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DIAGNOSTIC AND THERAPEUTIC MEDICAL APPLICATIONS FOR ISOTOPES

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INTRODUCTION

The stimulus provided by the recent establishment of the American Board of Nuclear Medicine should result in considerable progress in this field in years to come. By promotion of training programs and the setting up of independent departments of Nuclear Medicine, there should be an increasing number of physicians devoting full time to the areas of research, both basic and clinical, in this area.

As evidence of the maturing status of Nuclear Medicine, we are now able to discuss developments in areas where the methods of Nuclear Medicine can be brought to bear on clinical problems of substantial importance. The increased capability to progress in line with modern developments in other medical specialties such as Cardiology, Hematology, etc. to attack these problems is certainly a source of satisfaction. It is this type of progress that one can discuss today rather than the isolated development of a new piece of machinery or a new radionuclide with unknown biological application.

Of course, the quality of work that can be performed is dependent on materials that are available as well as knowledge of physiological and biochemical mechanisms. A major limitation, felt particularly in dynamic imaging procedures, is the relatively low information content compared to radiographic images. This has lead naturally to an interest in the shorter half-lived radionuclides, allowing administration of much larger quantities of radioactivity to the patient. It also requires

very high specific activity of radiopharmaceuticals in order to prevent perturbation of the biological system. Therefore, there has been a shift toward cyclotron-produced, carrier-free radionuclides for some of the newer applications. Cyclotrons have now been installed in a number of medical institutions, with particular emphasis on carbon-11, nitrogen-13 and fluorine-18. Other cyclotron produced radionuclides such as indium-111, gallium-67 and iodine-123 are being produced on larger accelerators.

I would like to discuss some recent work going on in three clinical areas of importance -- coronary artery disease, adrenal imaging and tumor localization. Many other areas could be discussed. For instance, the development of newer bone scanning agents or the development of pure iodine-123 production to replace iodine-131 are two important areas. However, the subjects of heart disease, tumor localization and adrenal imaging typify some of the newer multifaceted approaches in which Nuclear Medicine can contribute to clinical medicine today and tomorrow.

CORONARY ARTERY DISEASE

With coronary artery disease being a major cause of death and disability, it becomes imperative to develop methods for accurate diagnosis of type and extent of disease. This is particularly of importance when newer surgical methods are being applied therapeutically. These patients are usually very sick and techniques that are non-invasive and carry minimal risk are desirable.

A critical bit of information is the evaluation of regional myocardial perfusion. Radiographic techniques such as coronary arteriography can provide information regarding patency of larger vessels but cannot give quantitative information concerning the physiological consequences of partial obstruction

and narrowing of these arterial pathways. Radionuclide techniques can give this information and a variety of methods have been used.

Evaluation of myocardial perfusion can be carried out in conjunction with coronary arteriography. In one method the washout of radioxenon from the heart can be measured similar to methods used for regional renal and cerebral blood flow. A disadvantage is the necessity for the detection equipment to be available in the catheterization suite.

An alternate method is to inject particulate material such as macroaggregated human serum albumin labeled with either ^{99m}Tc or ^{131}I. These particles lodge temporarily in the capillary bed and provide an index of perfusion to the myocardium. When one radionuclide is used for the right coronary circulation and a second radionuclide for the left coronary circulation, the two regions can be separately imaged by pulse height discrimination. Computer processing allows appropriate recombining of the images. An advantage is that imaging procedures can be carried out at relative leisure after the patient has left the cardiac catheterization suite.

In Fig. 1 a normal pattern of left coronary artery perfusion with ^{99m}Tc macroaggregates and right coronary artery perfusion with ^{131}I macroaggregated albumin is seen. The combined images show good perfusion throughout the myocardium. Abnormal distributions of radioactivity in both coronary circulations are outlined in Figure 2. It should be noted that the proper projection is required for the most advantageous viewing of the perfusion defects.

Both of the above methods do require catheterization of the coronary arteries. It is desirable, however, to have a method applicable to very sick patients, and under emergency conditions. For this purpose it is necessary to have a radiopharmaceutical which is relatively efficiently extracted from the circulation by the myocardium. Most of the agents used for this purpose have been analogs of potassium, the major intracellular cation. These analogs have included cesium and rubidium. Radioisotopes of potassium have also been used. For one reason or another, because of inappropriately high or low energy gamma photons, inconvenient half-lives, high radiation dose or general unavailability, these radionuclides have not been completely satisfactory (Table 1). Recently we have been investigating radiothallium as a myocardial imaging agent. Its use for this purpose was first suggested by Harper because its physiological behavior closely mimics that of potassium, probably due to the close similarity in size of the hydrated thallous ion with that of potassium. The particular radioisotope of thallium that appears most promising is ^{201}Tl. It emits γ photons of 135 and 167 keV in 10% abundance as well as mercury x-rays. Because of the absence of particulate emissions, the radiation dose is low. It is obtainable in small quantities at present from the BNL 60" Cyclotron in carrier-free form following a rather tedious separation procedure. It will be produced on the Brookhaven Linac Isotope Producer (BLIP) in large quantities and the T 1/2 of 74 hours should give it a good shelf life, thus making it readily available for emergency use. The photon energies and permissible administered activity ($\sim$5 mCi) should allow good camera imaging. Initial animal

animal studies show rapid accumulation in the heart with about 8% present in the myocardium. (Fig. 3 and 4).

A second approach that we are considering is the use of ^{11}C-norepinephrine. Our Chemistry Department has been able to deliver millicurie quantities in the carrier-free state. The short half-life of 20 minutes and the 511 keV annihilation radiation are somewhat disadvantageous. It does allow multiple repetitive studies and concentrates to a degree comparable to thallium. Perhaps a longer lived label may enhance its usefulness in the future. (Fig. 5, 6).

Another cyclotron product useful in myocardial imaging is ^{13}N-ammonia. It has been investigated both by the group at Argonne Cancer Research Hospital and the Massachusetts General Hospital. This material is extracted by the myocardium as efficiently as potassium and produces excellent images representing myocardial perfusion. It apparently enters into the metabolism of glutamic acid in cardiac muscle (Fig. 7).Again, the short half-life and high photon energies present problems for clinical use. Images obtained following intra-coronary artery administration are far superior to those obtained after intravenous administration.(Fig. 8, 9).

A number of other approaches are also being investigated. The use of labeled fatty acids was suggested several years ago and is again under study. (Fig. 10, 11).The possibility of using labels other than iodine-131 (^{99m}Tc or ^{123}I) make this idea more interesting. Methods for positive identification of infarcts with labeled antibiotics are also a possibility.

ADRENAL IMAGING

The recent work of the group from Michigan under Beierwaltes has resulted in the development of an adrenal cortical imaging agent, ^{131}I-iodocholesterol. This material requires five to ten days for optimal concentration in the adrenal cortex and therefore the label must be a rather long-lived one. This work has helped to cover one of the "blind" areas in clinical medicine. Radiographic techniques are tedious and unsatisfactory. Particularly helpful is the use of iodocholesterol in looking for residual adrenal tissue following surgery (Fig.12).

We are engaged in investigation of an agent for adrenal medullary imaging, much needed in the study of hypertension and for certain types of tumors. Again, we are using carbon-11 to label a catechol amine-dopamine. Originally we worked with low specific activity material which was very unsatisfactory, including being severely toxic. The recently developed method to produce carrier free material produces no pharmacologic effect, thus allowing administration of multicurie quantities. In addition, its behavior and distribution are far superior to even the rather high specific activity material which we had been using recently (Fig.13). The concentration in the adrenal medulla is better than the iodocholesterol in the adrenal cortex. This general area is of interest because it opens up possibilities of using various monoamine oxidase inhibitors to improve localization. Hopefully, some day we will have a short-lived labeled L-Dopa for investigation of brain pathology.

TUMOR LOCALIZATION

Similar to the longed for blood test as a screening procedure for cancer, many investigators are seeking a radioisotopic method to determine the presence of malignant disease. In the past many agents have been used, but none have seemed especially reliable. More recently ^{67}Ga has been in favor (Fig.14,15) too lacks reliability, although proving to be helpful in many special situations. One useful area is in Hodgkin's Disease where it can be of assistance in proper staging and in uncovering areas of unsuspected disease.

Indium-111 is of more recent interest,and used as a label for bleomycin appears to be particularly effective. Large scale clinical testing is in progress.

As yet there is no adequate explanation for why some tumors will take up a particular preparation and other tumors of the same histologic type will not. Host immune factors and ability to be transported by a particular protein fraction in the blood are probably related to the ability to localize in tumors.

More gratifying is work with certain tumors where biochemical factors are better understood. One such case is melanoma, ocular melanoma in particular. Iodoquinolines labeled with iodine-125 have been shown to label those cells where melanin metabolism occurs. We have been investigating iodoquinolines labeled with iodine-123. The advantage is a lower radiation dose and no need to block the thyroid in order to prevent uptake of free iodine broken off the labeled compound. The thyroid can thus act as a filter, thereby reducing the

background noise and improving target-non-target ratios. Our work with a hamster melanoma has shown early and excellent localization in these tumors (Fig. 16).

OTHER AREAS OF INTEREST

There are two factors which should contribute greatly to future progress in the application of radionuclides to medical problems. The first of these is the potential availability, on a large scale, of a number of radionuclides that were heretofore extremely difficult to produce. The other factor is the increased application of biochemical knowledge leading to the use of biologically active molecules as tracers.

Chief among the interesting radionuclides is iodine-123(Table 2) produced in pure form it can reduce the radiation dose to the thyroid by a factor of 100 compared to iodine-131. As a label for a number of compounds such as Rose Bengal, Hippuran, etc., it can improve the information content of a number of clinical examinations. Other radionuclides of interest are ^{127}Xe for pulmonary diagnostics, ^{52}Fe for marrow imaging and ferrokinetics, ^{97m}Tc as a low energy radiographic source, ^{97}Ru as a general imaging agent and many others.

These nuclides can all be produced on the new large accelerators at Brookhaven, Los Alamos and Vancouver. Radionuclide production on these machines is parasitic to the physics research and therefore relatively inexpensive.

The applicability of ^{11}C-labeled catechol amines and amino acids are illustrative of the use of biological molecules as tracers. Hopefully, further exploration of the use of such compounds will open up whole new

areas of research and clinical utility such as imaging of specific areas of the brain.

There are many exciting possibilities ahead. We recently had a close call with our Nuclear Medicine program because of scheduled budgetary restrictions. Luckily, the medical community came to our aid in having this money restored. Hopefully, we shall be able to survive beyond the many monetary uncertainties of the immediate future in order to explore some of the intriguing possibilities for progress in Nuclear Medicine.

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ILLUSTRATIONS

Fig. 1 Normal distribution of ^{99m}Tc-MAA into the left coronary artery distribution and ^{131}I-MAA in the right coronary artery distribution in anterior, left anterior oblique and left lateral views. BNL Neg. #3-680-73 (Courtesy W. Ashburn, Univ. Cal., San Diego).

Fig. 2 Abnormal myocardial perfusion as shown by intracoronary injection of labeled MAA. BNL Neg. #3-679-73 (Courtesy W. Ashburn, Univ. Cal., San Diego)

Fig. 3 Thallium-201 distribution in heart, liver and kidneys of a rabbit at 15 minutes and 2 hours. Upper left hand image is from Polaroid print, others from oscilloscope screen of digitized image. Note relative loss of heart activity compared to liver at 2 hours. BNL Neg. #9-1184-72.

Fig. 4 Thallium-201 distribution in heart of a goat with induced infarction. BNL Neg. #12-300-72.

Fig. 5 ^{11}C-norepinephrine levels in blood. The rapid disappearance from blood is necessary for good myocardial imaging. BNL Neg. #5-971-73.

Fig. 6 Roentgenogram (left) and myocardial scintiphoto (right) on a dog. Scintiphoto was obtained on a gamma camera following administration of ^{11}C-norepinephrine. BNL Neg. #6-124-73.

Fig. 7 Metabolism of ^{13}N-ammonia in glutamic acid cycle in myocardium BNL Neg. #5-556-73.

Fig. 8 Sequential scintiphotos with a positron camera showing intracoronary administration of ^{13}N-ammonia in a dog's heart. (Mass. General Hosp.) BNL Neg. #5-1188-78

Fig. 9 Images of dog's heart after intracoronary (above) and intravenous administration (below) of ^{13}N-ammonia. Marker in a site of induced infarction. Note increased background after intravenous administration. (Mass. General Hosp.) BNL Neg. #5-1187-73.

ILLUSTRATIONS (cont'd)

Fig. 10 Scans performed with ^{131}I-oleic acid showing dog's heart pre- and post-induced infarction of the left anterior descending coronary artery. Defect is best seen in left lateral view. (Courtesy F. Bonte, Dallas, Texas). BNL Neg. #3-689-73

Fig. 11 Coronary arteriogram of dog shown in Figure 10. Site of mercury embolization in myocardium is shown. (Courtesy F. Bonte, Dallas, Texas) BNL Neg. #3-691-73.

Fig. 12 Localization of right adrenal scan with ^{131}I-iodocholesterol. (Univ. of Michigan) BNL Neg. #3-685-73.

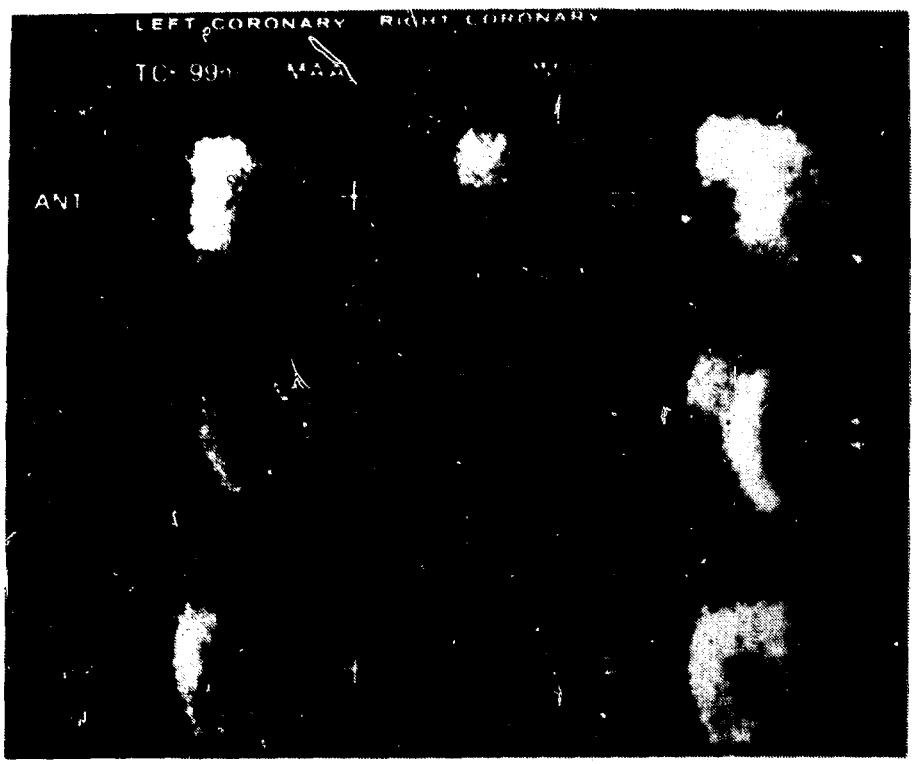
Fig. 13 Tissue distribution of ^{11}C-dopamine in dogs. Note much improved localization in adrenal medulla of the carrier-free material. BNL Neg. #1-559-73.

Fig. 14 Bony metastasis in left femur from unknown primary site imaged with ^{67}Ga. Note normal distribution of gallium in skeleton and liver. (Courtesy P. Mandel, Mineola, N.Y.) BNL Neg. #5-470-73.

Fig. 15 Technetium-99m colloid scintiphoto of liver (left) with defect in lower portion of right lobe visualized as a "cold" area. In the ^{67}Ga scan (right) the defect is now seen as a "hot" area confirming the presence of a malignancy. (Courtesy P. Mandel, Mineola, N.Y.) BNL Neg. #5-468-73

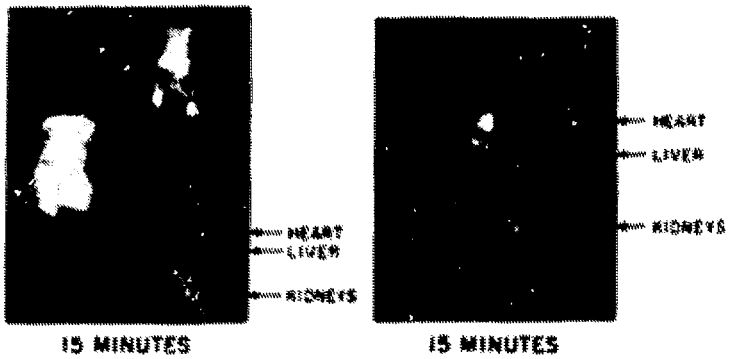
Fig. 16 Localization of ^{123}I-4,3 DMQ in hamster ocular melanoma. BNL Neg. #4-1159-73.

Superimposition of the left coronary perfusion patterns (^{99m}Tc-MAA) + right perfusion patterns (^{131}I-MAA) in three projections produces composite images **(right of = sign)** *of total regional contribution from each coronary artery.* ***ANT.*** *= anterior; L. LAT. = left lateral; and* ***L.A.O.*** *= left anterior oblique in this and other illustrations.*



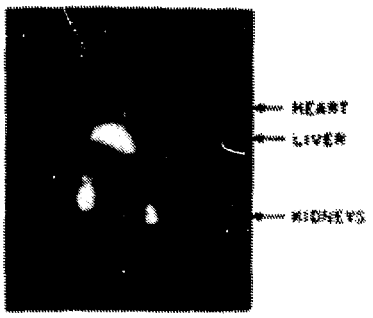
Patient M. C. Abnormal myocardial perfusion images with obstruction of the right coronary artery and the anterior descending branch of the left coronary artery. The composite images of the coronary perfusion patterns show two distinct regions of diminished perfusion (arrows). The larger region of reduced perfusion in the posterolateral aspect of the left ventricular wall (double arrows) does not appear to derive collateral flow via the right coronary circulation. Pronounced cardiac enlargement is also seen.

RABBIT SCINTIPHOTOS WITH THALLIUM-201



15 MINUTES

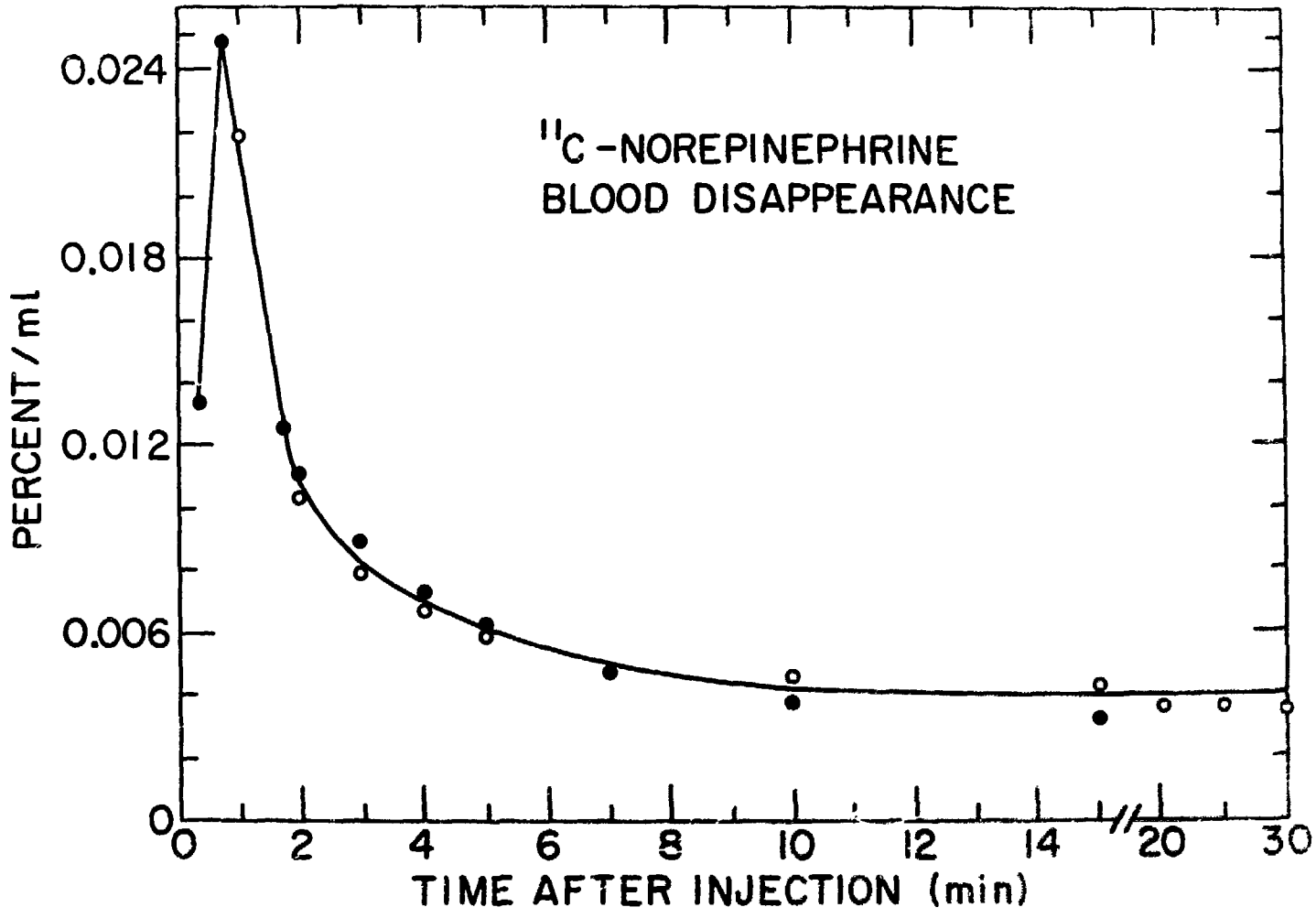
15 MINUTES



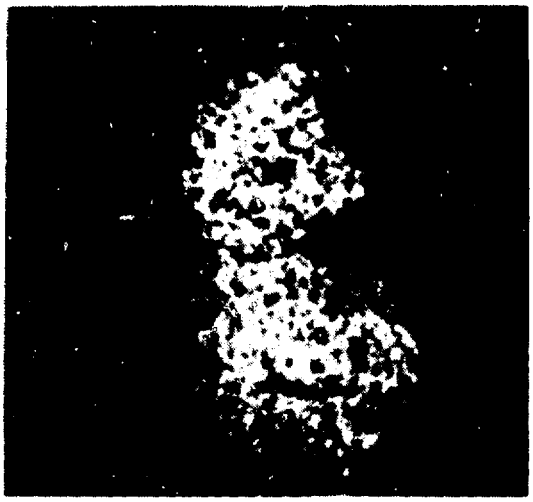
2 HOURS

THALLIUM ^{201}

IMAGED IN ISOLATED GOAT HEART


0.024
0.018
0.012
0.006
0
PERCENT / ml
^{11}C -NOREPINEPHRINE
BLOOD DISAPPEARANCE
0
2
4
6
8
10
12
14
20
30
TIME AFTER INJECTION (min)

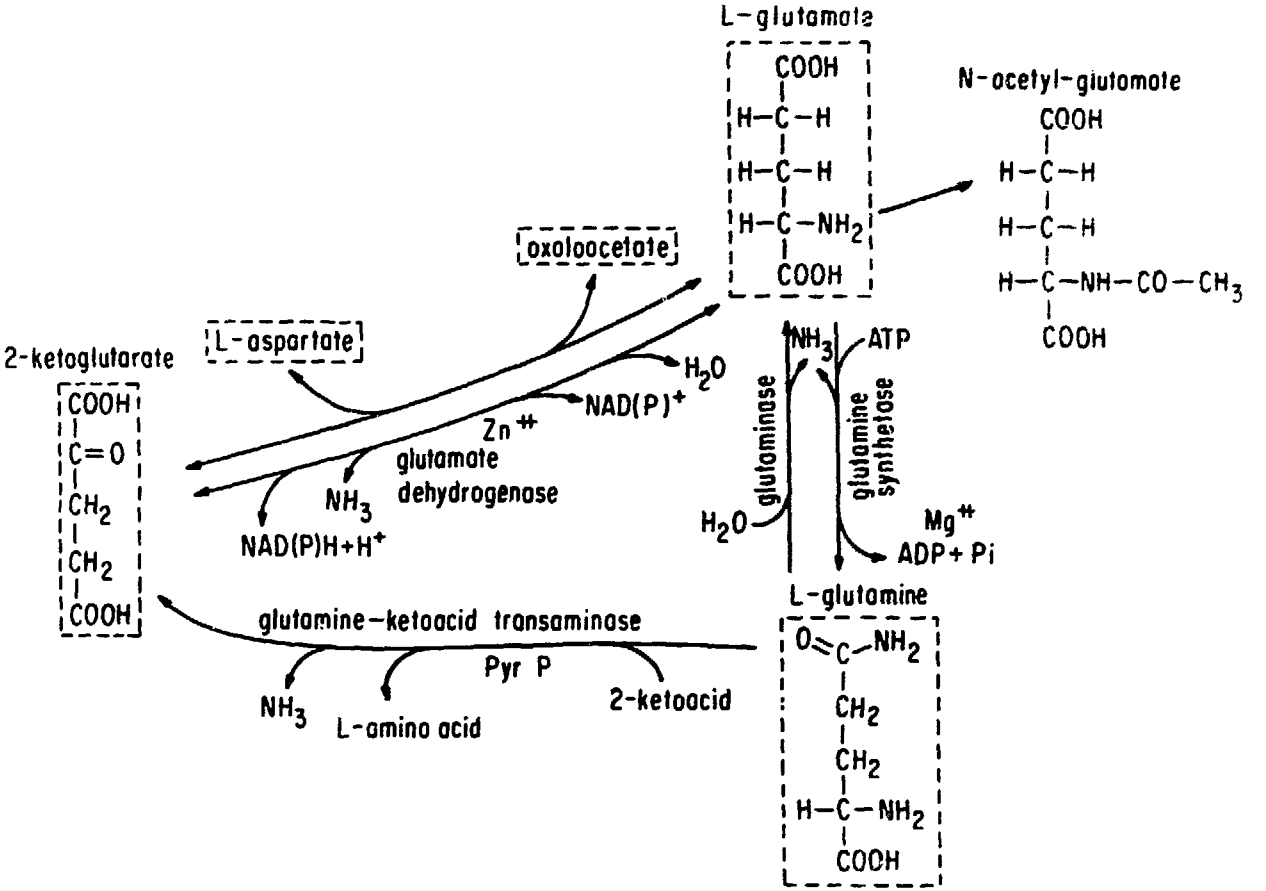
ANTERIOR



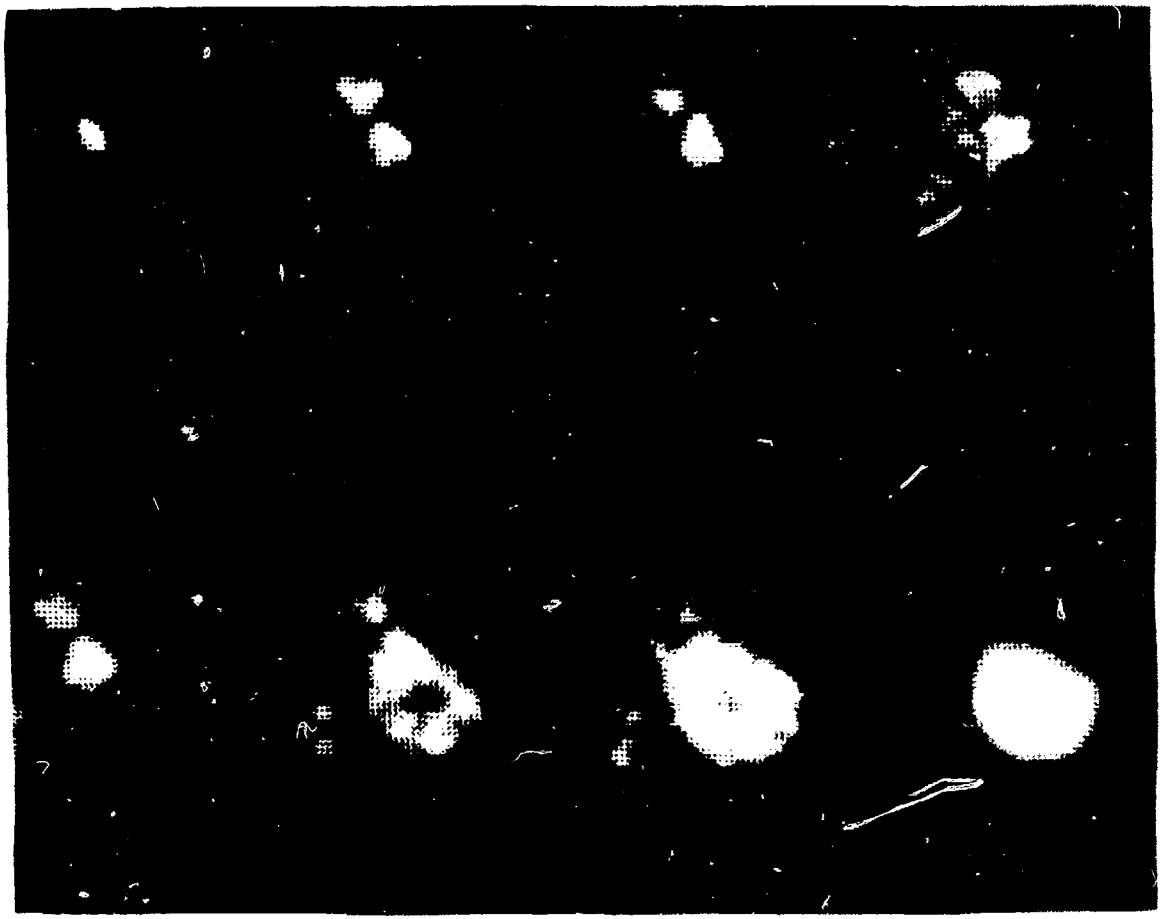
X-RAY

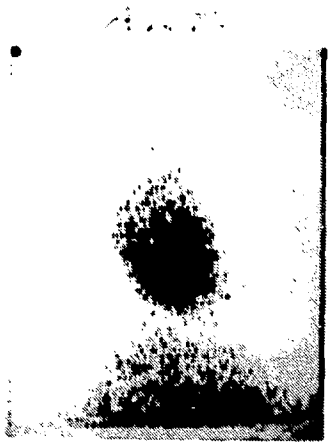
HEART SCAN

L. LATERAL VIEW



INCORPORATION OF $^{13}NH_3$ IN THE MYOCARDIUM





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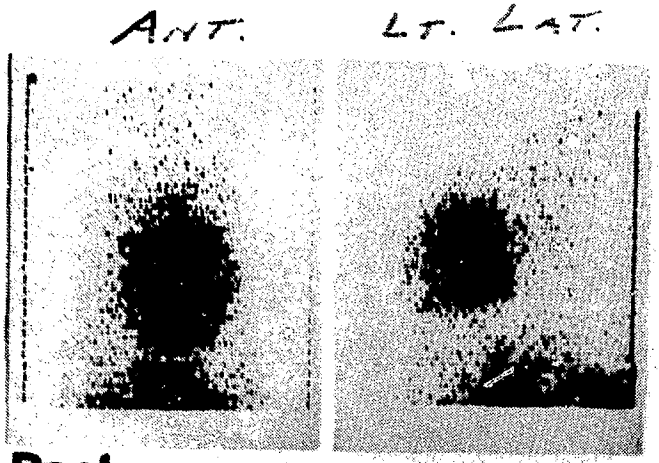

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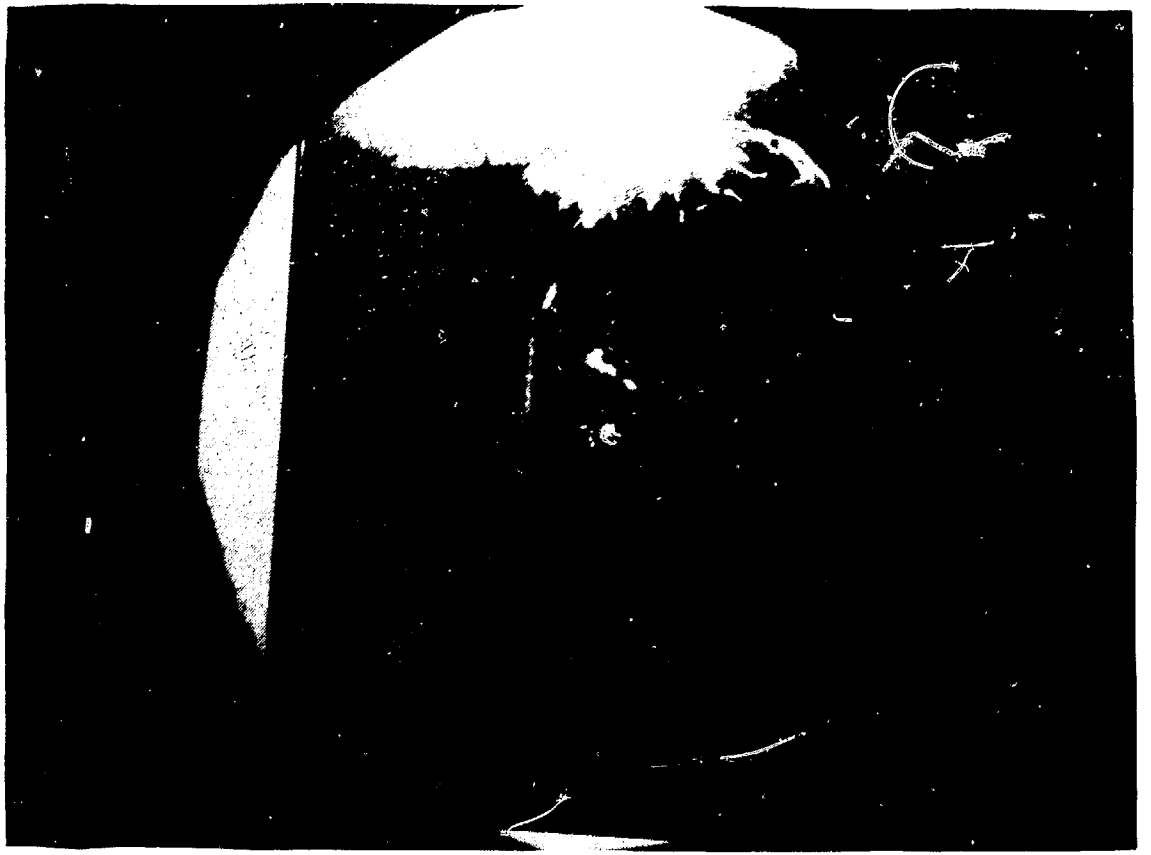
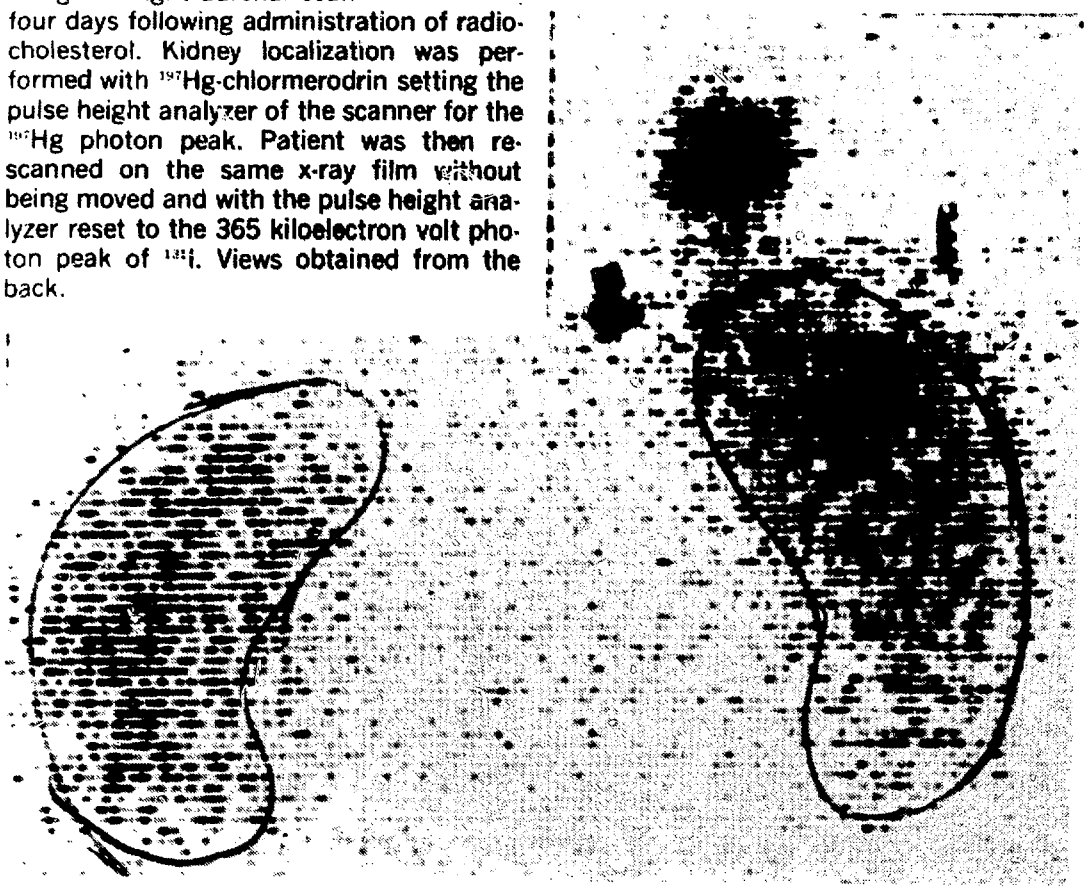
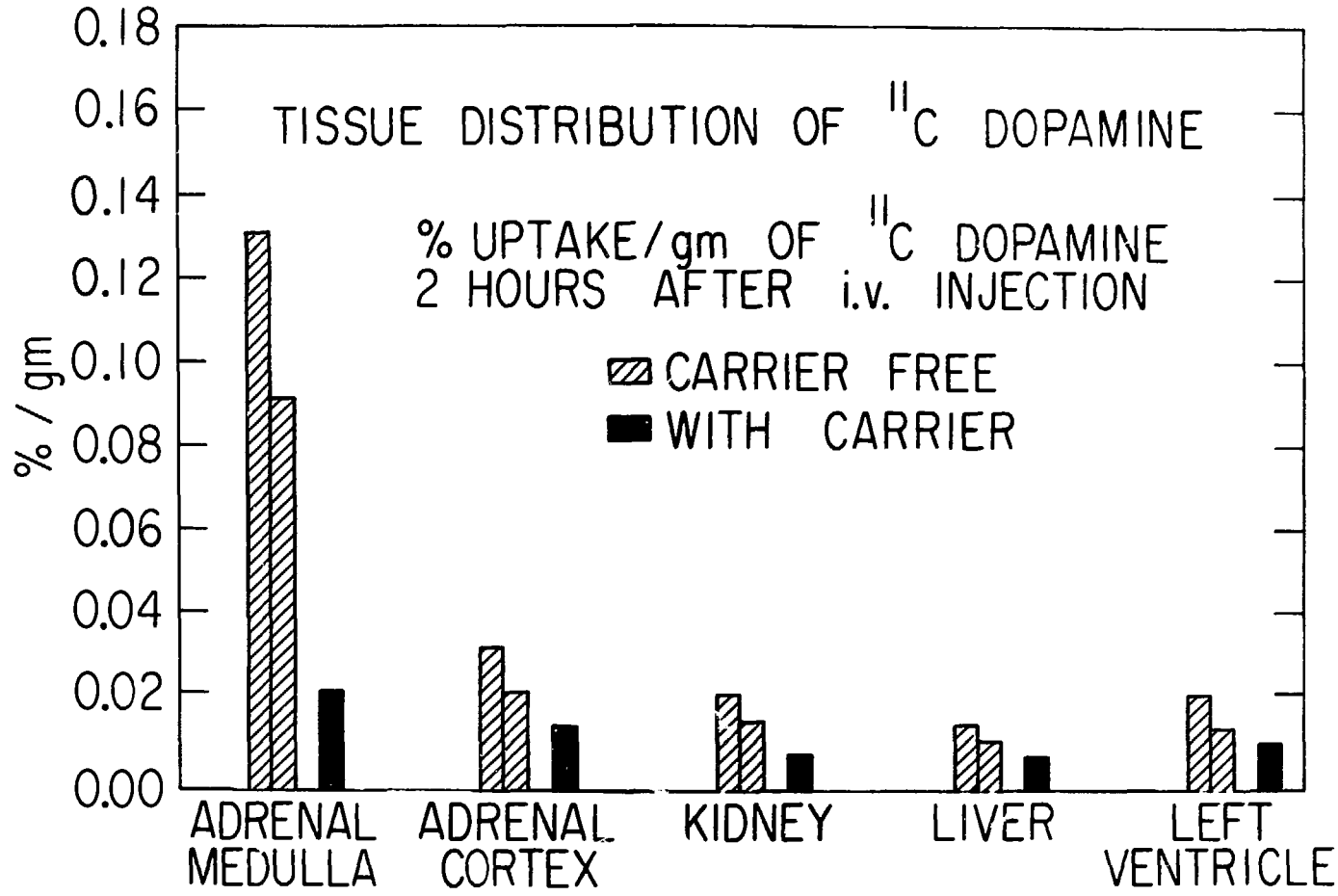
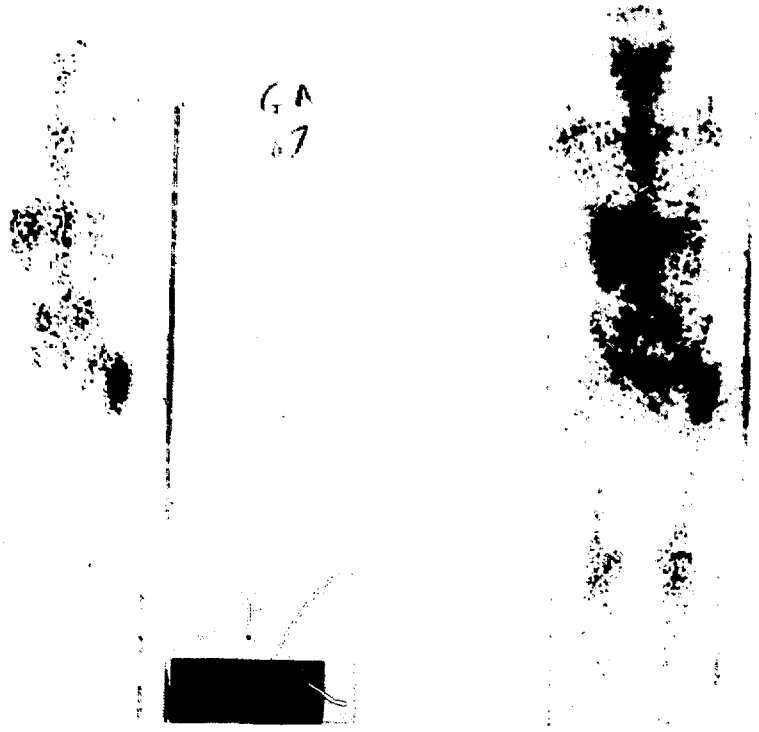


Fig 2.—Right adrenal scan four days following administration of radiocholesterol. Kidney localization was performed with ^{197}Hg-chlormerodrin setting the pulse height analyzer of the scanner for the ^{197}Hg photon peak. Patient was then rescanned on the same x-ray film without being moved and with the pulse height analyzer reset to the 365 kiloelectron volt photon peak of ^{131}I. Views obtained from the back.




TISSUE DISTRIBUTION OF ^{11}C DOPAMINE
% UPTAKE/gm OF ^{11}C DOPAMINE
2 HOURS AFTER i.v. INJECTION
CARRIER FREE
WITH CARRIER
% / gm
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
ADRENAL MEDULLA
ADRENAL CORTEX
KIDNEY
LIVER
LEFT VENTRICLE



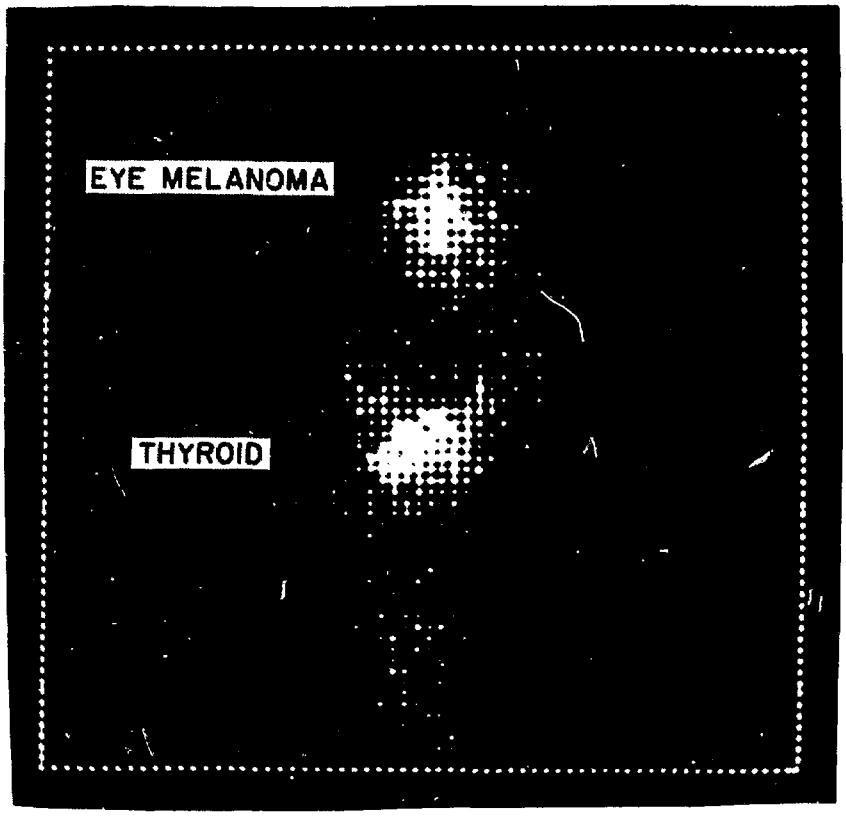

EYE MELANOMA
THYROID

Table 1

Physical Characteristics

Isotope	Half-life	Emission (MeV)
^{42}K	12.42 hr	γ 1.52
		β^- 3.52, 2.0
^{43}K	22 hr	γ 0.374, 0.619, 0.22-1.01
		β^- 0.83, 0.46-1.82
^{13}N	9.99 min	β^+ 1.19
^{129}Cs	32.3 hr	γ 0.37, 0.41, 0.55
^{131}Cs	9.69 d	γ .029
^{201}Tl	73 hr	γ 0.167, 0.165, 0.135
		(X rays from Hg) .068-.082
^{204}Tl	3.80 yr	β^- .763
^{202}Tl	12.2 d	γ 0.44, 0.96, 0.52
^{11}C	20.4 min	β^+ 0.97
^{82m}Rb	6.4 hr	e,β^+ 0.80
		γ 0.777, 0.554, 0.619, 0.698, 1.475
^{82}Rb	1.25 min	β^+ 3.5
		γ 0.777, 1.41
^{84m}Rb	20 min	γ 0.249, 0.88
^{84}Rb	33.0 d	β^+ 0.80, 1.65
		γ 0.880, 1.01, 1.90
		β^- 0.89
^{86m}Rb	1.0 min	IT 0.56
^{86}Rb	18.66 d	β^- 1.78, 0.71
		γ 1.08

TABLE II

Iodine-123 Disintegration Data

$T_{1/2} = 13.3$ hr

Gamma energy (MeV)		No./disintegration
	0.159	0.835
	0.530	0.020
$K_{\alpha-1}$	0.0275	0.472
$K_{\alpha-2}$	0.0272	0.242
$K_{\beta-1}$	0.0310	0.127
$K_{\beta-2}$	0.0318	0.026
	0.0038-0.504	0.13-0.0014
Electrons		
K int. con.	0.1272	0.134
Others	0.008-0.158	2.18-0.005