

PETT; QUANTITATIVE IN VIVO MEASUREMENT OF HUMAN FUNCTION AND METABOLISM *

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fig. 1

Positron emission transaxial tomography (PETT) is a new and rapidly evolving analytical technique for accurate quantitative measurement of regional radioactivity levels in animals and humans. The application of this technique is one of the most interdisciplinary and multidisciplinary efforts that scientists are involved in today. The relationship between the various disciplines is shown in Figure 1. Physicists, chemists, biologists, biochemists, computer specialists and physicians all working in a coordinated way are required to realize the information that can be produced by PETT. The nature of the analytical technique and its instrumentation, how a biological model (which is perhaps as sophisticated as the instrumentation itself) needed to be developed, how the compounds, materials and techniques for applying the model and the instrument were developed, and finally some results of this type of research constitute the framework of these efforts.

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PETT scanning is related to the more familiar CAT scanning which is now in common use in radiological practice. A description of the first CAT scanner by its inventor G. N. Hounsfield¹ was published in 1973. In a CAT scanner the radiation seen by the detectors is produced in an x-ray tube. The photons coming out of the x-ray tube are "seen" by detectors on a side opposite to the photon source. In PETT the radiation source is a radioactive isotope in the animal or human (introduced by injection or other methods) and the radiation being emitted by this source is sensed by rings of detectors external to the body. The information these detectors

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of 9

collect is transcribed ultimately into an image. A selection of reviews²⁻⁵ and original papers⁶⁻⁸ tracing the history and other aspects of PETT trace the growth of this new analytical modality. A recent comparison of PETT tomography and Nuclear Magnetic Resonance imaging places these two frequently compared techniques in perspective.⁹

Let us address the details of PETT and what this analytical technique is all about. PETT depends for its success on the properties of positron emitters. A positron can be thought of as a positive electron. It leaves its point of origin, which is usually the result of nuclear decay, and travels a very short distance, a distance which depends on the energy of the positron. For example, in water it can travel a fraction of a millimeter to a few millimeters. When it slows down and collides with an electron, it annihilates, that is to say that the two particles are converted to photons. The energy of these photons is governed by the $E = MC^2$ law. That is, if the mass of the positron, and the mass of the electron are summed and multiplied by the square of the velocity of light using the correct units, we obtain an energy = 1.022 MeV. The important point in positron annihilation, in order to understand what PETT is all about, is that when an annihilation event occurs, two photons are produced leaving the point of origin at almost exactly 180° to one another and each photon has exactly one-half the total energy, or 511 KeV. These photons are readily detected when they pass through an inorganic crystal of some sort, for example sodium iodide. When the photon passes through the crystal. The light pulses are detected by a phototube, amplified and a pulse or signal is emitted by the detector system. Dr. Cormack has described the "mind" of a PETT machine, but the "heart", of PETT, is the

crystal and its phototube detector. An x-ray of such a phototube and attached crystal can be seen in Figure 2.

fig. 2

In PETT scanning, a radioactive material is injected and as it decays in the body the photons that come out of the body are "seen" by the detection device. The photons resulting from the annihilation having the property of being of equal energy, i.e. 511 KeV and traveling at 180° to each other are then recorded by detectors operating in coincidence. This is shown schematically in Figure 3. The detectors are connected to a circuit that essentially is a timegate that performs as follows: if it senses a pulse coming from the detectors facing each other at nearly the same time, and if this timegate is very narrow, a pulse will come out of the timegate; but if there is too great a time difference between the pulses entering the gate, the gate will not let that signal go through. This means that only when an annihilation event takes place where both photons reach the detectors facing each other at essentially the same time, will a signal be recorded. If there are two detectors operating in this coincidence mode, they establish a field of view which is encompassed by the geometry of these two detectors, so these two detectors will only see what is happening in this field of view.

fig. 3

Another element to positron detection is attenuation by matter in the head. The advantage to using annihilation radiation from positron emitters is that the probability of the two photons escaping the absorber (the tissue and the bone in the head) depends only on the total amount of absorber traversed and not on the position within the absorber. This can be easily shown by considering an event taking place in a human head being a distance A from one side of the head and a distance B from the opposite

side of the head (Figure 4). As can be seen from the figure the probability that both escape the head depends only on the attenuation coefficient and the total amount of absorber.

If we had only two detectors in opposition the events that occur in the head would only be seen in the single "cylinder" defined by the detector. Thus in order to collect information from all parts of a "slice" of the head we must have detectors in a ring (Figure 5) or other similar configuration "looking" at the head from many angles. The process of ultimately converting the data collected to an image, or other suitable representation of the amount and distribution of this activity in the head, is called reconstruction and is effected by a mathematical device called an algorithm. A single ring of detectors would allow the reconstruction of a single slice of the object being studied. If one now took parallel planes of detectors and took coincidence information not only from opposite pairs of crystals but also from diagonal pairs of crystals we arrive at today's multislice machines. The PETT VI designed by Dr. M. Ter Pogossian and his colleagues at Washington University (St. Louis)¹⁰ is a seven slice machine with four parallel planes of crystals with 72 Cesium Fluoride crystals in each plane. The data from four planes plus data that can be used to reconstruct the three interstices results in the seven slices one ultimately reconstructs. A picture of this machine and its associated control room can be seen in Figures 6 and 7.

There are many facets to Positron Emission Transaxial Tomography and the reader is directed to reviews and papers on this subject. The emphasis here has been on the nature of positron emission, the detection of annihilation radiation and in general terms the conversion of the data

collected to suitable output. Touching on all facets of this analytical technique is outside the scope of this short review. The block diagram in Figure 8 summarizes the collection of data, manipulation of data and information delivery of positron tomography.

The application of this new analytical tool to biological and medical research is opening wholly new areas of insight into the physiological and biochemical processes occurring in humans. One of the most exciting areas currently under study is the quantitative measurement of brain glucose metabolism. How this is brought about involves the other three legs of the construction shown in Figure 1.

In order to probe the regional consumption of glucose in the brain a biochemical model which allows the use of a tracer as a probe had to be constructed. This model is detailed in the "classic" paper of Sokoloff, Reivich and colleagues.¹¹ A condensed version of the method has recently been published.¹² In essence it involves the use of a labeled tracer 2-deoxy-D-glucose which mimics the action of glucose itself and is transported into the brain by the same mechanism as is glucose. Once in the brain it is phosphorylated to 2-deoxy-D-glucose-6-phosphate by the same enzyme as is glucose but here the paths of these two substances diverge. Whereas glucose is metabolized to give a number of other products and in the process provides energy for the cells in the brain to function, the further metabolism of 2-deoxy-D-glucose-6-phosphate is blocked since the enzyme which carries out the next step for the metabolism of glucose-6-phosphate, i.e. glucosephosphate isomerase, does not recognize the deoxy compound as a substrate. Thus the deoxy compound is blocked or trapped in the tissue. By measuring the rate of uptake in

Fig. 8

ref. 11
ref. 12

the tissue and assaying the free deoxy compound and glucose itself in arterial plasma one can calculate the glucose metabolic rate for whatever tissue element has had its rate of uptake measured.^{11,12} Carbon-14 2-deoxy-D-glucose can be used in animals but in humans a labeled tracer which can be assayed and quantitated in vivo must be used. Such tracers have been prepared by labeling deoxyglucose with fluorine-18 to produce ^{18}F -2-fluoro-2-deoxy-D-glucose^{13,14} and carbon-11 ^{11}C -2-deoxy-D-glucose.¹⁵ The positron emitting radionuclides needed for the labeling of these tracers are prepared using charged particle accelerators (usually cyclotrons) to bring about the needed nuclear reactions. A new category of cyclotrons variously called medical cyclotrons, baby cyclotrons, etc. are commercially available and are characterized by ease of operation, reliability, small size (typically requiring no more than 300 or 400 square feet of floor space) and relatively low in cost. The JSW (Japan Steel Works) 1710 is such a machine especially designed for the facile production of the major positron emitters ^{11}C , ^{13}N , ^{15}O and ^{18}F . Other manufacturers of machines of similar capability include The Cyclotron Corp (USA), Scandatronix (Sweden) and CGR-MeV-Sumitomo (France and Japan).

The nuclear reactions used to prepare carbon-11 and fluorine-18, $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ and $^{20}\text{N}(\text{d},\alpha)^{18}\text{F}$ respectively, are readily carried out with these small machines and the necessary precursors for the synthesis H^{11}CN and $^{18}\text{F}-\text{F}_2$ easily prepared. Speed is of course essential when one considers the 20 min half-life of ^{11}C and the 110 min half-life of ^{18}F . An overview of the synthetic procedures and related topics has been published.¹⁶

Let us now consider the final step in the use of PETT, in measuring regional brain glucose metabolism in humans.

The procedure involves having the subject positioned in the PETT machine in such a way that the region of interest, in this case the head, is properly positioned in the ring of detectors. In addition arterialized venous blood is made available via a catheter inserted into a finger vein with the whole hand held at an elevated temperature. The radiolabeled tracer is injected into an arm vein and the data collection process started. A study takes approximately sixty to eighty minutes. Radiation burden to the subject is well within accepted limits and less than many routine radiological procedures. The PETT and blood data are then analyzed and a metabolic map of the slice or slices studied, prepared.

29. 9-11
Three such slices can be seen in Figures 9-11. In each figure the numbers accompanying the scale at the right are in milligrams of glucose being metabolized per minute per hundred grams of brain tissue. Figure 9 is a brain slice whose center is about 5 cm above a plane defined by the canthus of the eye and the center of the ear canal conventionally called the CM line or in this case the CM plane. The image was taken on a PETT III.¹⁶ It is of a normal male age 25. The eyes of this individual were closed typified by the moderate (red color) metabolic rate seen in the occipital (back of the head, top of the picture) region.

Figure 10 is the slice at CM-5 of a patient with "schizophrenia" as determined by research diagnostic criteria and concordant diagnoses by two physicians. Noteworthy is the depressed metabolic rate in the frontal region relative to the rest of the slice as compared to what is seen in the age matched normal. This depression of glucose metabolism in relation

to the posterior region of the slice can be seen in essentially all cases of schizophrenia studied to this date. Notice the high metabolic activity in the occipital region. This patient's eyes were open and the intense metabolic activity is a reflection of the energy "required" to process the "information" falling into this individual's eyes. Figure 11 shows two levels of the brain of a patient with senile dementia (Alzheimer's related). In all advanced cases one sees a general diminution of metabolic activity.

Many functions and disorders have been studied to date. General reviews of these have been recently presented^{18,19}

The study of regional glucose metabolism in humans is a rapidly expanding field encompassing diseases ranging from epilepsy to measuring the metabolic activity of tumors. However the application of PETT and appropriately labeled compounds can probe many functions and disease states. In addition to regional glucose metabolism, oxygen metabolism using $^{15}\text{O}-\text{O}_2$, blood flow using H_2^{15}O , blood volume using ^{11}CO or C^{15}O , neuroleptic sites and activity using a broad variety of compounds to probe dopamine and opiate receptors, etc., metabolism in the heart using ^{11}C labeled palmitic acid and numerous other functions are actively being studied. Basic research on brain function and sensory response, language perception and other areas involved in "what is mind" are actively being pursued. While it is clear that this new technique is not a universal panacea in our quest for new knowledge it nevertheless is opening many new areas heretofore inaccessible to other research modalities.

Positron Emission Transaxial Tomography as a new analytical technique for non-invasive measurement of brain and other organ function

is unique in that it allows, given an appropriate biological model, the measurement of dynamic processes in humans heretofore inaccessible by any other techniques. The next decade will see a wholly new area of research and clinical application built up around PETT and suitable radiotracers.

*Research carried out under the auspices of the U.S. Department of Energy under Contract No. DE-AC02-76CH00016 and Office of Health and Environmental Research NIH Grant #NS15638.

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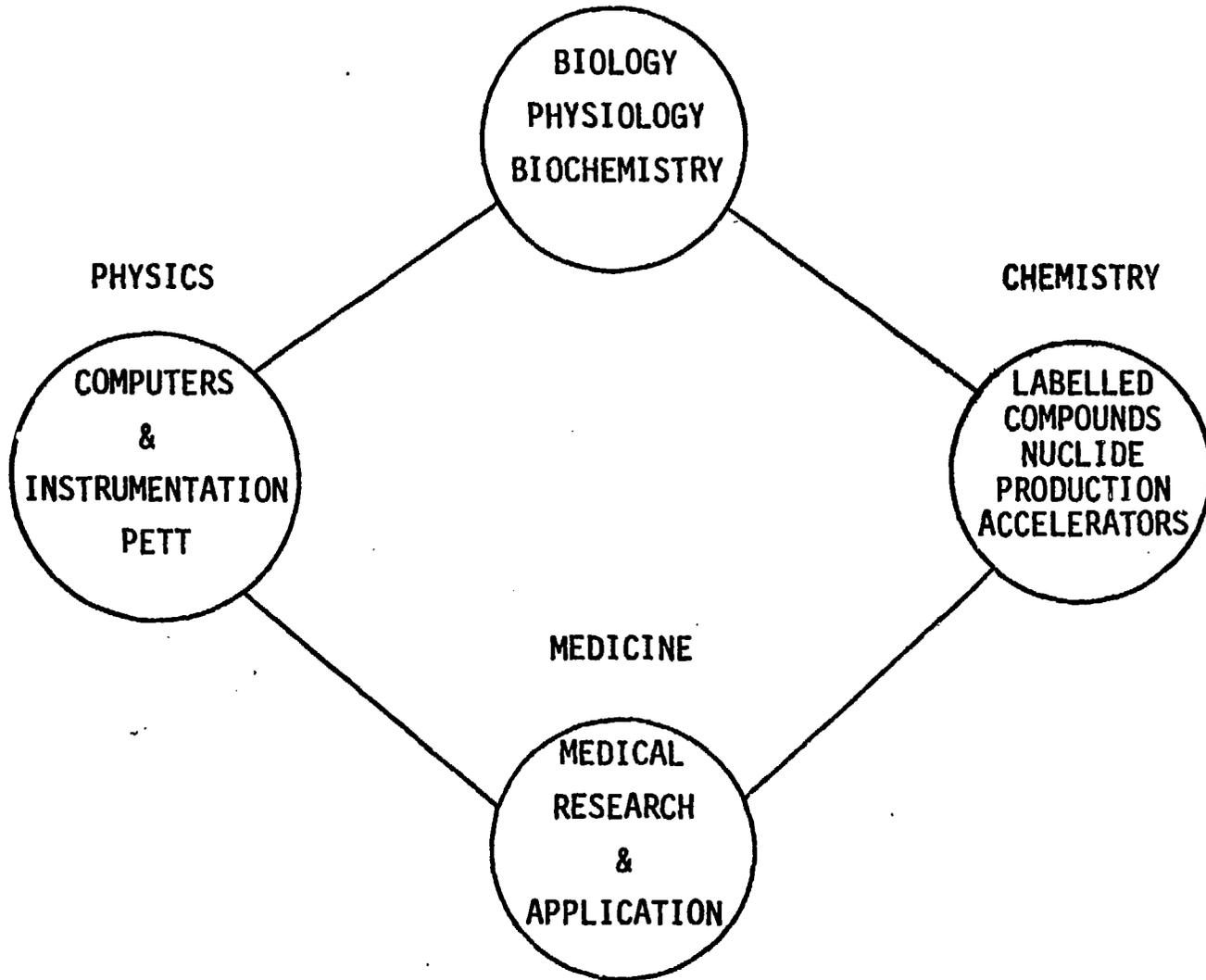
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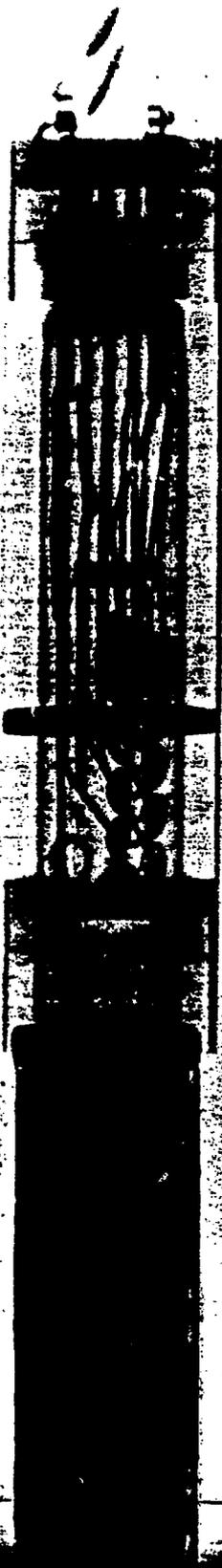
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Figure Captions

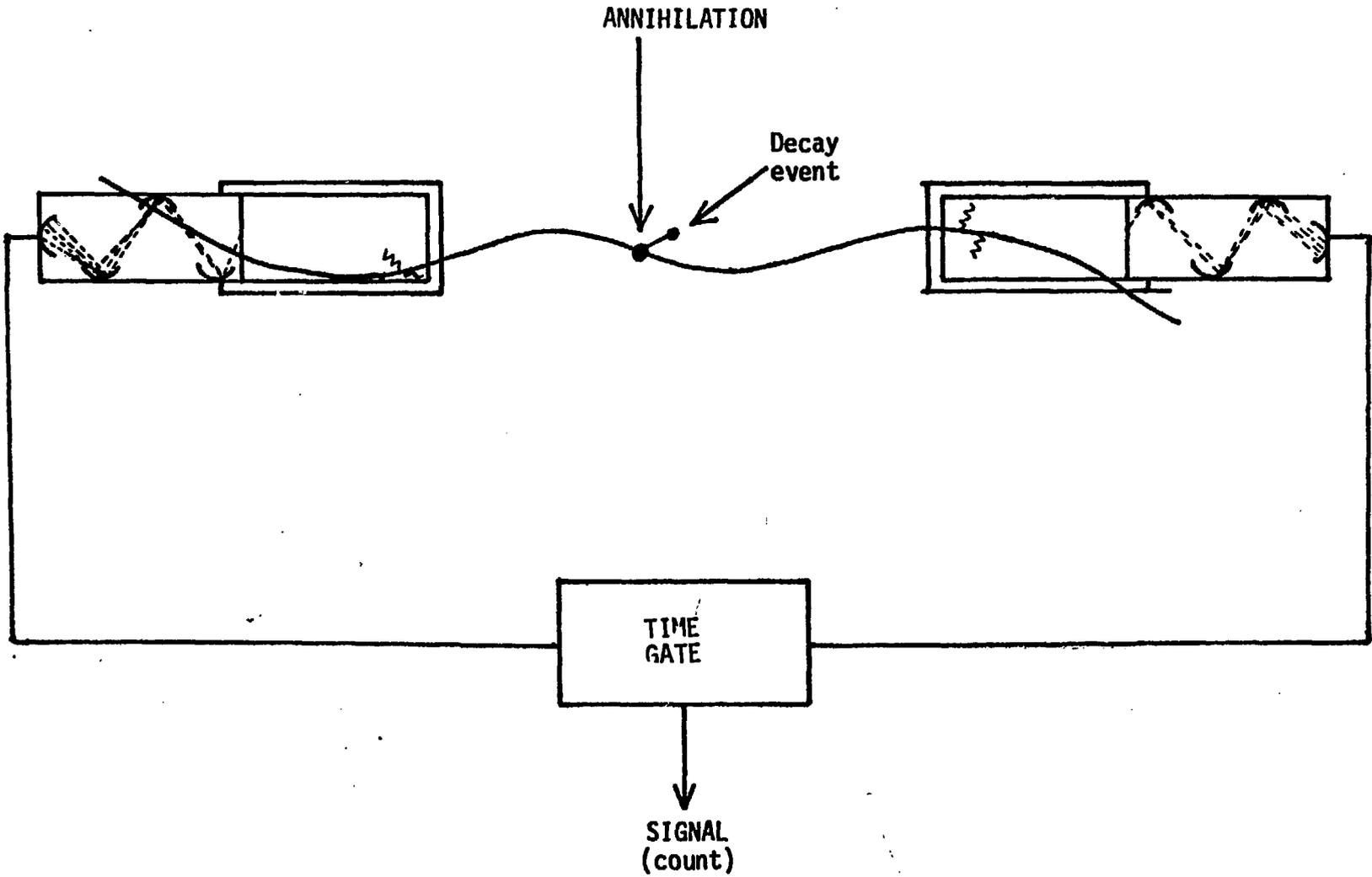
- Figure 1** Interrelation between Disciplines Involved in Application of Positron Emission Transaxial Tomography.
- Figure 2** X-Ray Photograph of Crystal (CsF)-Phototube Detector Used in PETT VI Tomograph.
- Figure 3** Coincidence Detection of Annihilation Radiation Resulting from Positron Emission.
- Figure 4** Escape Probability of Annihilation Radiation and Its Independence of Position within Absorber
- Figure 5** Ring of Detectors in PETT VIA--four rings (two shown), 72 detectors in each ring.
- Figure 6** PETT VIA and Associated Electronics.
- Figure 7** PETT VIA Operations and Computer Control Room.
- Figure 8** Operational Sequence in PETT VIA.
- Figure 9** Metabolic Contour Map, Normal Male, CM5, age 25. Scale in milligrams of glucose metabolized/min/100 mg brain tissue.
- Figure 10** Metabolic Contour Map, Schizophrenic Patient, Male, CM5, age 30. Scale in milligrams of glucose metabolized/min/100 mg brain tissue.
- Figure 11** Metabolic Contour Maps CM5 and CM7. Normal vs Patient with Senile Dementia. Scale in milligrams of glucose metabolized/min/100 mg brain tissue.

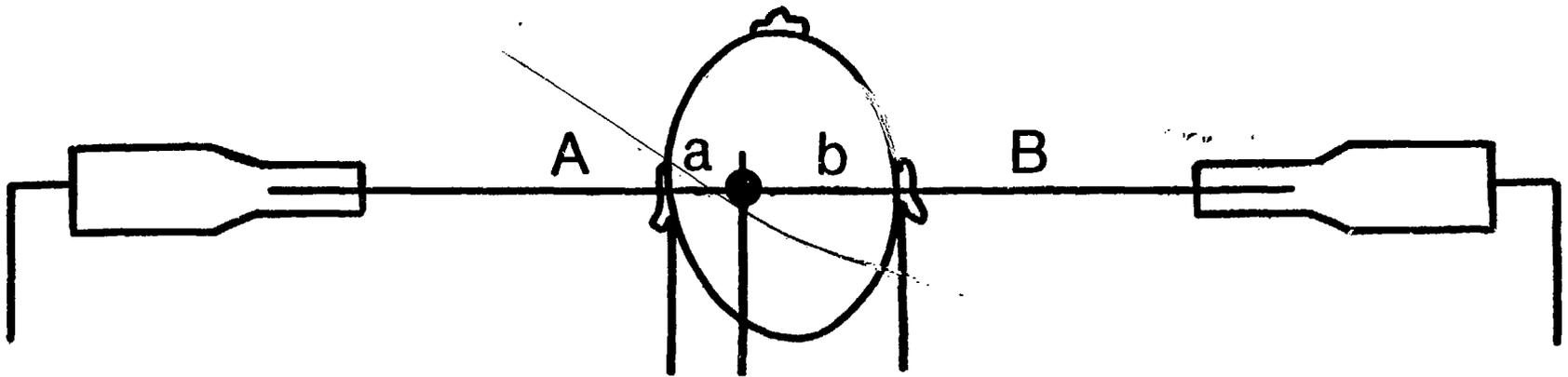
**PROPERTIES OF LIVING
SYSTEMS**





COINCIDENCE DETECTION



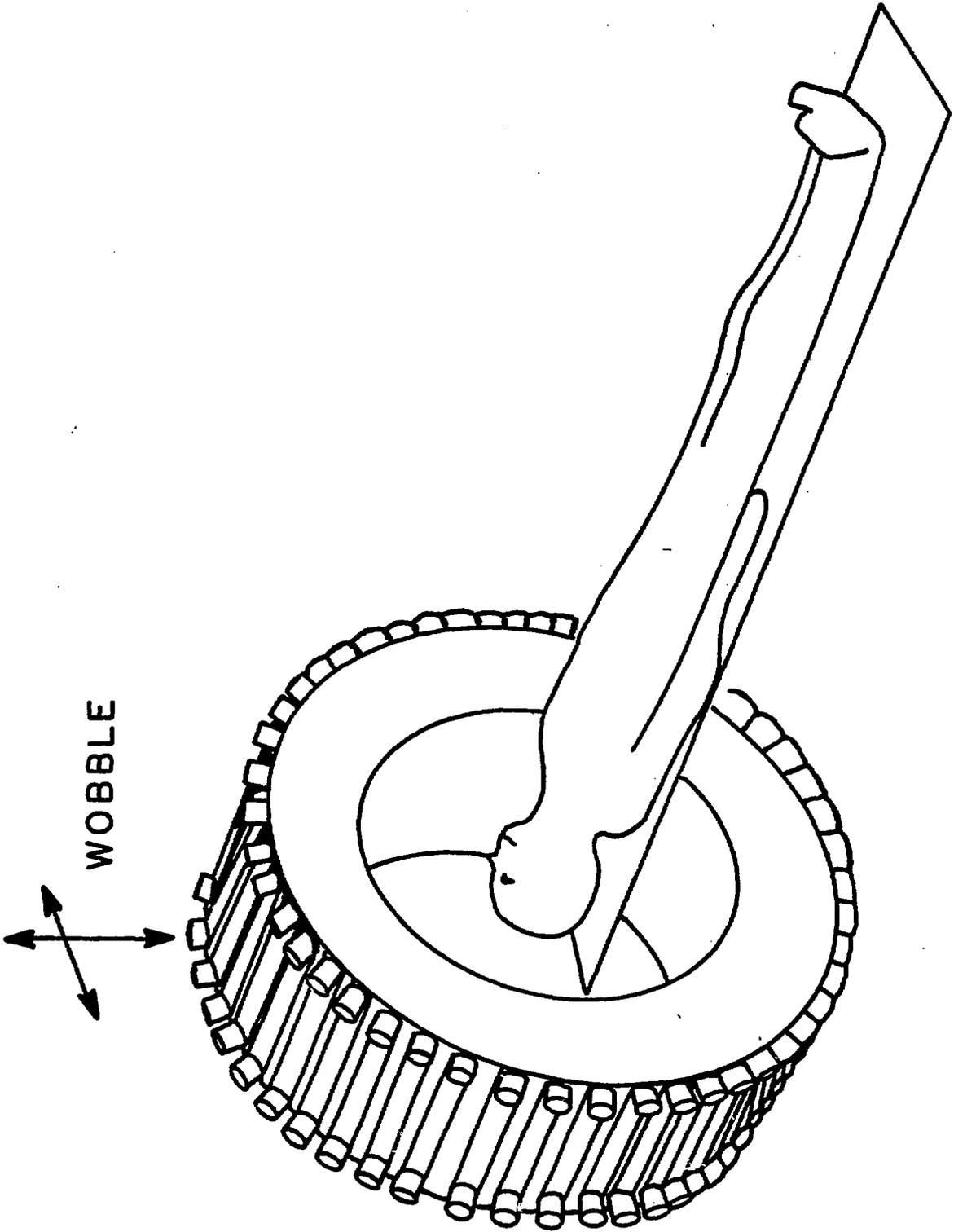


Escape probability to A = $e^{-\mu a}$

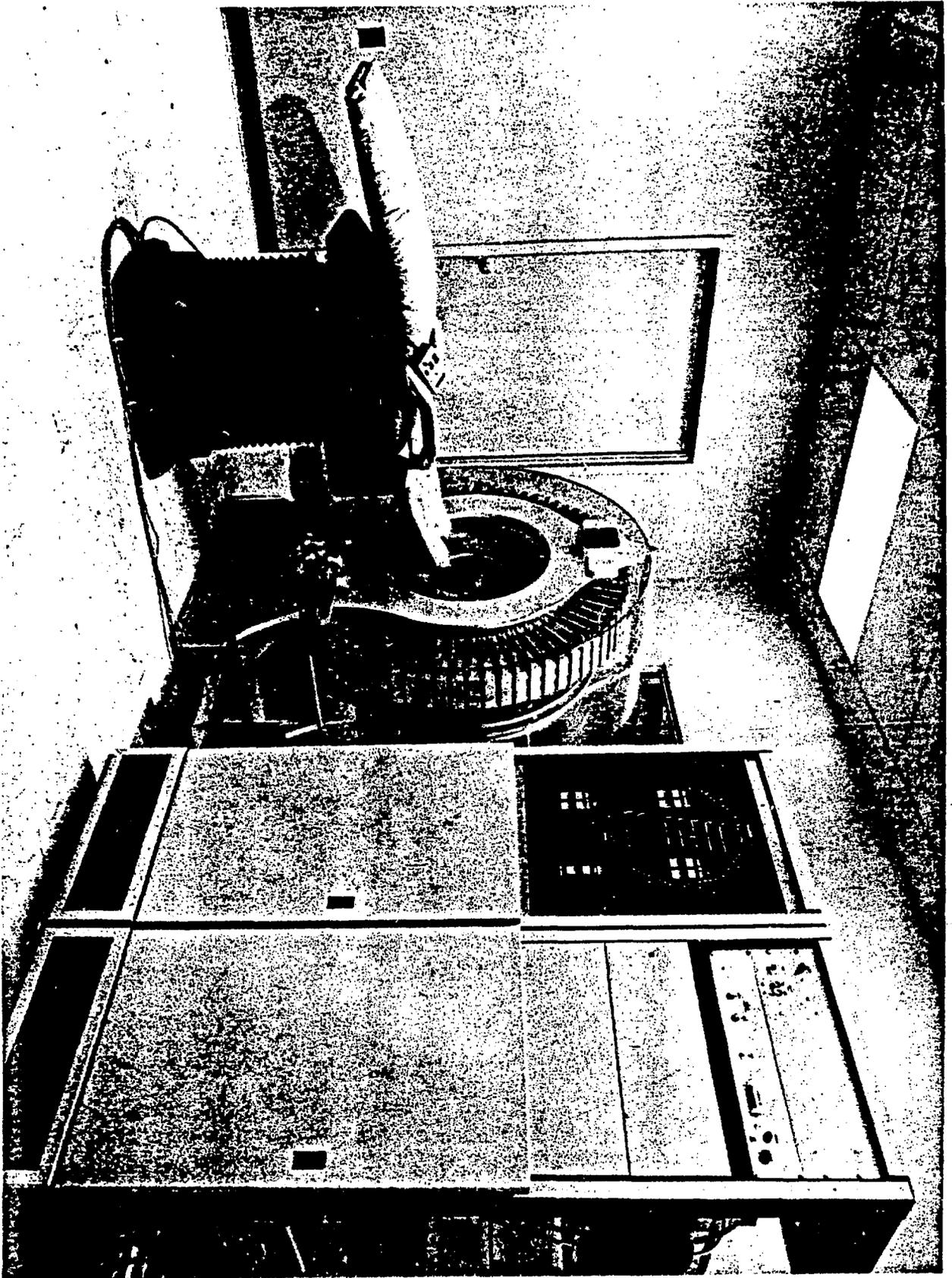
Escape probability to B = $e^{-\mu b}$

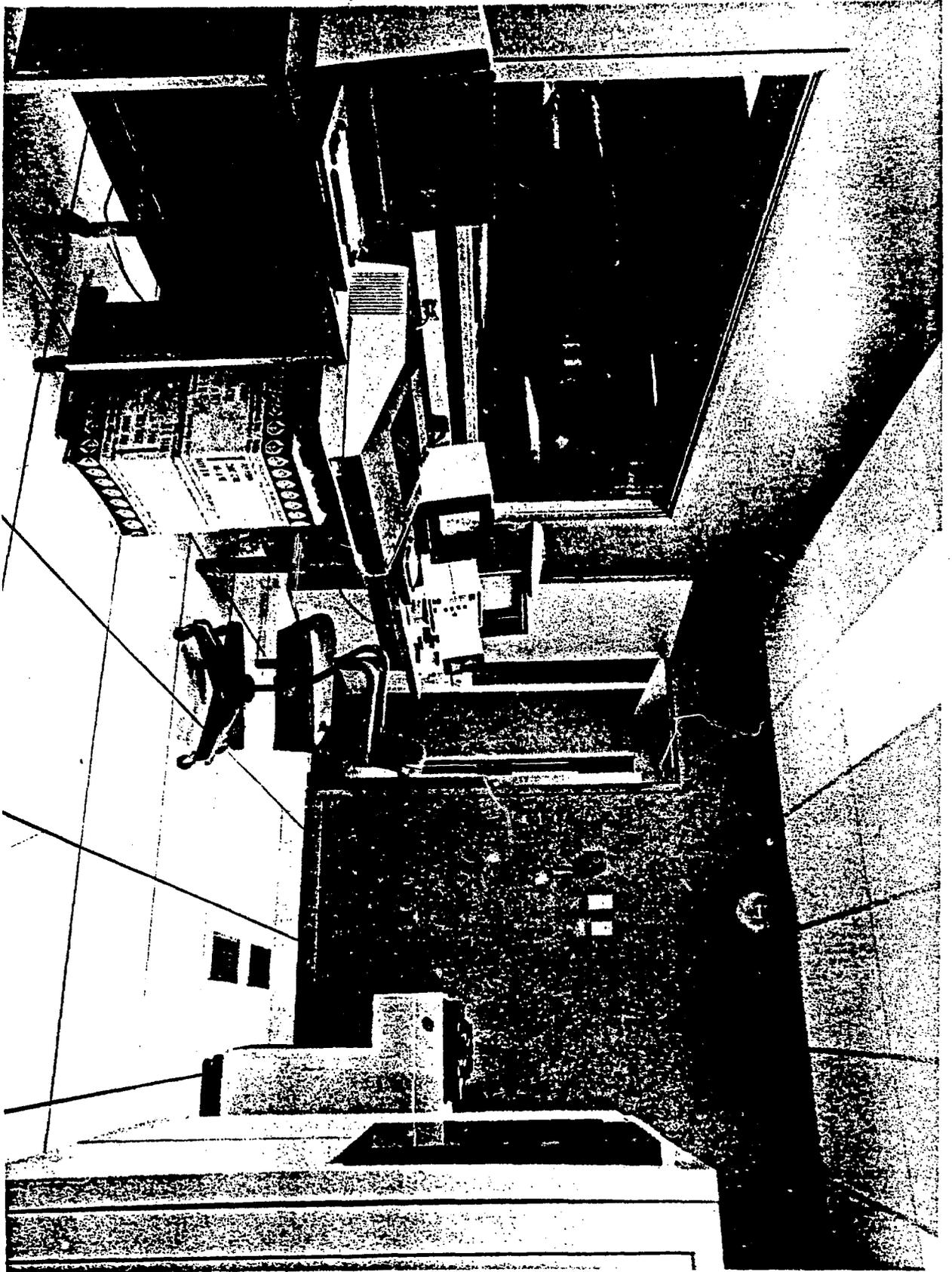
Probability that both escape = $e^{-\mu a} \times e^{-\mu b} = e^{-\mu(a+b)}$

$a+b$ = total amount of absorber



PETT VI A





NORMAL, CM 5, PROFILE

6.0



5.4

4.8

4.2

3.6

3.0

2.4

1.8

1.2

0.6

0.0

BNL/NYU PETT PROJECT

SCHIZO, CM 5. PROFILE

6.0

5.4

4.8

4.2

3.6

3.0

2.4

1.8

1.2

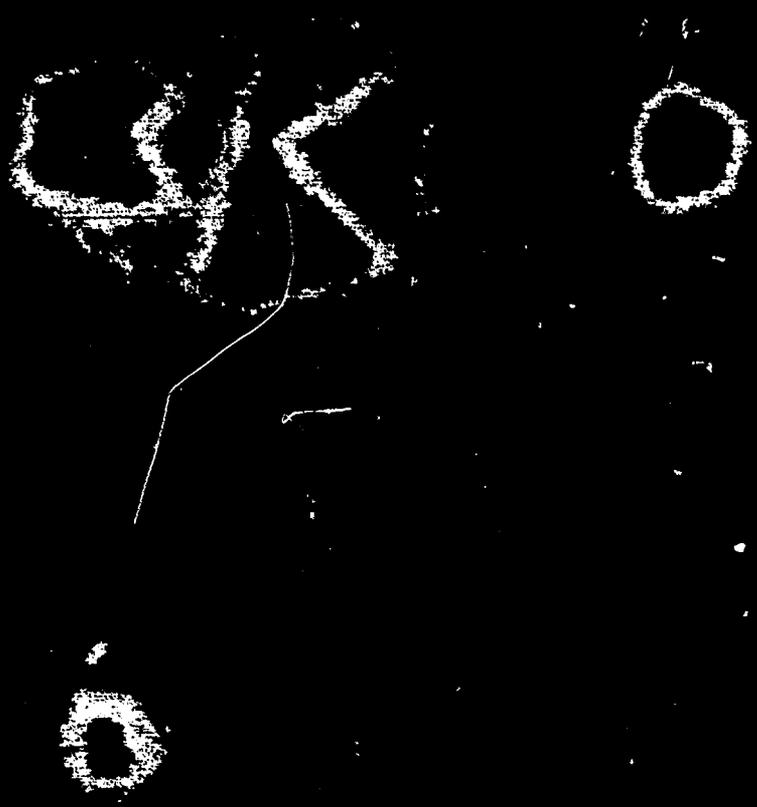
0.6

0.0



BNL/NYU PETT PROJECT

CM 5 -- DEMENTIA -- CM 7



BHL/NYU PETT PROJECT

6.0
5.4
4.8
4.2
3.6
3.0
2.4
1.8
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