VOLUME 5

# RECENT ADVANCES IN NUCLEAR MEDICINE

Edited by

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*Grune & Stratton*
*A Subsidiary of Harcourt Brace Jovanovich, Publishers*
*New York San Francisco London*

**Grune & Stratton, Inc.**
**111 Fifth Avenue**
**New York, New York 10003**

*Distributed in the United Kingdom by*
*Academic Press, Inc. (London) Ltd.*
*24/28 Oval Road, London NW 1*

Library of Congress Catalog Number 72-175696
International Standard Book Number 0-8089-1068-X
Printed in the United States of America

# Recent Advances in Nuclear Medicine

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# Preface

This is the fifth volume of this series—the first volume was published in 1948. The editors have selected a distinguished list of authors: Dr. Gordon Brownell of the Massachusetts General Hospital needs no introduction. His contributions to biophysics and nuclear medicine are well known throughout the world, and he continues to produce important additions to our knowledge. Dr. Michael Welch of Washington University, St. Louis, is noted for his excellent work on the chemistry of radioactive compounds, particularly the positron emitters. Dr. Cornelius Tobias and his associates, especially with the medical insights of Dr. Paul Capp, are pioneers in the new field of heavy ion radiography. Dr. Robert Parker of the University of California, Los Angeles, is an experienced and able radiotherapist who has had extensive experience in the use of neutrons and the therapy of certain types of advanced cancer. The Donner Laboratory has been active in the field of heavy ion therapy since our early work on the biological effects of neutrons in 1935, and now this work is being extended into the use of very heavy particles such as oxygen, neon, etc. We are fortunate now to have the therapeutic expertise of Dr. Joseph Castro in this program. This volume was prepared as both a historical review and a presentation of the state-of-the-art in nuclear medicine instrumentation and radiopharmaceuticals and in the use of neutrons and heavy ions for tumor therapy and radiography. It is intended that these selected topics will be helpful to investigators in nuclear medicine, radiotherapy, and medical physics.

John H. Lawrence
Thomas F. Budinger

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Gordon L. Brownell
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# 1
# Positron Instrumentation

## INTRODUCTION

The potential of positron imaging has been known since the early 1950s. The attractive features of high sensitivity and resolution as well as the desirable chemical characteristics of some positron-emitting radionuclides have resulted in continuous effort toward their use in biology and medicine. However, clinical applications have been limited because of the necessity for basic developments in three areas. The first is the development of a convenient source of short-lived, cyclotron-produced radionuclides within a medical setting. The second is the development of appropriate labeled radiopharmaceuticals. The third is the development of instrumentation for high resolution imaging. Although further development is required in each of these areas, they no longer remain a hurdle to medical applications. Small cyclotrons are now available for use in medical facilities. Advances in rapid chemical syntheses of radiopharmaceuticals, described in Chapter 2, now permit a large number of labeled compounds to be prepared in times comparable to the half-lives of the radionuclides. Positron instrumentation, to be described in this chapter, has made great strides in recent years and a variety of instruments are now available or will shortly become available for positron imaging.

Transverse section positron techniques for emission-computed tomography (ECT) have been stimulated by development of transmission-computerized tomography (TCT). Positron techniques for ECT offer promise of extending the capability of TCT and the combination of emission and transmission techniques may well provide more information than the sum of the individual procedures. This is particularly true since ECT

tends to provide information on the physiological and biochemical state of the organ or tissue that is imaged whereas TCT provides structural or morphological information.

Emission-computed tomography is not limited to positron-emitting isotopes and many investigators are attempting to perform ECT using gamma emitters and single photon detection systems. This development does not fall within the scope of this chapter.

The great potentials of physiologic imaging (in both conventional and in transverse section mode) are now becoming recognized by basic medical scientists and nuclear medicine clinicians. This chapter describes the developments and present state of new commercial and university instrumentation advances in this field.

## HISTORY OF POSITRON IMAGING

Imaging of positron-emitting radionuclides was suggested independently by Wrenn et al.[1] and Brownell (reported by Sweet[2]). The first practical device as described by Brownell and Sweet[3] used a pair of sodium iodide detectors to image positron annihilation photon radiation emerging from the head for the detection of brain tumors. The detectors scanned mechanically over the head to record the number of annihilation photons detected in coincidence. A second scan portrayed the unbalance in total counting rate of the two detectors.

Using this scanning detector pair system for evaluating the localization of As-74 in brain tumors and abscesses, Sweet and Brownell[4] in 1955 reported a lesion detection accuracy of 75 percent for tumors and 83 percent for abscesses. Subsequently, other organs of the body such as liver, pancreas, kidney, and lung were scanned with positron-emitting radionuclides $^{64}Cu$ and $^{62}Zn$.[5]

Based on these results, a more sophisticated single pair scanning system was developed for brain tumor localization in routine clinical practice.[6] This device together with its successors has been in continuous use at the Massachusetts General Hospital (MGH) for both clinical applications and research.

After his initial description of the scintillation camera in 1958,[7] Anger demonstrated in 1966[8] that two static scintillation cameras detecting the annihilation photons subsequent to positron emission could produce images without the use of a conventional collimator. The system produced excellent, high resolution images of positron emitters in a variety of biological applications. The instrument further demonstrated the tomographic properties that are inherent in any device using nonparaxial rays

and similar focusing techniques have been widely used in subsequent positron instrumentation. Limitations in count rate, however, discouraged widespread application of the device.

The Hybrid Positron Scanner,[9,10] developed at MGH in 1970, was the first of a series of multiple detector positron devices. The scanner used two rows of nine detectors each to yield higher sensitivity than the single pair systems. The resultant images could be focused on planes lying between the two detectors. This instrument was designed principally for brain tumor localization and has been used routinely for that purpose.

This device led directly to the development of the first MGH Positron Camera, PC-I.[11,12] The camera uses two banks of 127 NaI(T1) detectors coded to 72 photomultipliers. Each detector in one bank is in coincidence with 25 in the opposite bank yielding 2549 coincidence pairs or data channels. Images are prepared by focusing the data channels on planes lying between and parallel to the detector banks. The use of discrete detectors allows high single photon count rates (in excess of $10^7$ hertz per detector bank) and high coincidence count rates (up to $10^5$ Hz for sources in air). Since the detectors are separated by 2.8 cm this device incorporates a small translational motion to permit higher sampling frequency and eliminate off-focal plane patterning.[13] Dynamic images containing 2000 to 5000 events may be obtained on a time scale as short as 0.1 sec. Static images (using interpolative motion) typically take 10 to 100 sec.[14] PC-I also served as a test device for the development of PC-II, a transverse section positron camera, since transverse section images of phantoms and animals can be obtained with PC-I by rotation of the object.

Transverse section scanning in nuclear medicine was pioneered by Kuhl and Edwards[15,16] who demonstrated the use of backprojection to image gamma-ray sources in transverse section mode. Kuhl and coworkers[17,18] subsequently used reconstruction techniques to produce corrected transverse section images.

The possibility of the use of annihilation radiation for transverse section imaging has also been realized for some time. Rankowitz et al.,[19] Robertson and Bozzo,[20] and Robertson et al.[21] developed a ring system using discrete detectors for the detection of annihilation quanta. This device was somewhat ahead of its time since reconstruction algorithms had not then been developed. The device did, however, demonstrate the concept of transverse section imaging.

The development of transmission-computerized tomography (TCT) by Hounsfield[22] marked a pivotal point in the development of positron imaging, despite the fact that his device used x-rays rather than positrons. This device demonstrated that transverse section images of high resolution could be prepared using small computer facilities. This development

was soon followed by the appearance of new positron imaging devices, including a further refinement of the Brookhaven ring system.[23–25]

One of the most successful instruments of this type is the Positron Emission Transaxial Tomograph (PETT) developed at Washington University. This instrument uses discrete detectors in a hexagonal array with translational and rotational motion to provide necessary sampling.[26–28] This system has formed the basis for the development of the Ortec ECAT. Both instruments are described in detail later.

Another positron imaging device currently under development by the group at Washington University is a multiplane device called PETT IV. PETT IV uses one-dimensional Anger logic to determine the location of a photon interaction in a long NaI(T1) detector positioned normal to the transverse section plane. By this method, four planes may be reconstructed simultaneously. The use of cross-plane coincidences may permit the number of planes to be increased to seven. Ter-Pogossian and co-workers plan two versions of this device, the NeuroPETT and the Cardio-PETT, for brain and heart imaging.

Cho and co-workers at UCLA[29] and Derenzo and Budinger at Donner, UCB[49] are developing static ring systems consisting of discrete NaI(T1) detectors. In principle, these rings can be used for dynamic imaging if adequate count rates can be achieved since no motion is involved. The Donner system uses 280 detectors in one ring to achieve adequate sampling and high sensitivity. An elaborate light pipe system is employed to connect each crystal to its phototube. Both devices are discussed later.

Studies at the Massachusetts General Hospital also dealt with transverse section imaging. The first transverse section radionuclide image using the method of backprojection of filtered projection data was reported in 1971 by Chesler.[31] The data were from a single coincidence channel which obtained projection data by mechanical translation and rotation of the detectors using a phantom source. Subsequently, a transverse section version of the MGH Positron Camera, PC-II, was developed for both conventional and transverse section imaging. Transverse section images are produced by rotation and translation of the two camera heads about the object to be imaged. Multiple transmission and emission images can be constructed from one set of emission and one set of transmission data. A commercial version of this camera has been developed by The Cyclotron Corporation of Berkeley.

The double scintillation camera approach for positron imaging has been steadily improved by a number of groups. Kenney[32] and Monahan and associates[33] have developed a system using two large scintillation cameras for this purpose. Their system exhibits high spatial resolution and sensitivity. The count-rate limitations of the positron camera of Anger

have been partly overcome by Muehllehner and co-workers[34] with the use of graded filters and fast electronics in an instrument, produced by Searle Radiographics, to be described later.

Efforts have been made to develop alternative detection schemes. Perez-Mendez et al.[54] have developed a positron detection system using large area gas proportional chambers. Similar developments are being carried out at CERN.[36] In general these devices have not been used for the preparation of transverse section images, but an alternative approach[37] has been used to produce longitudinal tomograms. Considerable improvement in image quality has been demonstrated.

Although not included in this chapter, continuous efforts have been made to improve transverse section images using gamma emitters. Kuhl and Edwards[38] have led in this area with the development of the Mark IV system. Keyes et al.[39] have used a rotating gamma camera. Mallard et al.[40] and Walters et al.[41] have produced transverse section images of the brain using gamma emitters. Budinger and co-workers have produced transverse sections of the brain and gated heart images using single photon gamma emitters.[30,68,69]

Many new detector materials have been suggested for positron systems. Cho has examined the possible use of high purity germanium[42] and bismuth germanate[70] for ring systems. Derenzo[43] has also discussed the use of bismuth germanate. However, the sodium iodide scintillation detector still remains the detector of choice for most discrete and area imaging devices.

## BASIC PRINCIPLES OF POSITRON IMAGING

The principle of positron imaging is based on the unique physical process that positrons undergo following their emission by a beta-unstable radioisotope. As in the case of negative electron decay, positrons are emitted with a range of kinetic energies from zero to a well-defined maximum. The average and most probable energy is roughly equal to 0.4 times the maximum energy. After emission, the positron, like an electron, follows a tortuous ionization path through the material in which it is emitted. After the positron slows down (in about $10^{-10}$ sec), it combines with a valence electron (usually) and the two-electron system undergoes the process of annihilation with the creation of two photons each of energy 0.511 MeV (the energy corresponding to the electron or positron rest mass, $E = m_0C^2$). In order for energy and momentum to be conserved, the two annihilation photons are emitted in opposite directions: that is, the two 0.511-MeV photons travel at an angle of $180° \pm 0.3°$.

### Detection of Annihilation Radiation

Consider two detectors arranged as shown in Figure 1-1. The system shown is designed to register a "count" only when both detectors record annihilation photons simultaneously (or within some finite resolving time). Whenever an annihilation event is detected in coincidence by the two detectors, the event is assumed to have originated somewhere along a line joining the detector centers. It can be seen that a form of electronic collimation is thereby achieved. This is analogous to the straight bore lead collimation employed in a conventional photon imaging system. It is clear that an analog of the multihole lead collimator can be realized by employing more than one set of coincidence detectors arranged in various configurations.

A positron imaging system has at least two major advantages over a conventional photon imaging system such as a gamma camera or rectilinear scanner. First, since the positron system requires no physical collimation to achieve spatial resolution, sensitivity may be greatly in-

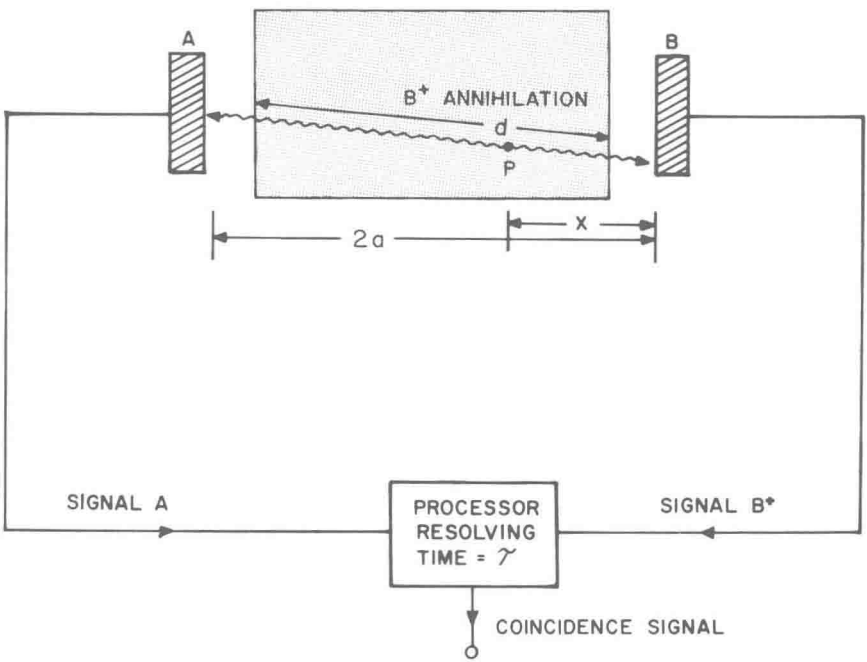


Fig. 1-1. Illustration of a coincidence detector pair having a resolving time $\tau$. The detection of an annihilation event occurring at a distance $x$ from the righthand detector is illustrated.

creased. This is particularly true for positron imaging systems with multiple or large area detectors. Second, since the production of a true coincidence count requires both annihilation photons to escape unscattered from the section of the body being imaged, the positron imaging system, unlike the conventional photon imaging system, is isosensitive to positrons emitted along a coincidence line through the body. This may be understood by considering the probability that both annihilation photons escape following an annihilation at point $P$ (see Fig. 1-1). The individual probabilities are $e^{-\mu(x)}$ and $e^{-\mu(d-x)}$, while the probability of both events occurring is their product, $e^{-\mu(x)}\, e^{-\mu(d-x)} = e^{-\mu d}$, which is independent of $x$. Here $\mu$ is the total linear attenuation coefficient for 0.511-MeV photons in tissue. Since the sensitivity with which an annihilation event is detected is constant along a coincidence line, quantitative analysis of the radioisotope distribution may be carried out by comparison with a known external source.

As a comparison, consider a conventional photon imaging system, such as a gamma camera, employed to quantitate the distribution of $^{99m}$Tc within a 25-cm-thick body section. The relative sensitivity to photons originating at the surface closest to the camera to those originating at the back surface is approximately $e^{-25\mu}$. Since $\mu = 0.16$ (in $H_2O$) for the 140-keV photons of $^{99m}$Tc, the variation in sensitivity is a factor of about $e^4 = 55$.

The concept may be extended to describe the variation of sensitivity to annihilation events not only along a particular coincidence line but also between different coincidence lines. Since the relative sensitivity between coincidence lines is proportional to $e^{-\mu d}$, coincidence lines passing through different thicknesses of tissue will produce different sensitivities. However, unlike conventional photon imaging, this non-uniformity may be readily measured by the use of external transmission measurements.

### True and Random Coincidences

A coincidence system can be characterized by two time parameters, the resolving time $\tau$* and the dead time $T$. The first is a measure of the time interval allowed between detection of the two quanta and the limit is usually set by basic detector parameters. For example, the minimum value of $\tau$ for scintillation counters is proportional to the phosphor decay time divided by the total light output per pulse. $\tau$ is typically a small

*$\tau$ is sometimes defined as the pulse width for each channel. That value will be about one-half the observed value since the time interval between two coincidence events could be twice the pulse width. We use here the observed or "total" value of the resolving time for $\tau$.

fraction of the phosphor decay time. For example, the decay time for NaI(T1) is about 250 nsec whereas $\tau$ is usually between 10 and 20 nsec.

The dead time $T$ of any system is the interval required for most of the light to be collected in a scintillation counter, or charge to be collected in an ionization or proportional chamber. For a scintillation device, $T$ is usually set equal to a value larger than the decay time. For NaI(T1), $T$ is usually set at about 1 $\mu$sec.

The effect of detector dead time is a reduction of observed single channel and true coincidence rates. The observed values are related to the values with zero dead time, $N_{A0}$, $N_{B0}$, and $N_{C0}$ (for small values of $N_{A0}T$ and $N_{B0}T$) as follows:

$$N_A = N_{A0}\,(1 - N_{A0}T)$$
$$N_B = N_{B0}\,(1 - N_{B0}T)$$
$$N_C = N_{C0}\,(1 - N_{A0}T)\,(1 - N_{B0}T).$$

The effect of a finite resolving time is the introduction of a random coincidence rate $N_R$ equal to

$$N_R = N_A N_B\,\tau.$$

The effect of dead time is a reduction in the true coincidence rate $N_C$, whereas the effect of finite resolving time is the introduction of spurious or random pulses $N_R$ in the coincidence channel. This effect is discussed further under signal-to-noise considerations.

### Spatial Resolution

There are a number of factors which, in a realistic situation, influence the spatial resolution attainable with positron imaging systems. Most of these have been known for some time[3] but recent measurements have considerably increased our understanding of these effects. The most important of these is the detector size. The circles on the two parallel planes in Figure 1-2 represent the sensitive surfaces of two opposed detectors (discrete detectors or resolution areas of area detectors). When a coincidence event is recorded by the detectors, the annihilation event which caused it is assumed to have originated along the line joining the detector centers, say at point $Q$. The shaded area, however, demonstrates that even if the annihilation event occurred at point $P$, there is a finite probability (proportional to the shaded area) that the detectors will still record a coincidence event. In fact, it can be shown that the maximum sensitivity of the system occurs for annihilations at point $Q$, with an approximately

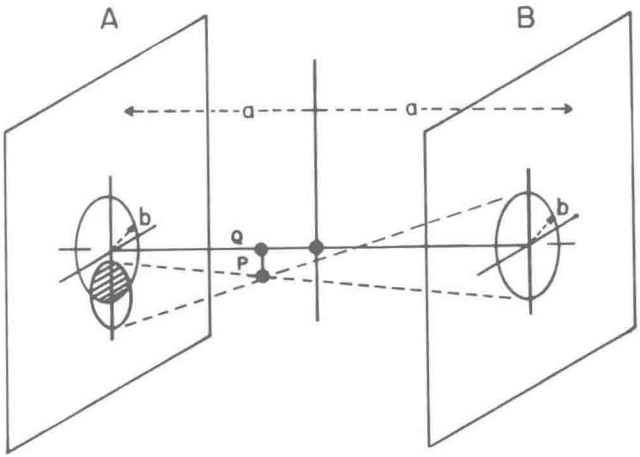


Fig. 1-2. Sensitive areas of a coincidence pair of detectors illustrated as circles on the two parallel planes. Even if an event is off the central axis of the cylinder defined by the detectors, there is still a finite probability of coincidence detections which is proportional to the shaded area shown. The response as a point source is moved across the sensitive cylinder parallel to the detector faces is approximately Gaussian.

Gaussian decrease in sensitivity as the annihilation position is moved up or down along the line passing through points $P$ and $Q$. Figure 1-3 shows a family of isosensitivity curves for two cylindrical detectors. It can be seen that the measured value of full width at half-maximum $(\text{FWHM})_G$ perpendicular to the coincidence line at the midplane is about 0.42 times the detector diameter. The value for rectangular detectors is 0.5. Consequently, the detector diameter or width constitutes a geometric limit to spatial resolution.

It is useful to characterize spatial resolution by a single parameter such as FWHM. It should be realized that this approximation is not always valid since the shape of the line spread function (LSF) or the corresponding modulation transfer function (MTF) may significantly affect the image quality. However, the advantage of the Gaussian approximation and the single FWHM is that multiple contributions to the final LSF can be treated without multiple convolutions. For example, if a series of multiplicative factors contribute to the degradation of resolution, the final FWHM can be obtained from the relation

$$(\text{FWHM})^2 = (\text{FWHM})_A^2 + (\text{FWHM})_B^2 + \ldots .$$