinical diagnosis. However, the research potential is great, allowing investigation of quantities and processes which essentially have not been previously amnenable to study in the detail afforded by this technology.

Various approaches in the development of positron emission computed tomographic devices have been pursued in recent years. In a general sense, the various designs can be considered in terms of the configurations and type of detectors used. Examples of four such configurations are discussed briefly to provide some overview. The four configurations involve the use of two opposing banks of NaI(Tl) detectors, linear arrays of detectors arrayed on sides of the polygon, opposing large field-of-view scintillation cameras, and circular ring detector arrays.

Opposing NaI(Tl) Detector Bank Systems

This type of system is represented by the Massachusetts General positron camera system PC-II developed by Brownell and colleagues for whole-body imaging, a commercial version of which has been designed by the Cyclotron Corporation. The two opposing banks of detectors each consist of 144 NaI(Tl) crystals placed in a square array. Each detector in one bank is electronically connected

in coincidence with the directly opposing detector and its surrounding 24 nearest neighbors in the opposite bank. The gantry supporting the two detector banks is designed to rotate about the patient with provisions for adjustment of patient-detector separation and for linear scanning motion in both the horizontal and vertical directions to improve sampling over that achievable in the rotary motion alone.

A convolution-based reconstruction algorithm is used for tomographic image reconstruction and display. With this system spatial image resolution of approximately 15 mm is obtainable. Corrections for attenuation of photons in the subject are obtained by placing an external sheet distribution of positron emitting material in front of the detector banks and recording data with and without the subject interposed. Investigations with this system have included blood-flow imaging of the brain ($^{13}NH_3$, $^{15}CO_2$), oxygen metabolism ($^{15}O_2$), brain tumor detection (^{68}Ga-ATP), lung imaging ($^{13}N_2$), and cerebral metabolic studies (^{11}C-glucose) among others.

Polygonal Detector Array Systems

This general design, based on mounting of linear arrays of detectors as sides of a polygon structure, has been used by Phelps, Hoffman, Ter Pogossian and colleagues in the sequential development of a series of positron emission transaxial tomographs referred to generally as PETT. A commercial version, known as ECAT, has been jointly developed by Phleps and Hoffman with ORTEC Inc.

The systems denoted by PETT-II, III, IV, and ECAT employ hexagonal arrays of NaI(Tl) detectors in which each detector on opposing linear array banks is connected in multiple coincidence. The PETT-III system, for example, uses 48 5 x 7.5 cm NaI(Tl) detectors mounted eight to a side on a gantry which rotates through an angle of 60° in 3° steps, with a synchronous linear scan of all six banks performed at each step. A convolution-based image reconstruction

algorithm is used with photon attenuation correction obtained either by geometric modeling or by direct measurements of attenuation with an external ring source of positron emitters. The PETT-IV system is similar in design except that the detector array and shielding are modified in such a way as to provide the capability for four simultaneous tomographic cross-sectional images. Event identification for the four slices is derived from position sensitive logic pulses from phototubes mounted on opposite axial ends of each of the NaI(Tl) detectors. The system is designed for whole-body studies. Spatial resolution available with these devices range between about 9 and 25 mm.

Development of the PETT series of systems is continuing with PETT-V for head studies, PETT-VI in which CsF detectors replace the NaI(Tl) detectors, and PETT-VII with CsF or possibly BGO detectors for evaluation of the potential for a time-of-flight mode, whole body imaging system. In the latter system, the presently unused information provided by the time delay between arrival of the two annihilation photons may be used to further define the point of origin of the emitted photon pair within the subject.

Opposing Large Field-Of-View Scintillation Cameras

Representative of this design is the Searle-University of Chicago collaborative effort by Meuhllenhner and Harper and coworkers consisting of two directly opposing large field-of-view gamma cameras mounted on a gantry for continuous 180° rotation. Modified versions of the Searle high-speed electronics camera are adapoted to this purpose by using 1-inch thick NaI(Tl) crystals and other changes to optimize detection of the 511-keV annihilation photons. All possible coincidence combinations between the opposing detector heads are recorded serially on magnetic tape and indexed appropriately for various imaging formats. In addition to the transaxial image format, the system

is capable of also generating multiple longitudinal tomographic images in a stationary gantry mode. Spatial resolution of about 10-14 mm is typical with this design.

Circular Ring Arrays

Several circular ring systems have been developed including the Circular Ring Transverse Axial Positron Camera by Cho and coworkers at UCLA, and the LDL positron camera by Derenzo, Budinger and others at the Lawrence Donner Laboratory at Berkeley. These systems, designed for whole-body static and dynamic imaging investigations, consist of complete circular arrays of NaI(Tl) detectors surrounding the subject. The latter design employs 280 crystals in a circular gantry providing a 31-cm diameter field of view. This version is completely stationary, i.e., no angular rotation or wobble is employed. Tomographic slice thickness is adjustable from a few mm to 1.5 cm, and spatial resolutions of about 8-15 mm have been demonstrated. In the UCLA camera, each detector on the ring is connected in coincidence with 23 detectors on the opposite side of the ring. The ring can be used in either a stationary mode, or with a rotation over an arc equal to one-half the interdetector spacing (2.8^{o}). Approximately 18 mm image resolution is possible with the rotation mode. Further development considerations include, at UCLA, replacement of the NaI(Tl) with BGO detectors and multi-ring systems to provide greater system sensitivity.

Although some of the current and potential research and clinical applications of each of these systems have been mentioned, a more detailed summary of applications of both SPECT and PECT systems is presented in the following section.

3. POTENTIAL APPLICATIONS OF ECT TECHNOLOGY

As indicated above near-future use of this technology is expected to be

primarily in research. ECT provides tomographic images yielding information on normal and pathological metabolis, and when compared with traditional techniques for investigation of these processes, allows for in vivo examination of substruc turalphysiology in a manner which is relatively uninvasive to the subject. The research utility of ECT lies not only in the study of organic processes, but also in the study of intervention into those processes. These studies include the investigation of the effects of treatment (medical and surgical) and the development of new treatment techniques.

Clinical applications of ECT may eventually evolve from "intervention research". Because of its ability to image metabolic processes, ECT may be used to demonstrate the viability of tissues damaged by trauma or circulatory insult (ischemia,infarction) and may therefore play a role in diagnosis, prognosis, and treatment planning.

The potential research and clinical applications of ECT are discussed in more detail in the following sections.

3.1. Research

3.1.1. Brain

In the brain, ECT may be used to study epilepsy, and the effects of stroke and trauma. Epilepsy and drug kinetics in the treatment of epilepsy are currently studied by observation of glucose metabolism. It has been found that hypermetabolism of glucose accompanies epileptic seizures, while the inter-seizure intervals are characterized by glucose hypometabolism.

Deoxyglucose is also being used to study normal brain function in a way which may aid stroke and trauma victims. Increased metabolism serves as an indicator of focal brain activity under varying conditions of focus of attentive thought (reading, seeing), type of thought (logical, such as in reading or listening to a familiar language, or abstract, such as in detecting a specific phrase spoken in an unfamiliar language or listening for a specific passage in

a piece of music), and manipulation or stimulation of extremities (motor control). Thus, metabolic studies of the brain may be used to map centers of brain activity associated with various thought and motor skills. Neuroanatomical function mapping by positron ECT is expected to contribute to the understanding of cerebral metabolic changes in aging, senile dementia, schizophrenia, and demyelinating diseases.

Metabolic studies, along with measurements of blood flow and blood volume, may also be used to determine the viability of brain tissue following trauma or stroke. Infarcted tissue is manifested by increased blood flow and decreased metabolic activity. Using the knowledge of brain activity obtained from studies of normal function, the extent and severity of the effects of trauma or stroke may be determined in such a way that prognosis in these cases may be more accurate and treatment plans may be more specifically tailored to the individual patient's needs.

Other subjects currently under study or representing potential areas of study by positron ECT "metabolic encephalography" are protein synthesis, Huntington's disease, cerebrovascular disease, metabolism in altered states of consciousness, neuroendocrine regulation of brain water permeability, the neurotransmitter receptor system, and dopamine and opiate receptor sites.

3.1.2 Circulatory System

In the normal heart, gated ECT may be used to produce high-spatial-resolution images of cardiac dynamics in three dimensions, while providing information about cardiac tissue physiology. ECT studies gated by cardiac cycle signals may also be used to study and diagnose heart failure.

ECT is being used to study myocardial infarction and atherosclerosis. The latter is presently investigated by blood flow differential studies, but in the future may be studied by observation of endothelial metabolism. Of

particular current interest are the rate of progression of atherosclerosis and ischemia, its major complication. Ischemia may be studied by observing the washout of labelled ammonia from the myocardium; washout is slower for ischemic tissue than for normal tissue. Labeled ammonia has also been used to study hyperemia due to stenosis in the heart.

3.1.3 Others

ECT may be used to investigate inflammatory lesions and primary and metastatic malignant tumors in the lungs, liver, kidney, and spleen. ECT delivers a better image, with enhanced tumor-tissue contrast, then does gamma-camera scintiscanning. Blood flow ECT procedures have been used to study pulmonary metastases of osteosarcomas, the extent of neuroblastomas, and metastases of rhabdomyosarcomas. An additional target for study by ECT is bone infarction.

Research in organ physiology using positron ECT is currently limited to "small" organs such as the heart rather than "large" organs such as the liver. This is due to limitations caused by the larger doses of radionuclide required to achieve sufficient counting statistics in a large organ. Delivered dose is, and will continue to be, an important factor in determining the appropriateness of human in vivo research using ECT. Delivered dose depends on the quantity, physical and biological half life, and details of the decay scheme of the radionuclide. Improvement in the sensitivity of image systems, along with further development of radiopharmaceutical technology will reduce the required integral dose and may expand the application of ECT to the study of processes in large organs.

4. CLINICAL DIAGNOSIS AND PROGNOSIS

While it is unlikely that the widespread use of ECT in clinical

applications will occur in the near future, the potential for direct contributions to clinical practice by ECT should not be overlooked. As discussed in Section 3.1.1, ECT may be used to gain knowledge of both the purpose of local activity in the normal brain, and the extent or capacity for local activity and tissue viability in the pathologic brain. This information may eventually yield more accurate and meaningful prognoses and rehabilitation strategies for victims of stroke and head trauma. In addition, ECT can demonstrate physiological changes in brain tissue function which preceed the structural changes detectable by transmission CT, enabling earlier diagnosis of certain conditions than now possible. It has also been mentioned that gated ECT imaging of the heart can produce information regarding cardiac physiology while simultaneously allowing a diagnosis of heart failure with accuracy similar to that of cardiac angiography.

Thus, while the cost of acquiring and operating an ECT site will no doubt preclude its availability to many local markets, it is not inconceivable that ECT may have an impact on clinical practice since specialized diagnosis and treatment planning could be performed at regional ECT research centers.

5. POTENTIAL MEDICAL AND ECONOMIC IMPACT OF THE ECT: ILLUSTRATION

It is currently too early in the development and application of ECT technology to formulate reliable projections of the medical and economic impact this new technology will have on health care in the United States. Past and present costs of managment of the diseases for which ECT research is likely to be of use are largely unstudied and unknown. The National Instutute for Neurological and Communicative Disorders and Stroke (NINCDS) has undertaken a series of national surveys in an attempt to obtain statistics on incidence, prevalence, and cost of stroke, multiple sclerosis, epilepsy and spinal cord injury. Of these surveys, only that for stroke has been completed. Highlights of that study have been published as NIH Publication

No. 80-2069, "National Survey of Stroke", January 1980. Some figures from that publication are cited here to indicate the potential of ECT technology for cost reductions related to a particular disease. As discussed previously, ECT has already been used in the investigation of focal metabolic activity and tissue viability in the brain; this may provide information enabling more accurate and meaningful prognosis and rehabilitation managment for stroke victims. Consideration of the cost of management of this disease alone may provide a reference point for the assessment of potential yield from investment in ECT research and development.

According to the NINCDS survey, the incidence of stroke in the U.S. in 1976 was approximately 414,000 cases; the prevalence of stroke on 1 July 1976 was approximately 1.7×10^6 cases. From 1971 to 1976, both incidence per 10^5 persons and death due to stroke per 10^5 persons declined from 152.1 and 104.2, to 137.0 and 91.3, respectively. The difference between the rates of incidence and death represents the rate of new surviving cases per 10^5 persons per year. For 1971 this figure is 47.9; for 1976 it is 46.6 Thus, the number of new stroke victims in need of ongoing care and management has remained virtually constant, despite decreased incidence. It is for the population of surviving victims that improved management strategies made possible by ECT research will affect cost.

The national survey produced estimates of direct and indirect annual costs of management of stroke in 1976 dollars. For purposes of this illustration we assume that improved rehabilitation strategies will not have an appreciable effect on indirect costs, estimated at $\$4.1 \times 10^9$, due to loss of earnings. Among direct costs of care, we also assume no appreciable effect on the cost of hospital care and physician services, estimated at $\$1.5 \times 10^9$. Some reduction should be expected, however, for costs associated with extended care, ancillary medical and social services, and aids and appliances, estimated

to total $\$1.8 \times 10^9$.

Although a savings of some fraction of these latter direct costs (say 20%, or $\$360 \times 10^6$ (1976) per year) is small compared to the total estimated direct cost of management of stroke ($\$3.3 \times 10^9$), it is of significant value when compared to the cost of continued development and research applications of ECT technology. The NINCDS, for example, has committed $\$32.5 \times 10^6$ over the years 1980-1984 in support of extramural research programs applying ECT to the study of brain function.

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