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RADIOISOTOPES IN MEDICINE

Radioactive tracers had been used in the investigation of biochemical and physiological problems on a research basis long before the establishment of the field of Nuclear Medicine. More recently the marked advances in instrumentation technology combined with improved radionuclide production capabilities have resulted in rapid progress in the application of methods utilizing radioactive tracers to the solution of clinical problems. Nuclear Medicine has recently been established as a medical specialty with its own certifying examination, attesting to its importance in the everyday problems encountered in medical care.

This presentation is concerned with the diagnostic rather than the therapeutic utilization of radioactive isotopes. In diagnosis we use radioactively-labeled substances as indicators of pathways and distribution of non-labeled substances. It is assumed that in the process no perturbation of the natural handling of these materials by the body is caused by the introduction of them into the living organism. That this has not always been so, is apparent from some of the early work, when carrier-free radionuclides were not available. At the present time this can be a serious obstacle in the development of newer radiopharmaceuticals labeled with radioactive nuclides of very short half-life.

Objectives

Radioisotopes are used to obtain information concerning several types of processes. These are:

1. To study and quantify dynamic processes.
2. To measure the size of physiological compartments or pools.
3. To measure functional capacity of organs.
4. To delineate morphology.

The kinds of procedures used in Nuclear Medicine are often compared or contrasted to radiographic procedures, particularly where imaging is concerned. Whereas the radiographic image is merely dependent on the physical absorption of photons interposed between radiation source and recording medium, in radioisotopic procedures the localization of a radiopharmaceutical in a region or organ of interest is dependent upon physiological processes which are susceptible to quantitative measurement. This factor enables one to use radioisotopic procedures as a more sensitive indicator of an abnormal physiologic state, despite the process having relatively poor spatial resolution compared to roentgenography. In other words, the two procedures are usually complementary.

Radiopharmaceuticals

The key factor in the successful use of radiotracers in the investigation of disease is the use of an appropriate radiopharmaceutical. Until about 10 years ago, the variety of radiopharmaceuticals available for clinical purposes was extremely limited. Most uses centered about iodine-131 for thyroid uptakes and imaging, ^{203}Hg-chlormerodrin for brain imaging, ^{51}Cr labeling of erythrocytes, ^{85}Sr for bone imaging, and a few others. The introduction of ^{99m}Tc resulted in an explosive increase in radiopharmaceutical development. The reasons for this are the nearly ideal physical properties of ^{99m}Tc for medical purposes and it became extremely desirable to incorporate technetium into as many useful compounds as possible (about 2.9×10^6 examinations in 1972, est.)

A consideration of the characteristics of the ideal radiopharmaceutical are in order since this is probably the most active area in development in Nuclear Medicine at this time.

a) Physical characteristics: Physical parameters such as half-life and type and energy of emission are important with regard to the detection efficiency and patient radiation dose. The physical half-life should be appropriate to the time at which radioactivity determinations must be performed. It has been calculated that the ideal physical half-life of a radionuclide used in medicine should be 0.693 x time at which observations are made. This will result in the lowest radiation exposure for a given level of information. Since most physiological processes are very rapid, the interest in short-lived radionuclides is very great.

The simplest measurement to be performed with radionuclides, particularly for in vivo determination is gamma ray counting. Any other type of emission, such as alpha or beta particles, only results in increased radiation dose without contributing to useful information. In addition, the gamma rays should be appropriate energy for efficiency of detection and ease of collimation. They must be of high enough energy to escape in sufficient numbers from deep-seated structures when external monitoring of radioactivity distributed in the body is required. An additional problem with low energy nuclides (below 100 keV) is the difficulty of rejection scatter out of the photopeak. Therefore, the most appropriate range of gamma energies is approximately 120-250 keV.

b) Availability -- The early use of radionuclides was based on cyclotron production. When the atomic era arrived, the cheaper production of radionuclides in reactors spurred the use of specific radioisotopes such as ^{131}I and ^{198}Au. Now the emphasis has returned to accelerator produced materials, particularly because of the interest in short-lived radionuclides.

Although, ideally, the appropriate radionuclide for short-term studies should have a short T 1/2, the problem of availability arises, the convenience of taking a radiopharmaceutical "off the shelf". This problem was resolved by exploiting the parent-daughter decay relationship. The six-hour ^{99m}Tc is available from 67-hour ^{99}Mo by elution or extraction. A number of such radionuclide generator systems have been developed, taking advantage of the chemical differences between the parent and daughter.

Another aspect to the use of such short-lived radionuclides from these generator systems is the development of simple "kits" in which the chemical manipulations required to produce a radionuclide can be carried rapidly in a closed system such as a serum vial. This allows manufacture of the desired radiopharmaceutical at the hospital or clinic just prior to use. Such "kits" have been developed for technetium to be used for manufacture of agents used in imaging the liver and spleen, kidneys, blood pools, the skeleton and brain. They have therefore brought the possibility of high quality Nuclear Medicine procedures with low radiation dose to patients in hospitals far from reactors or cyclotrons.

c) Radionuclide purity -- Fission product radionuclides as well as many made in accelerators or by neutron capture can contain varying

amounts of other radionuclides either of the same or differing atomic numbers. In some cases these may cause no difficulty, but in most instances where present they severely detract from the use of certain radionuclides in medicine. A specific example is the isotope of iodine ^{123}I. It has a 13.3 hour half-life and gamma emissions at 159 keV and about 27.5 keV. A method of production on the cyclotron was developed at this laboratory which resulted in a product containing only 0.2% ^{125}I as a radionuclide contaminent. This was done by producing ^{123}Xe which could be separated from any iodines present and which subsequently decayed with a T 1/2 of hours to ^{123}I. Other methods for producing ^{123}I were handicapped by a significant percentage of ^{124}I.

Table 1 shows the radiation dose to the thyroid from each of a number of isotopes of iodine. It can be seen that ^{123}I is very favorable from this aspect, giving a radiation dose factor of 100 less than the more commonly used ^{131}I. However, contamination of ^{123}I by as little as 1.4% of ^{124}I doubles the radiation dose to the thyroid. In addition, the higher energy gamma rays of ^{124}I or of other radioiodines would cause degradation of imaging by scatter and septal penetration of collimators.

d) Radiochemical purity: In order to obtain valid results, it must be certain that an administered radiopharmaceutical is indeed what the label purports it to be. For instance, the determination of effective renal plasma flow by measurement of the clearance of radiohippuran is not possible if a substantial amount of the radioactivity administered is in the form of free iodine, rather than labeled to the iodo-hippuric acid. If not all of the ^{51}Cr in a sodium chromate solution is in the

correct valence state, there will be inefficient labeling of red blood cell mass determination.

3) Biochemical behavior: This is a most critical factor. It is an area that requires much investigative work in order to find chemical compounds which will localize to the greatest extent in the region or organ of interest in order to provide the highest target to non-target ratio. One such simple example is the comparison of images of the thyroid obtained using ^{123}I and ^{99m}Tc. Technetium-99m as pertechnetate localizes quickly in the thyroid following intravenous administration, but is only trapped, not further incorporated into the formation of thyroid hormone. The maximum normal concentration in the thyroid is less than 4% with considerable radioactivity still circulating at the time of administration. Radioiodine, on the other hand, concentrates in the thyroid normally at about 15-40% of the administered dose. At the time of examination (18-24 hours) most of the remainder of the radioactivity has been cleared by the kidneys. Thyroid images performed with radioiodine are therefore of better quality as shown in the example (Fig. 1).

Another example where appropriate biochemical behavior is crucial is in pancreas imaging. At the present time the agent used is ^{75}Se-selenomethionine, but it is an unsatisfactory agent. The concentration ratio in the pancreas compared to the liver is only about 3 or 4 to 1. Because of the much greater bulk of the liver the pancreatic image is often obscured by the liver and resort must be made to special techniques, such as subtraction (Fig. 2) in order to view the poorly-visualized pancreas. An agent that would localize to a much greater extent in the pancreas would

provide images of superior quality with less radiation and with more simple methods.

f) Specific Activity: The biochemical specificity of a labeled compound may be lost if too much carrier is present. Well known is the example of abnormally depressed radioiodine uptakes in the thyroid following the administration of various iodinated x-ray contrast agents. Iodine, released from these compounds floods the iodine pool in the thyroid and any administered radioiodine is excreted in the urine.

The question of specific activity is particularly important in preparation of biologically active compounds of very short half-life. In our work with ^{18}F (T 1/2 - 1.8 hours) as a label for the amino acid tryptophan, it was not initially realized that the degree to which the fluorotryptophan concentrated in the pancreas was a fraction of the total amount (mg/kg) administered to the animal, despite the amount of radioactivity administered (Fig. 3). In the use of "C-dopamine for adrenal medullary imaging, a very significant difference in degree of concentration between carrier-free material (~80,000 mCi/mg) and the previously obtained, rather high specific activity (~40 mCi/mg) material is obvious. In this latter instance another necessity for very high specific activity is the potential toxicity of injecting large amounts of dopamine (Fig. 4).

g) Sterility and Pyrogenicity: The preparation of radiopharmaceuticals of very short half-life and from "kits" manufactured at the site of use places difficulties before the physician who wishes to be assured the preparation he administers is sterile and will not produce a pyrogenic reaction. There is no time, after preparation, to do the usual in-vivo

tests and cultures usually required for non-radioactive intravenous medications. Constant monitoring of materials and the system used is necessary. A newly developed in vitro procedure for pyrogen testing (the limulus amoebocyte lysate gelation test) derived from the blood of the horseshoe crab may be very helpful in solving this problem.

a) Use of Radiocolloids: Colloidal radiopharmaceuticals are ingested by phagocytic cells of the reticulo-endothelial system. These cells are localized mainly in the liver, spleen and bone marrow. About 90% are in the liver and the extraction efficiency is so high that the plasma clearance is inversely related to the rate of liver uptake (Fig. 5). Abnormal physiological and morphological states of the liver, spleen and bone marrow can be delineated (Fig. 6). The lymph node system can also be visualized (Fig. 7).

The effect of increased carrier can be used to measure the phagocytic function in various immune states. Microaggregates of iodinated human serum albumin are rapidly phagocytized by the liver as are the colloids. In low concentration, the extraction efficiency is close to 100% and rate of disappearance is dependent on liver blood flow. As carrier is increased beyond a certain critical level, the extraction efficiency decreases, the liver cannot handle all the particles, and the plasma clearance is dependent on immune factors related to phagocytosis. These are affected by certain disease states such as bacterial infections, Hodgkins Disease, etc.

b) Use of Chelates: Many chelates are useful compounds when labeled with radionuclides. One such chelate, recently developed, is

^{99m}Tc-DTPA. It is readily prepared from a simple kit and is rapidly distributed throughout the extracellular space. It is therefore useful as a brain scanning agent.

Another use is the study of renal anatomy and physiology. It is cleared by glomerular filtration and the clearance rate is a good estimate of renal function. Because large quantities can be safely administered, it is possible in one study to obtain several kinds of information such as aortogram, renal perfusion, functional capacity of the kidneys and determination of renal obstruction (Fig. 8, 9).

d) Labeled Red Blood Cells: Red blood cells stay within the vascular compartment and therefore the dilution of a known quantity of labeled cells can be used in the determination of red cell mass. As labeled cells senesce, they are culled from the blood stream by the spleen. With a long-lived label such as 28-day ^{51}Cr, the disappearance rate from the blood and evidence of splenic sequestration can be determined.

Heat damaged red cells rapidly sequester in the spleen and can be used for splenic imaging. When the cells are labeled with ^{99m}Tc they can be used to image the vascular pools including heart, placenta and major blood vessels (Fig. 10).

Instrumentation

The most commonly used detector in Nuclear Medicine is the sodium iodide scintillation crystal. The sensitivity and speed of these crystals have clear advantages over the older Geiger-Müller tubes. More recently, there has been interest in the newer semiconductor detectors, particularly Ge(Li) and GE(HP). High energy resoultuion is of definite value in a number of special applications.

For imaging purposes, the standard instrument has been the rectilinear scanner. This device consists of a 5 x 2" sodium iodide crystal with a field of view defined by a focussed collimator. The detector moves in a raster pattern over the area of interest and a plotter displays, on film, the distribution of radioactivity in the body. The disadvantages of such a device is its relative insensitivity due to the limited field of view (solid angle) and consequent long time to cover the area of interest. Dynamic studies are extremely difficult, if not impossible, to carry out, and spatial resolution deteriorates rapidly off the plane of focus of the collimator.

Isotope cameras of various types have been devised. These instruments are stationary and view a large field, thus allowing rapid sequential imaging in dynamic precesses. They are readily interfaced to multichannel analyzer-computer combustion to facilitate quantitative evaluation of studies. A common type of camera is the one invented by Anger and produced commercially by a number of companies. It contains a single thin crystal 10-12" in diameter and 1/2 inch thick. More recently, 16" cameras have been constructed. A bank of photomultipliers collects light from scintillation events and position information is derived from the distribution of light among the photomultipliers. This is displayed on an oscilloscope and photographed or digitized and stored in 32 x 32, 64 x 64, etc. matrices in a multichannel analyzer or computer. In addition to the straight bore collimators used for looking at areas the size of the crystal, diverging, converging and pinhole collimators are used for special purposes.

The advantages of the camera device are high sensitivity due to large solid angle of view, relatively little dependence of resoultion on distance from the collimator surface and the speed at which dynamic processes can be recorded. On the other hand, the thin crystal limits use to lower energy photons below about 400 keV. Resolution is comparable to rectilinear scanners for higher energies but becomes degraded below 100 keV on statistical grounds.

Another method of imaging involves coincidence counting of annihilation radiation from positron emitters. Instrumentation has been developed for this using two or multiple opposing crystals. It is not in widespread use, but may become more popular when cyclotron produced radionuclides prove useful for certain types of studies. One advantage of coincidence counting is the three dimensional information available.

A number of hybrid devices and tomographic scanners have been developed for special purposes such as whole-body imaging and for clearer delineation of distributions of radioactivity in specific planes. None of these is as yet commercially available or in widespread use.

With the availability of semiconductor devices with energy resolution nearly an order of magnitude better than sodium iodide crystals some new methods have been developed. Fluorescence scanning is a method whereby an element, such as iodine, can be imaged by detection of the characteristic x-rays following excitation by a high energy photon (Fig. 11). Another method of doing this is by detection of the differential absorption of two beams of photons on either site of a critical absorption edge.

Imaging devices using germanium detectors are being developed. The good energy resolution improves spatial resolution by efficiently rejecting scattered radiation. Isotope cameras constructed with such detectors will probably be commonplace in the not too distant future.

Computers are becoming more and more a part of Nuclear Medicine. They are indispensible for the very rapid dynamic processes such as in angiocardiography. They enable one to quantify results, provide accurate storage and can be used to generate curves of the time course of radioactivity for multiple regions in the field of view. Corrections for decay, dead-time losses, non-homogeneity of detector response, etc. are also possible. By various forms of data processing and filtering, it has been possible to improve the quality of images and aid diagnosis (Fig. 12) but this has not become a useful procedure as yet in clinical practice.

Areas of Current Interest

1. Cyclotron produced radionuclides -- Cyclotrons have been installed in a number of hospitals and research is going on with a number of interesting short-lived radionuclides such as ^{13}N, ^{15}O, ^{11}C, ^{18}F. Some of these are of interest since they are in all or most organic molecules. One of the more interesting areas is myocardial imaging where $^{13}NH_3$ has shown promise.

2. New radionuclides -- BLIP and LAMPF are new accelerators capable of producing in large quantities many radionuclides not readily available before. The cost of most of these should be low because most of the cost of these macnines has been borne by the physics experimental program. A drawback is that they cannot be used for routine production purposes for vitally needed radionuclides such as ^{123}I if physics priorities prevent such a utilization.

3. Unsolved areas -- Among the greatest interest, at this moment are problem areas such a myocardial imaging for detection of areas of

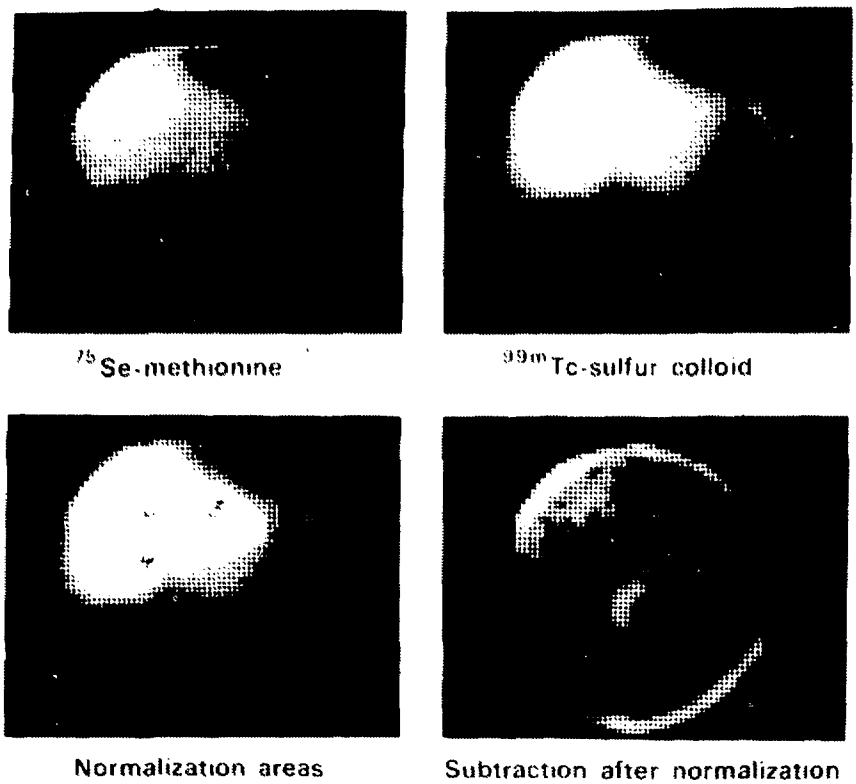
impaired blood flow and pancreas imaging. The $^{13}NH_3$ mentioned above is one promising approach to myocardial imaging. Another is the use of potassium analogs such as rubidium and ^{201}Th which we hope to obtain from BLIP.Amino acids labeled with ^{18}F, ^{11}C or ^{123}I may be successful for the pancreas. Small animal work has so far shown some promise, but results with larger animals has not yet been encouraging.

4. Fresnel Zone Plate Imaging -- A new approach using diffraction rings as collimation results in more efficient detection of low energy gamma emitters. A side advantage is 3 dimensional information available from the image reconstruction process. This is an intirely new development which will probably result in significant progress in the near future.

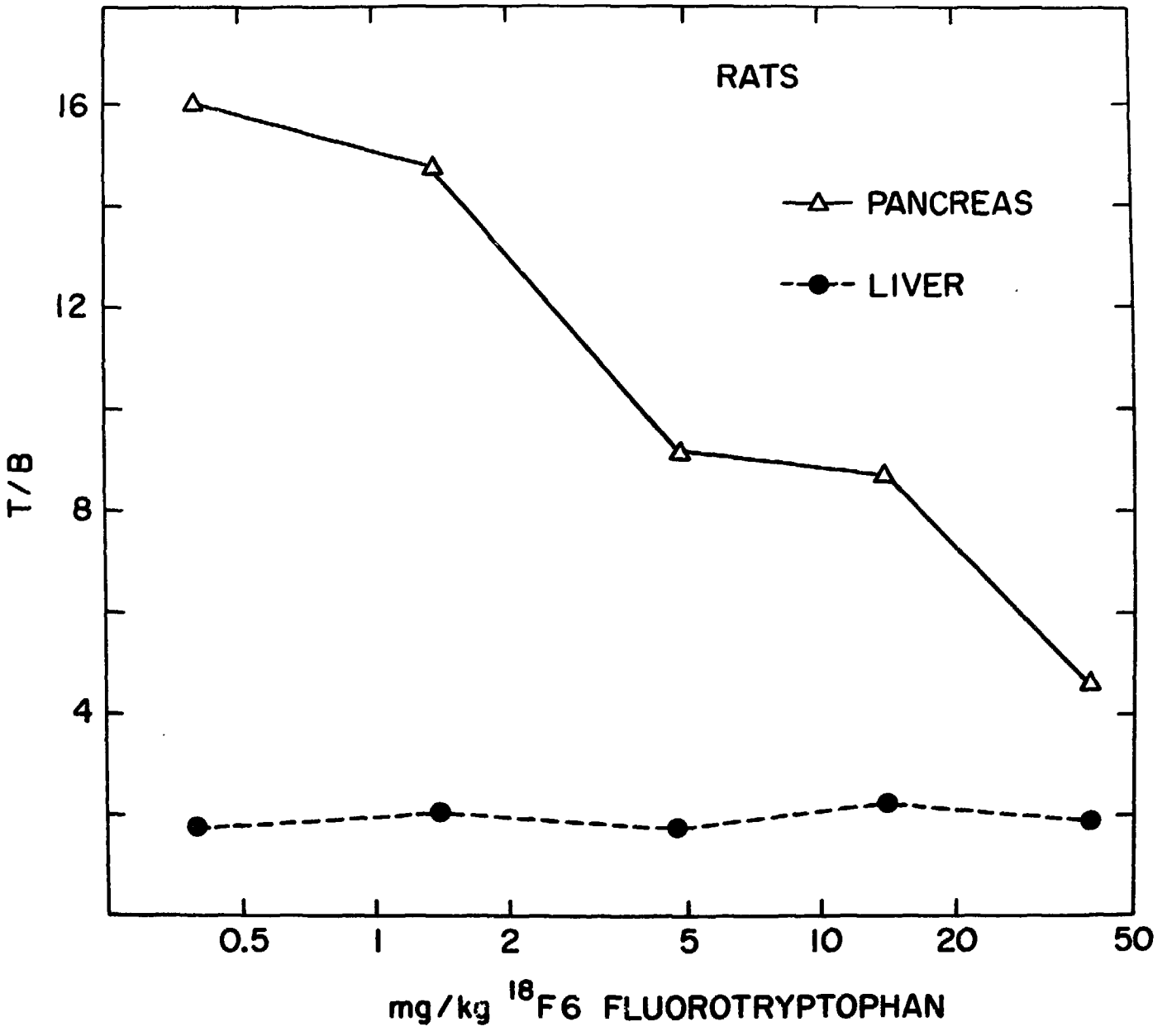
R.H. 38 ♀

$^{99m}Tc\ O_4^-$
1.91%

$^{123}I^-$
29.1%



Pancreas extraction by subtraction of the ^{99m}Tc-sulfur colloid image from the ^{75}Se-methionine image after normalizing one to the other, using three regions over the liver.


RATS
PANCREAS
LIVER
T/B
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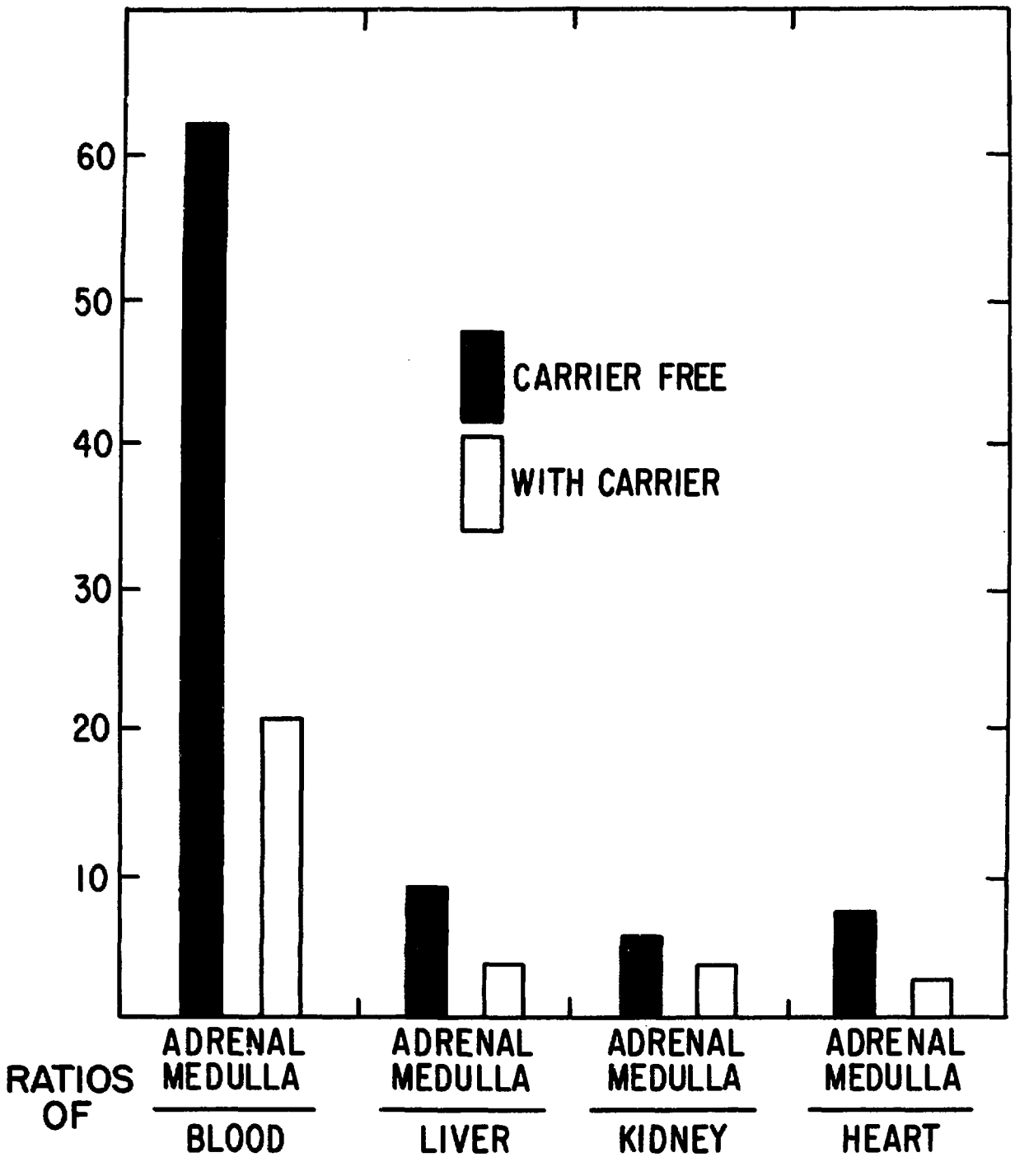
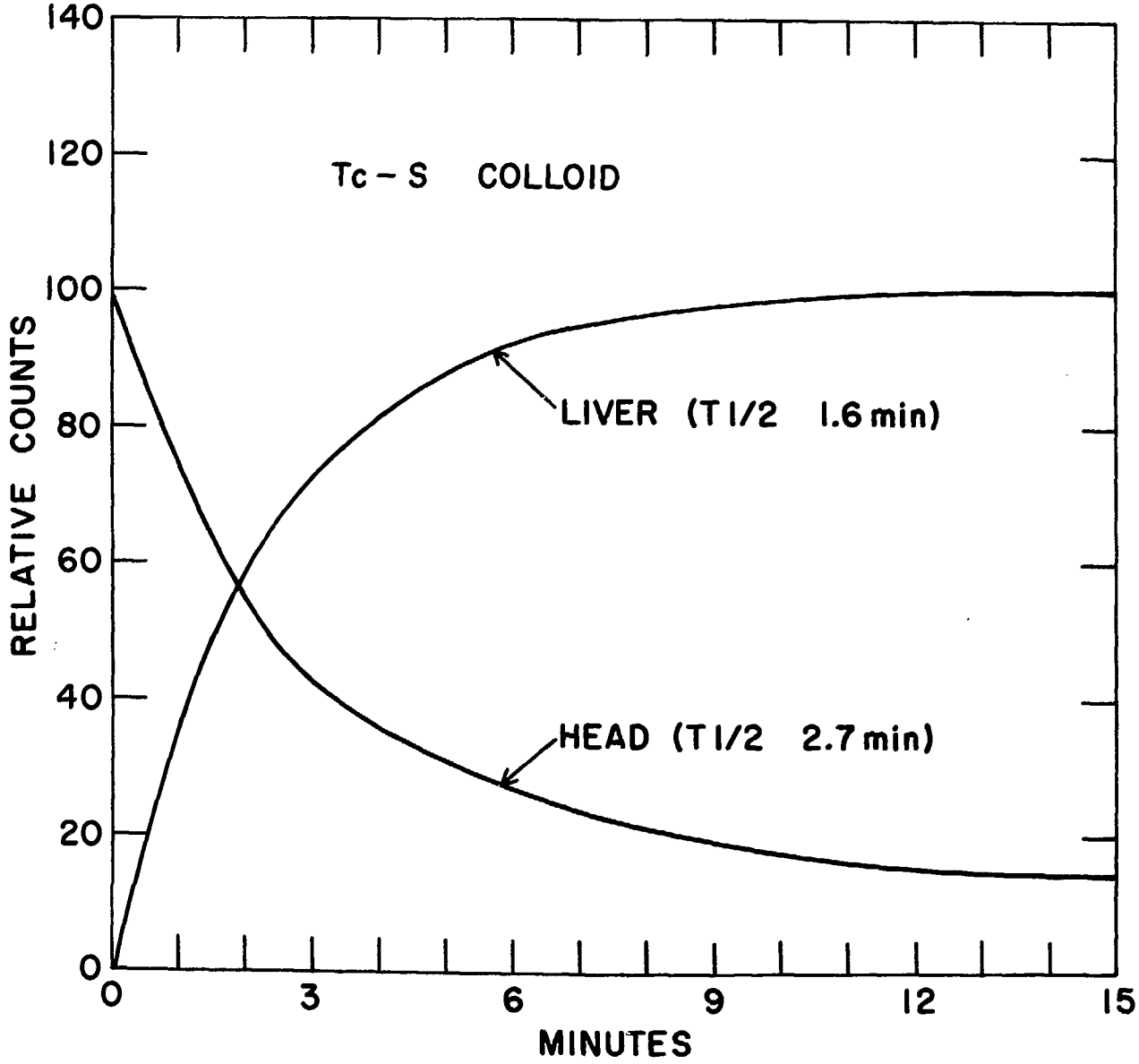
12
8
4
0.5
1
2
5
10
20
50
mg/kg ^{18}F6 FLUOROTRYPTOPHAN


60
50
40
30
20
10
CARRIER FREE
WITH CARRIER
RATIOS OF
ADRENAL MEDULLA / BLOOD
ADRENAL MEDULLA / LIVER
ADRENAL MEDULLA / KIDNEY
ADRENAL MEDULLA / HEART


140
120
100
80
60
40
20
0
RELATIVE COUNTS
Tc – S COLLOID
LIVER (T 1/2 1.6 min)
HEAD (T 1/2 2.7 min)
0
3
6
9
12
15
MINUTES

HODGKIN'S DISEASE

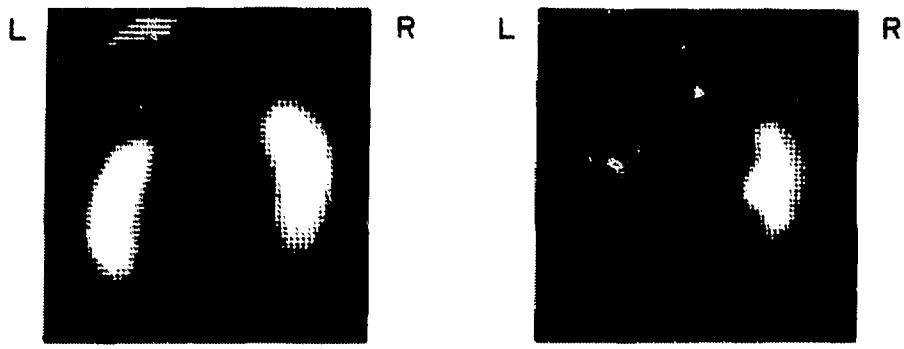
M. LaF. 35a ♀

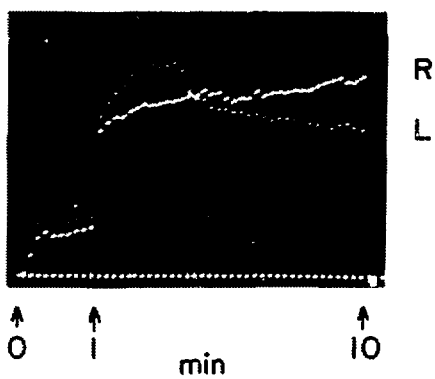
K.B. 17 ♀ HODGKINS DISEASE ENLARGED
PARAAORTIC NODES

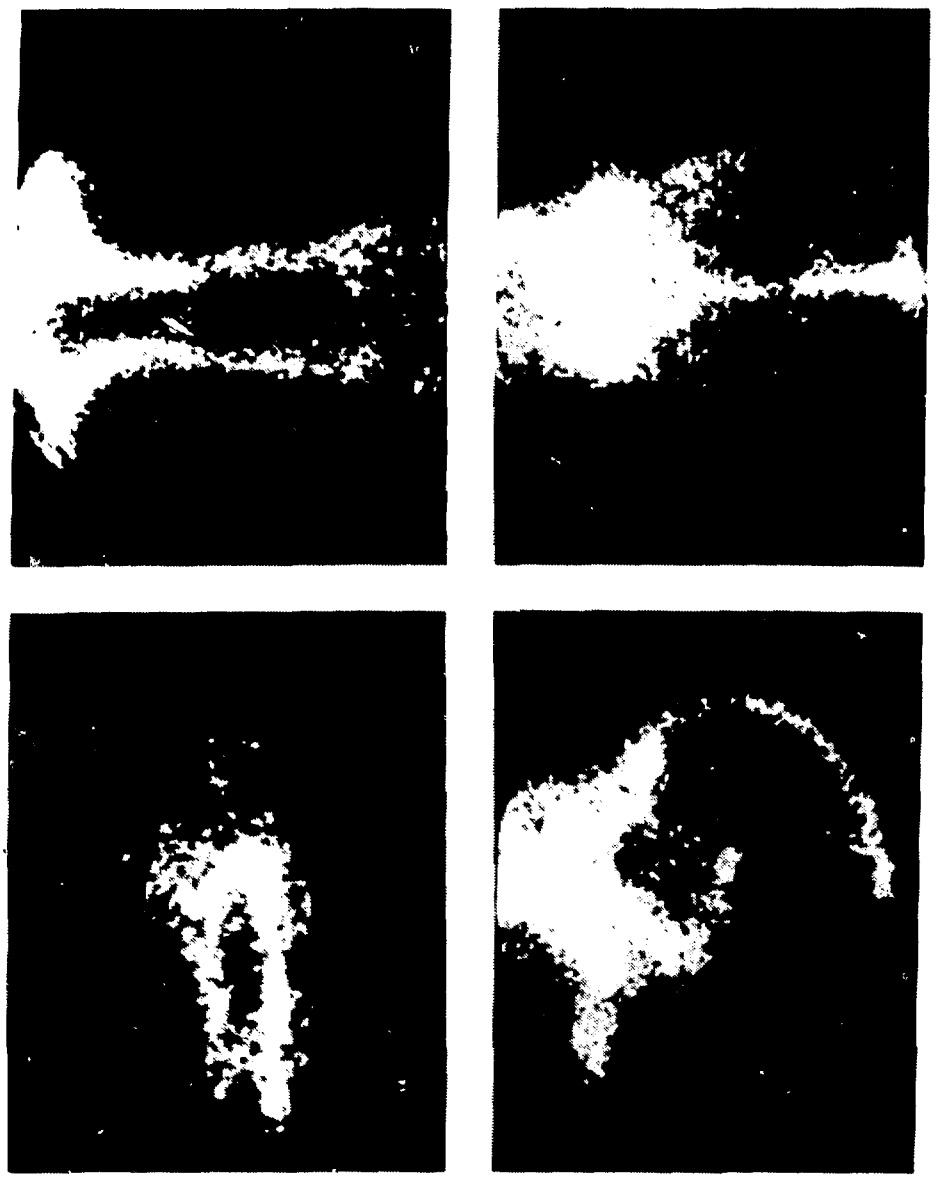
E.O. 60 ♂

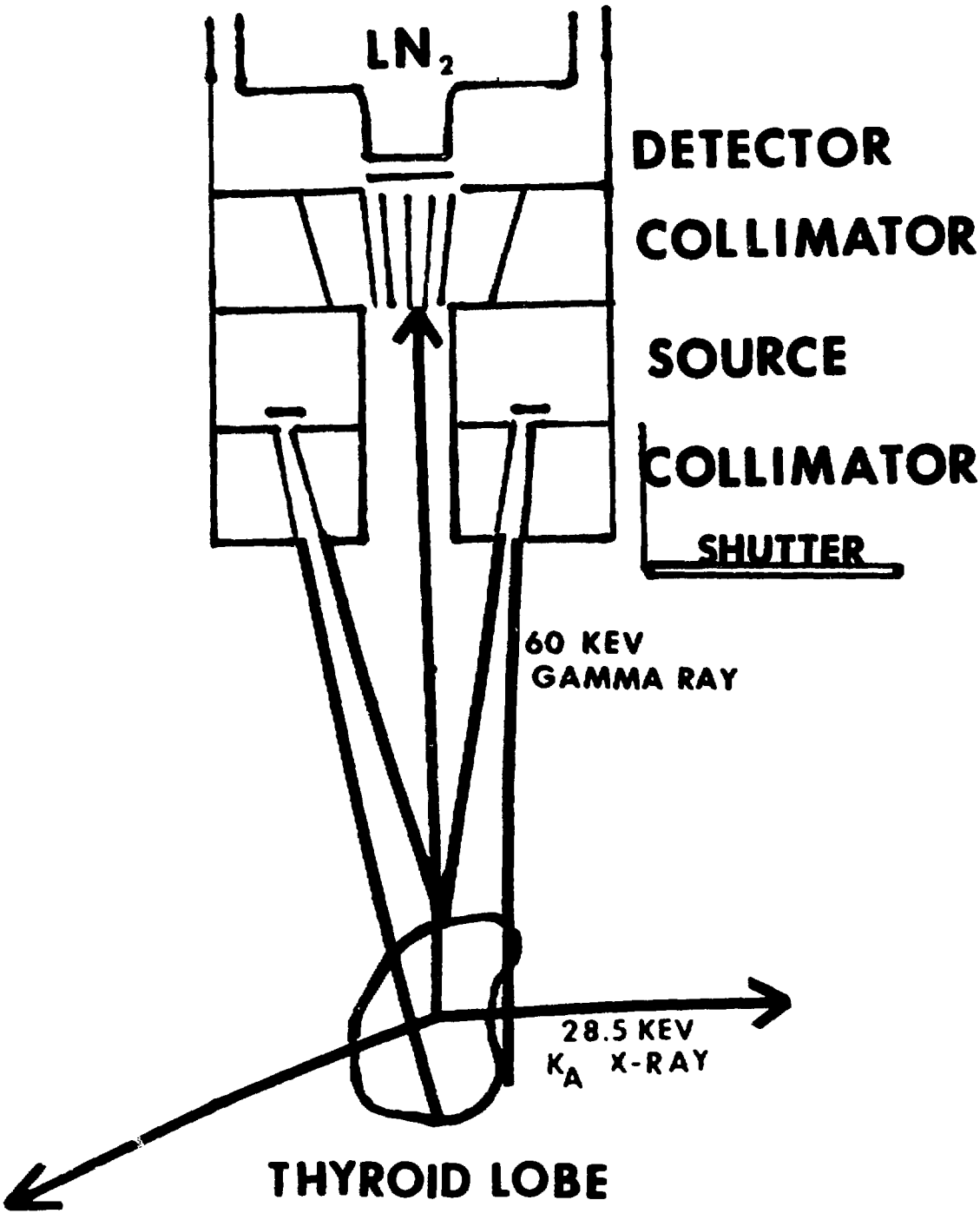
3 min　　20-25 sec　　15-20 sec

E.C. 37 ♀ HYPERTENSION








LN2
DETECTOR
COLLIMATOR
SOURCE
COLLIMATOR
SHUTTER
60 KEV
GAMMA RAY
28.5 KEV
KA X-RAY
THYROID LOBE

Examples of methods of contrast enhancement and smoothing easily implemented by control of the display module.

TABLE I

Radionuclide	Usual Administered Activity	Radiation Dose to Thyroid in Rads/μCi
^{123}I	100 μCi	0.01 - 0.02
^{124}I	---	0.73 - 1.46
^{125}I	50 - 100	0.74 - 1.48
^{126}I	---	0.79 - 1.58
^{130}I	---	0.08 - 0.15
^{131}I	50 - 100	1.06 - 2.12
^{132}I	10	0.008- 0.015

ILLUSTRATIONS

1. Comparison of thyroid image made with ^{99m}Tc (above) and ^{123}I (below). There is clearer delineation with iodine, particularly the pyramidal lobe in the center, due to a lower background activity. BNL Neg. # 12-108-71.

2. Pancreas extraction by subtraction of the ^{99m}Tc-sulfur colloid image from the ^{75}Se-methionine image after normalizing one to the other, using three regions over the liver. (Courtesy Dr. T. Budinger, Donner Laboratory, Univ. California) BNL Neg. #5-93-73.

3. Tissue to blood ratios for pancreas and liver in the rat as a function of loading dose. As dose increases there is less selective uptake by the pancreas of ^{18}F-6-fluorotryptophan. BNL Neg. #6-72-71.

4. The effect of carrier is to reduce the concentration of ^{11}C-dopamine in the adrenal medulla relative to other organs and the blood. BNL Neg. #2-245-73.

5. Liver uptake and blood clearance of ^{99m}Tc-sulfur colloid following intravenous administration. BNL Neg. #2-1654-69.

6. Distribution of ^{99m}Tc-sulfur colloid in liver, spleen and bone marrow. Normally there is minimal uptake of radioactivity below the hips. BNL Neg. #10-859-70.

7. Lymph node distribution of ^{99m}Tc-sulfur colloid in inguinal, pelvic and periaortic lymph nodes following subcutaneous injection between the toes. The periaortic nodes are enlarged. The liver and spleen are also partially visualized. BNL Neg. #8-887-71.

8. Sequential scintiphotos obtained at 15-20 sec. and 20-25 secs. after intravenous injection of ^{99m}Tc-DTPA and another image of kidneys at 3 minutes. The aorta is tortuous and has an aneurysmal dilatation just above the bifurcation. BNL Neg. #10-413-71.

9. Computer processed images of ^{99m}Tc DTPA study showing a block to urine flow on the right due to ureteropelvic obstruction. This is confirmed in the curves of counts vs. time for the two kidneys which show lack of discharge of radioactivity from the right kidney. BNL Neg. #10-60-72.

10. Scintiphotos of vascular structures in the head, neck and forearm following administration of ^{99m}Tc labeled red blood cells. BNL Neg.#11-454-71.

11. Diagram of fluorescence scanning system. The 60 keV gamma rays from ^{241}Am irradiate the thyroid and fluorescent radiation from iodine in the gland is detected by a semiconductor detector. (Courtesy of Dr. Paul Hoffer, Argonne Cancer Research Hospital, Chicago, Ill.) BNL Neg. #3-1342-72.

12. Examples of methods of contrast enhancement and smoothing easily implemented by control of the display module. (Courtesy Dr. T. Budinger, Donner Lab., University of California) BNL Neg. #5-92-73.