ABSTRACTS OF WORKS IN PROGRESS PAPERS

PRESENTED AT 19TH ANNUAL SNM MEETING

Clinical Evaluation of a Simplified Indirect Method of Measuring Serum Free Thyroxine (T_4) BY CYNTHIA M. ABREAU AND LEWIS E. BRAVERMAN, St. Elizabeth's Hospital, Boston, Mass.

The concentration of free or non-protein-bound T_4 in serum accurately reflects thyroid gland function, as contrasted to total serum T_4 concentration which is influenced by the concentration of the major T_4 binding protein (TBG) and the secretion of T_4 by the thyroid. Various methods for measuring free T_4 in serum have been described. The direct measurement is laborious and time consuming while most indirect methods, such as the free T_4 index (FTI), require two tests, a total T_4 or PBI and a T_3 uptake. An isotopic displacement technique for measuring serum T_4 has recently been described, employing small Sephadex columns. This method has been adapted for the one-step determination of the FTI which accurately evaluates thyroid status irrespective of variations in serum TBG concentration. By using a portion of the patient's serum to help elute ^{125}I-T_4 from the Sephadex column, the serum binding capacity also becomes a factor in the percent retention of ^{125}I-T_4 on the column. The unknown serum is compared with a concomitantly assayed reference standard. The method requires 0.32 ml of serum and 26 tests can be performed in 1 hr. The present method was compared with the standard FTI ($T_4 \times T_3$ uptake) in 62 euthyroid (N), 20 thyrotoxic (T), 21 myxedemic (M), 10 pregnant (P), and 5 subjects with absent serum TBG (A). The two methods gave similar results. Mean values (±s.d.) for the present index were: E, 1.01 ± 0.13; T, 1.61 ± 0.20; M, 0.22 ± 0.09; P, 1.00 ± 0.10; A, 0.57 ± 0.07. No patients with T or M had values in the normal range, while all P patients were normal. The present method for indirectly measuring free T_4 concentration is simple, rapid, accurate, and reproducible.

Evaluation of Exhaled $^{14}CO_2$ Patterns after Ingestion of ^{14}C-Labeled Fat as a Test for Malabsorption BY MOHAMED A. ANTAR, RICHARD P. SPENCER, AND HENRY BINDER, Yale University School of Medicine, New Haven, Conn.

To assess the specific activity of expired $^{14}CO_2$ after ingestion of ^{14}C-labeled fat as a test in fat malabsorption, we studied eleven normal subjects and 22 patients divided into three groups (11 patients with true malabsorption due to nontropical sprue or massive intestinal resection, 6 patients with digestive disorders such as chronic pancreatitis, 5 patients with treated nontropical sprue). After an overnight fast, 5 μCi of radiolabeled fat, 1-^{14}C-sodium palmitate (NaP), and/or ^{14}C-tripalmitate (TP) mixed with 1 meq/kg body weight of the carrier were given orally. At hourly intervals for 8 hr, subjects breathed into a tube connected to a vial containing a known amount of CO_2 absorber (Hyamine-OH) (R). Three parameters, the maximum specific activity of $^{14}CO_2$ as percent dose $\times 10^{-4}$/mmole CO_2, the area under the curve and the percent dose of cumulative $^{14}CO_2$ exhaled for 6 hr (based on the calculated body surface area and basal metabolic rate) were compared with the fat absorption coefficient (FAC) as determined by fat intake and fecal fat (chemically determined). The results for NaP are given in the table below.

There were significant differences between the controls and those with true intestinal malabsorption ($p < 0.01$) for the parameters studied. The cumulative $^{14}CO_2$ as percent dose was found to have the highest correlation with the fat absorption coefficient for controls and intestinal malabsorption ($r = 0.84$

Parameter	Peak value	Area	% $^{14}CO_2$	FAC
Controls	41.42 ± 10.18	15.58 ± 3.06	12.76 ± 2.51	96.8 ± 2.3
Intestinal malabsorption	19.58 ± 7.45	8.01 ± 2.74	5.81 ± 1.70	72.2 ± 9.5
Digestive disease	53.22 ± 13.08	19.33 ± 5.54	12.52 ± 3.65	80.1 ± 8.1
Treated sprue	67.26 ± 11.07	20.78 ± 3.78	14.48 ± 3.02	93.4 ± 2.3

and regression line $y = 9.98 + 2.23x$, where x is fat absorption coefficient). Patients with digestive disease showed significantly low $^{14}CO_2$ values after TP but normal values after NaP ($p < 0.01$ for the parameters). The correlation coefficient between fat absorption and cumulative $^{14}CO_2$% was highly significant ($r = 0.90$, $p < 0.001$). The findings suggest that expressing the results in terms of cumulative $^{14}CO_2$ as percent dose exhaled, based on body surface area and BMR, increased the sensitivity and accuracy of the test. The $^{14}CO_2$ specific activity and accuracy of the test. The $^{14}CO_2$ specific activity of the breath after ^{14}C-sodium palmitate and tripalmitate may serve as a simple, adequate test in malabsorption. (Supported by Grant Nos. USPHS CA-06519 and Conn. Heart Assoc. No. 437.)

Fresnel Zone Plate Imaging with X-Ray Film Cassettes BY H. H. BARRETT, G. D. DEMEESTER, AND D. T. WILSON, Raytheon Research Division, Waltham, Mass.

The use of a Fresnel zone plate as a high-efficiency aperture for an Anger camera has been previously reported (*J Nucl Med* 13: 382–385, 1972). The zone plate has a collection efficiency two or three orders of magnitude greater than conventional direct-imaging pinholes and collimators but results in the detection of a coded image. The decoding is accomplished with a laser beam as in optical holography. However, the spatial resolution obtainable with this system is limited, in practice, to about 15 mm.

We have recently begun to evaluate standard x-ray film cassettes as an alternative to the Anger camera in this application. Of course, film is much less sensitive than an Anger camera, but this disadvantage is partially offset by the high collection efficiency of the zone plate. Good quality images can therefore be obtained with reasonable exposures (<30 mCi-min). We have achieved resolutions of 5 mm and are working towards 2.5 mm with ^{99m}Tc sources.

As in ordinary optical holography, three-dimensional information about the object distribution is recorded on a single film. Different tomographic planes can be selected for viewing simply by changing a lens position in the optical decoding system. The depth of field is only a few millimeters.

Representative images of various phantoms will be presented.

Development of ^{201}Tl for Medical Use BY E. BELGRAVE AND E. LEBOWITZ, Brookhaven National Laboratory, Upton, N.Y.

We are developing ^{201}Tl for use in medicine beginning with its evaluation as a myocardial scanning agent.

The properties of ^{201}Tl are well suited for use as a myocardial scanning agent. As reported by Harper in suggesting radiothallium for use in myocardial visualization, the biological behavior of thallium is similar to potassium. Thallium-201, which decays by electron capture, emits Hg x-rays (~70–80 keV), and photons of 135 and 167 keV in 10% total abundance; therefore it has good imaging characteristics without excessive patient radiation dose. The 73-hr half-life gives this radiopharmaceutical a good shelf-life for emergency use.

The medical use of thallium requires a high radioisotopic purity to minimize high-energy photons and long-lived impurities arising from contaminants. Furthermore, due to the high toxicity of thallium, a high-specific activity is of prime importance.

The production technique which we have developed satisfies the above criteria. Our method involves the irradiation of a thallium target with protons to give the reaction ^{203}Tl(p,3n)^{201}Pb. The ^{201}Pb decays to ^{201}Tl which is obtained carrier-free. The production rate is estimated to be ~0.5 mCi/μA-hr with natural thallium as the target. The separation is carried out in two stages. First the thallium target material is affixed to an ion-exchange column while complexed lead activity is eluted. The lead, in turn, is fixed to another ion exchange column from which the thallium is milked. Through careful choice of target thickness and incident proton energy, as well as by timing of the chemical separations, radioisotope purity of better than 99% is obtained.

Results in animals will be presented and clinical evaluations will follow. (Performed under the auspices of the USAEC.)

^{117m}Sn Complexes for Skeletal Imaging BY L. RAO CHERVU, M. D. BLAUFOX, W. C. ECKELMAN, AND P. RICHARDS, Albert Einstein College of Medicine, Bronx, N.Y., and Brookhaven National Laboratory, Upton, N.Y.

The use of Sn(II) for reduction of ^{99m}Tc produces complex intermediaries, the exact nature of which is not known. The physical characteristics of the short-lived ^{99m}Tc are well known, and its biological distribution has been widely studied, but localization of tin and its biological disposal in these preparations is unclear. The use of radionuclides of tin alone for diagnostic purposes has not been explored adequately. The present study is directed towards an assessment of the application of ^{117m}Sn as a skeletal imaging agent and other uses in clinical nuclear medicine.

The ^{117m}Sn ($T_{1/2}$ = 14 days, gamma energy 158

keV, 87% abundance) can be produced through the neutron irradiation of enriched ^{116}Sn isotope, but the cross section for this reaction is not favorable for forming the high spin isomeric state. Helium ion bombardment of enriched ^{114}Cd leads to the formation of ^{117}Sn through the α,n reaction, and it is estimated from the reaction systematics that the total cross section would be of the order of 250 mb and the high spin isomer formation cross section greater than 150 mb with alpha bombarding energy of about 15 MeV. This is an energy range easily available at all medical cyclotron facilities. The subsequent radiochemical separation and recovery of the desired radionuclide from the enriched target presents few problems.

The introduction of STPP and polyphosphate complexes of ^{99m}Tc has spurred interest in the preparation of similar complexes of ^{113}Sn as a preliminary to the application of ^{117m}Sn as a possible radionuclide in skeletal imaging. Complexes of ^{113}Sn with STPP and NaH_2PO_4 with varying ratios of reagent/Sn were prepared, and the biological distribution of each preparation was studied in three mice following the administration of 0.1 ml of the preparation. After 1-hr intervals, the wet organs were removed and weighed; the activities were measured after 1 day to determine the distribution of ^{113}Sn. At a mole ratio of PO_4/Sn of 495, typical organ distribution data are: 0.8, 2.1, 0.6, 0.7, and 15% of activity per mouse per gram in blood, kidney, liver, lungs, and bones, respectively. The distribution data with other complexes are similar. It appears that these Sn complexes have good bone-seeking properties with very little blood, kidney, liver, or lung background. From the absorbed dose calculations, the radiation dose to the skeleton is estimated to be 14 mrad/μCi, for ^{117m}Sn which is less by a factor of two than ^{85}Sr. The additional advantage of higher detection efficiency and ease of production would seem to offer many advantages over other longer-lived radionuclides suggested as potential skeletal imaging agents. A comprehensive study of the mechanism of localization of the complexes of tin in each technetium preparation should lead to an insight of the pharmacokinetics of the Tc-Sn complexes, enabling the development of better ^{99m}Tc radiopharmaceuticals. (Performed under the auspices of the USAEC.)

New Radiopharmaceuticals for Thrombosis Localization BY MARY ANN DUGAN, JOHN J. KOZAR, GERALD GANSE, AND CURT QUAP, Temple University School of Pharmacy, Philadelphia, Pa.

The search for an effective radiopharmaceutical for localization of deep venous thrombosis has resulted in the development of such agents as ^{125}I-fibrinogen, ^{131}I-fibrinogen, and ^{131}I-streptokinase. In addition to these agents, we have been investigating in our laboratories the use of ^{111}In-fibrinogen, ^{99m}Tc-streptokinase, and ^{99m}Tc-leukocytes for identification of actively forming and pre-existing thrombosis using scanning techniques.

Comparative scintiscans will be presented which demonstrate the use of these radiopharmaceuticals in dogs where deep femoral thrombi have been surgically produced with contiguous sham procedures in the opposite femoral vein. The use of ^{111}In as a label for fibrinogen allows for increased administered radioactivity with diminished radiation absorbed dose to the patient. Indium-111-fibrinogen lays down in actively forming thrombosis. The development of ^{99m}Tc-streptokinase as a localizing agent for pre-existing thrombosis was undertaken for essentially the same reason—increased photon flux at the site with decreased patient dose—when compared to ^{131}I-streptokinase.

The use of ^{51}Cr-WBC for localization of thrombosis has been reported in the literature. We felt that using ^{99m}Tc as the label for leukocytes would allow scanning procedures to be employed and thus would offer more diversity and flexibility in using leukocytes as the transport and localizing agents for identification of thrombosis.

The ratio of activity per milligram clot to activity per milligram whole blood is greater than 10 for each agent. Clottability of ^{111}In-fibrinogen is 90–92%. The basic procedure of an acid reduction of pertechnetate using stannous chloride is used for the radioactive labeling of both the streptokinase and autologus leukocytes. The general procedure for labeling fibrinogen with ^{111}In or ^{113m}In is as follows: to 1 ml of 1 *M* acetate buffer, 0.1 ml of 0.1% tween 80, 1 ml of 0.5 *N* NaOH and 1 ml acidic-indium, 1.5 ml of 0.05 *M* Borax solution, and 10 mg of fibrinogen are added. The vial is incubated with shaking at 37° for 30 min. The labeling yields of each radiopharmaceutical range between 60 and 95% of the initial activity. This report will describe and compare the biological activity of ^{99m}Tc-streptokinase, ^{99m}Tc-WBC, and ^{111}In-fibrinogen in dogs, comparing uptake of the radiopharmaceuticals at the site of the thrombosis, resolution of scintiscans using the radioactive drugs, and optimum scanning procedures employed for each agent. (NIH Grant No. 535-286-61.)

Clinical Myocardial Imaging with ^{13}N-Ammonia BY P. V. HARPER, J. SCHWARTZ, L. RESNEKOV, P. HOFFER, H. KRIZEK, V. STARK, N. LEMBARES, AND K. LATHROP, University of Chicago and The Argonne Cancer Research Hospital, Chicago, Ill.

The report of Hunter and Monahan of the myocardial localization of the 10-min positron emitter ^{13}N as carrier-free ammonia led us to explore the use of this material as a clinical scanning agent. Thirty-eight subjects have been studied, 15 normals and 23 patients with histories suggesting myocardial infarction. The ^{13}N-ammonia was produced by the method described by Tilbury, et al of bombarding methane with 8-MeV deuterons and recovering the ammonia by bubbling the methane flowing from the target chamber through isotonic saline. Intravenous injection of 10 mCi gave good clinical images using a Nuclear-Chicago H.P. Anger camera and a special high-energy collimator. The total-body absorbed radiation dose is ~50 mrad. Count densities of 4,000–5,000/cm^2 over the normal myocardium were easily attained. The use of tungsten for the collimator material improves the images substantially by reducing the collimator pattern and increasing the sensitivity twofold without degradation of the geometric resolution or increase in septal penetration. Nitrogen-13 entering the heart remains fixed during the 30-min period of observation in humans and mice (~2% of the injected ^{13}N). The blood disappearance curve of the tagged ammonia is very rapid, 85% leaving the circulation in the first minute. In heavy smokers the lung activity may persist at a high level for 10–20 min, somewhat obscuring the heart image. Preliminary clinical observations indicate that patients with substantial clinical and laboratory manifestations of myocardial infarction had defects in their myocardial images which were sometimes surprisingly large. On the other hand, patients with definite ECG changes without enzyme changes or marked clinical signs often had slight or negligible defects in their myocardial images. The obvious utility of the myocardial scan thus appears, at this point, to be a noninvasive method for early screening of patients with presumed infarcts to determine the extent of the lesion and to allow early institution of aggressive therapy before the onset of cardiogenic shock in patients with massive lesions.

Radioimmunoassay of α-Fetoprotein BY HIDEMATSU HIRAI, SHINZO NISHI, AND HIROYUKI WATABE, School of Medicine, University of Hokkaido, Sapporo, Japan.

α-fetoprotein (α_f), a specific fetal serum α-globulin, appears specifically in the serum of patients with hepatoma so that the detection of α_f is very valuable for the diagnosis of the liver cancer.

The conventional assay method at present relies mostly on the precipitin reaction in agar gel, the sensitivity of which is approximately 10 μg/ml, and α_f was detected in 70% of hepatoma patients by the method.

More sensitive methods are now required to diagnose the disease in the earlier stage and to analyze more precisely the phenomenon of occurrence of this protein. The radioimmunoassay technique was developed for this purpose.

α_f of human or rat was highly purified and crystallized. The chemical and physicochemical properties investigated were quite close to those of serum albumin, e.g., sedimentation constant 4.5 S, mol.wt. about 65,000, isoelectric point 4.7, and sugar content less than 3%.

The purified α_f was labeled with ^{125}I, and the radioimmunoassay was designed using a double antibody technique. The sensitivity was about 2 mμg/ml which is about 5,000 times more sensitive than that of the conventional precipitin method.

From about 100 cases examined by radioimmunoassay of α_f the following results were obtained: (A) α_f was found in 90% of the hepatoma patients in Japan. The α_f plasma level of the patients was distributed as widely as from 2 mμg/ml to 10 mg/ml. Ten percent of the patients remained negative. From the results we classify the hepatoma into two types, i.e., α_f-producing and α_f-nonproducing hepatoma. (B) α_f was also found in low concentration among metastatic liver cancer patients (20%). (C) α_f was detected in low concentration among the patients with hepatitis, liver cirrhosis, and in pregnant women. (D) The appearance of α_f in the blood of rat during hepatocarcinogenesis by feeding an azo dye, DAB, was precisely followed up, and was found that α_f appeared transiently in the early stage of the feeding before the development of hepatoma.

From these clinical and experimental observations a possible correlation between hepatoma and cirrhosis and/or hepatitis was found.

α-Fetoprotein (α_f) Radioimmunoassay as a Useful Aid for Liver Scan Reading BY MASAHIRO IIO, HIDEO YAMADA, KAZUO CHIBA, YASUHITO SASAKI, AND MASAHIKO IUCHI, Tokyo Yoikuen Hospital, University of Tokyo Hospital and Kofu Municipal Hospital, Tokyo, Japan.

Liver scintigraphy is useful for the diagnosis of hepatic malignancy. However, lack of specificity of the scintigram with regard to the nature of space-occupying lesion is also emphasized. Biochemical data of liver function are also neither sensitive nor specific for the diagnosis of liver malignancy.

α-fetoprotein (α_f), a specific fetal serum α-globulin, appears specifically in the serum of patients with hepatoma, so that the detection of α_f is very valuable for the diagnosis of liver cancer. The conventional

assay method at present relies mostly on the precipitin reaction in agar gel, the sensitivity of which is approximately 10 μg/ml, and α_f was detected in 70% of hepatoma patients by the method. Therefore more sensitive methods are required to diagnose the disease in the earlier stage and to analyze more precisely the time course of occurrence of this protein. Thus the radioimmunoassay technique was applied for this purpose.

The purified α_f (with molecular weight approximately 65,000, isoelectric point, 4.7) was labeled with ^{125}I, and the radioimmunoassay was performed by a double antibody technique. The sensitivity was 2 mμg/ml. This is about 5,000 times more sensitive than that of the conventional precipitin method. This radioimmunoassay method enabled us to detect 90% of hepatoma among cases examined. Cases with liver cirrhosis, hepatitis, and pregnancy are found to have a low amount of α_f in the plasma.

Combined evaluation of liver scanning and radioimmunoassay of α_f was performed. In our preliminary study on 300 cases, it became evident that combined use of α_f radioimmunoassay and liver scanning created definite improvement of the diagnosis of the nature of hepatic lesions.

The results obtained were as follows: (A) α_f was found in 90% of the cases with hepatoma ranging from 2 mμg/ml to 10 mg/ml. (B) Followup study revealed the continuous increase in an amount of α_f in cases with hepatoma. This indicates that the careful observation of cirrhotic case enabled us to diagnose hepatoma early. (C) Cases with nondetectable, small space-occupying lesion frequently showed increased α_f, which is backed either by followup study or autopsy to be due to hepatoma. (D) The nature of doubtful space-occupying lesion of the liver was able to be differentiated.

In conclusion, by the addition of α_f radioimmunoassay to conventional liver scanning more accurate diagnosis of the space-occupying lesion of the liver became possible. This new immunoassay is especially useful for the diagnosis of early or latent hepatomas undetectable by scintigraphy and hepatomas in the deformed liver.

Experimental Communicating Hydrocephalus: Preliminary Results BY A. EVERETTE JAMES, JR., Johns Hopkins Hospital, Baltimore, Md.

Communicating hydrocephalus was produced by a catheter technique for injection of a mixture of silastic (silicone) and a small amount of pantopaque selectively in the anterior cisterns and parasagittal area of eight mongrel dogs. Following the injection of silicone, communicating hydrocephalus developed in 14 days to 4 weeks. Serial cisternograms and monitoring of radiopharmaceutical transfer from the subarachnoid space into the blood were used to detect communicating hydrocephalus.

Pathologically there is gross ventricular dilatation with the silicone distributed as a rubbery mass mainly over the cerebral hemispheres and in the parasagittal area. On histological sections the parasagittal subarachnoid space is obliterated and some inflammatory reaction in this region is present. Autoradiographs (^{131}I) demonstrate that, in the normal animal, radioactive material (seen as grains) are infrequent in the ventricular lining and choroid plexus. No radioactivity is present in the periventricular area of normal animals. In animals with hydrocephalus, a large amount of radioactivity is present in the ependymal lining and choroid plexus of the lateral ventricle. Radioactivity is present in the periventricular tissue and surrounding the cerebral veins.

At various time intervals after subarachnoid injection the percentage of the total radioactivity in the animal plasma is measured. Blood samples are obtained (at 1, 2, 4, 6, 8, 12, 24, and sometimes 48 hr), and the amount present is determined by counting in a well counter (corrected for distribution). Comparing normal animals (controls) and animals before development of hydrocephalus (animals serving as their own controls), the radiopharmaceutical transfer from the subarachnoid into the intravascular compartment is decreased for the time periods measured (thus delayed) in communicating hydrocephalus.

These findings suggest that with communicating hydrocephalus the lining of the ventricle changes structurally and may change in its function. Transependymal migration of the labeled albumin suggests that the ependymal lining may be participating in CSF absorption. If this is correct, it would explain the "reversal" of CSF flow and "stasis." The development of an experimental model makes extension of these preliminary studies possible.

Improved Spatial Resolution from Scintillation Cameras Using Electronic Signal Processing and a Movable Filter Plate BY RONALD J. JASZCZAK, Nuclear-Chicago Corp., Des Plaines, Ill.

A method is discussed which significantly improves the spatial resolving power of the overall system when used in conjunction with an Anger scintillation camera. By systematically sampling selected and isolated regions of the scintillator (with a movable filter hole plate) and executing an electronic correlation and manipulation of the resultant signals (on an event-by-event basis), it is possible to resolve a 1/8-in. lead bar phantom when placed near the surface of the system. A 3/16-in. bar phantom can be

resolved when placed at a distance of 4 in. from the system surface. Due to the radiation filter the sensitivity of the system is approximately 30% of the normal collimator-scintillator camera system sensitivity.

A Computerized Scintigraphic Technique for Performing Dynamic Studies of the Right and Left Heart BY D. L. KIRCH, P. P. STEELE, R. S. TROW, D. C. VAN DYKE, AND D. H. DAVIES, Veterans Administration Hospital, Denver, Colo.

A method for performing radionuclide angiocardiography is described which allows accurate determination of atrial and ventricular volumes and assessment of cardiac function while encountering less invasiveness than with contrast angiographic techniques. Two significant difficulties must be overcome in order to extract time-activity curves from dynamic scintigraphic data which are indicative of the true washout characteristics of the individual cardiac chambers. These two problems are defined and accommodated as follows: (A) To identify and quantitate regurgitation, it is necessary to present both the right and left atria of the heart with a reasonably good bolus of radionuclide. This is accomplished by using two separate injections of a radionuclide with the catheter positioned in the pulmonary artery wedge and the superior vena cava, respectively. (B) The time-activity washout curves are degraded by "cross-talk" from isotope which enters adjacent anatomical structures. Therefore a semi-annular background area of interest is defined for each chamber and the corresponding background time-activity curve is subtracted from each chamber washout curve prior to analysis.

The procedure is performed with the patient in the RAO position. A bolus of 6 mCi of $^{99m}TcO_4^-$ followed by a saline flush is administered through a Swan-Ganz catheter placed in the pulmonary artery wedge position. The catheter is then withdrawn to the superior vena cava, and a second injection is made. Following each injection, sequences of images are collected for 25 sec at a rate of 10 frames/sec using an Anger scintillation camera interfaced to a PDP-12 digital computer. The computer is then used to define areas of interest coincident with the four heart chambers and the associated background areas. The time-activity curves are then extracted and analyzed following subtraction of the time-varying background activity.

By means of this technique we have studied 35 patients immediately after cardiac catheterization. Computer analysis allows accurate determination of cardiac output, stroke volume, ejection fraction, forward ejection fraction, and atrial, ventricular, and regurgitant volumes. Cardiac output is obtained by indicator dilution technique. Left ventricular ejection fraction and end diastolic and systolic volumes have been determined by three methods which correlate well: (A) beat-to-beat analysis of systolic/diastolic ratios of the ventricular radionuclide concentration over several cardiac cycles, (B) single exponential fitting of the ventricular washout curve, and (C) computer analysis of the left ventricular cine-angiogram using the longest-chord ellipsoid formula. The presence of regurgitation is indicated by a discrepancy between the beat-to-beat ejection fraction and the forward ejection fraction which is determined from the exponential fit of the chamber washout curves. A measure of tricuspid and mitral regurgitation is obtained from the difference between the ejection fraction and the forward ejection fraction for the right and left atria, respectively. It is also possible to identify and quantitate aortic regurgitation in the presence of mitral regurgitation by applying the appropriate atrial-ventricular model to the data.

Our experience with this procedure indicates that it is possible to make accurate and repeatable determinations of cardiac chamber volumes and valvular competence by injecting radionuclide through a single venous catheter. (Supported by U.S. Veterans Administration research Grant No. 01/1103.1/69-01.)

Novel ^{18}F Intermediates for the Synthesis of Radiopharmaceuticals BY RICHARD M. LAMBRECHT, CONSTANCE MANTESCU, JOANNA S. FOWLER, AND ALFRED P. WOLF, Brookhaven National Laboratory, Upton, N.Y.

The advantages and potential medical applications of ^{18}F-labeled radiopharmaceuticals have been a topic of increasing interest. The $^{16}O(^3He,n)^{18}F$ and the $^{19}F(p,pn)^{18}F$ nuclear reactions on a water or a salt target (e.g. $LiBF_4$), respectively, are presently the popular nuclear reactions for producing ^{18}F. The limitation of the methods presently employed is that one obtains only ^{18}F as fluoride. Unfortunately drying carrier-free aqueous $^{18}F^-$, or the quantitative oxidation of $^{18}F^-$ is impractical. The synthesis of new compounds in high specific activity has thus been restricted by the limited chemical routes adaptable to the $^{18}F^-$ intermediate.

Many synthetic requirements for labeling ^{18}F-labeled radiopharmaceuticals can be met if new ^{18}F intermediates are available. We have initiated an investigation of the parameters affecting the synthesis of novel ^{18}F-fluorinating reagents. Use of the $^{20}Ne(d,\alpha)^{18}F$ and the $^{20}Ne(^3He,^4He,n)^{18}Ne$ (β^+, 1.5 sec)^{18}F nuclear reactions can be a source of multimillicurie quantities of high purity, carrier-

free, anhydrous ^{18}F. In addition, the $^{18}Ne(\beta^+)^{18}F$ nuclear transformation is a potential method for ^{18}F-recoil labeling in the absence of a high irradiation dose. With either nuclear reaction on neon, ^{18}F can be dynamically recovered as ^{18}F-F_2 or $H^{18}F$ if a scavenger concentration of F_2 or H_2 is present in the irradiation vessel. Further the ^{18}F from the neon target can be converted to aqueous fluoride by dissolution of $H^{18}F$ or by washing the walls of a static target.

We have developed a design of a nickel irradiation vessel, and the required passivation procedures to affect the efficient transfer of anhydrous ^{18}F from the target to reaction bombs in which radiopharmaceuticals can be prepared. Results of our experiments to synthesize intermediates such as ^{18}F-F_2, CF_3OF-^{18}F, IF_5-^{18}F, and carrier-free $H^{18}F$ and $^{18}F_2$ will be discussed. The integrity of the ^{18}F-labeled intermediates is verified by the synthesis of model compounds such as steroids and pyrimidines. For example, we have used F_2-^{18}F to synthesize 5-fluorouracil-^{18}F at a specific activity of 1.1 mCi/mg in >98% chemical purity and >87% overall chemical yield. The ^{18}F intermediate is prepared in situ during the cyclotron irradiation, and less than 40 min of workup time is required for the synthesis, purification, and delivery of the radiopharmaceutical. This study has shown that the nuclear reactions on neon facilitate the rapid preparation of new fluorinating reagents required for certain synthetic methods leading to new ^{18}F-labeled radiopharmaceuticals. (Performed under the auspices of the USAEC.)

Development of ^{99m}Tc-Mannitol for Renal Visualization BY E. LEBOWITZ, N. SOLOMON, N. SIDDHIVARN, J. STEIGMAN, M. DEGRAFF, S. LORBER, R. KAPPES, H. ATKINS, J. KLOPPER, P. RICHARDS, AND J. BARANOSKY, Brookhaven National Laboratory, Upton, N.Y., and Downstate Medical Center, State University of N.Y., Brooklyn, N.Y.

A very simple ^{99m}Tc preparation has been developed using $NaBH_4$ and mannitol which gives good kidney uptake and rapid background clearance in rabbits, thus allowing excellent kidney visualization with low radiation dose over a time span of hours, beginning from the time of injection. In addition, the nontoxicity of the materials used and the ability to inject at a pH close to physiological are further advantages.

The procedure involves simply mixing TcO_4^- in dilute HCl with mannitol and sodium borohydride and then injecting. Animal data are presented, demonstrating the excellent renal visualization obtained, and comparing this preparation with other preparations used for this purpose. Because of the promising animal results, clinical evaluations of this material are also planned. (Performed under the auspices of the USAEC.)

A Rapid Enzymatic Synthesis of 10-Min ^{13}N-glutamate and Its Pancreatic Localization BY N. LEMBARES, R. DINWOODIE, I. GLORIA, P. HARPER, and K. LATHROP, The Argonne Cancer Research Hospital, Chicago, Ill.

Nitrogen-13-labeled glutamic acid has been synthesized enzymatically and prepared for injection within 10 min after the production of $^{13}NH_3$ with the cyclotron by deuteron bombardment of methane. Its tissue distribution has been studied in mice and rabbits. In both species the concentration of ^{13}N by the pancreas is approximately three times that found for other nearby organs, making this material appear promising for imaging the pancreas. The synthesis is accomplished by the addition of NADPH, α-ketoglutarate, and L-glutamate-dehydrogenase (20 μmg of protein) to 4 ml of 0.2 *M* potassium phosphate buffer (pH 7.6) containing 100 mCi or more of $^{13}NH_3$. After 5-min incubation at 25°C and removal of protein and unreacted $^{13}NH_3$ by boiling and filtering the solution through a 0.2-micron membrane filter, about 8 mCi (15%) of the ^{13}N remains. At 20 min after intravenous injection of this preparation in the rabbit, concentrations of ^{13}N observed were: pancreas, 0.31; heart, 0.15; lungs, 0.12; kidney, 0.11; liver, 0.10; spleen, 0.10; intestine, 0.04; and blood, 0.2%/gm tissue. Organ distributions were: intestine, 12; liver, 11; stomach, 5; kidneys, 2.4; lungs, 1.6; heart, 1.3; spleen, 0.3; and pancreas, 0.4% of the injected ^{13}N. These values agree with those found with mice. The pancreas also concentrates ^{13}N from NH_4OH, but the observed values are approximately ⅔ those with glutamic acid, and pancreas-to-tissue ratios are lower. These relative organ concentrations are comparable to those achieved with ^{75}Se-L-selenomethionine. Higher counting rates should be achievable with ^{13}N because of the larger amounts of radioactivity that may be administered.

A Comparison of the Uptake and Disposition of Radioiron and ^{111}In-Chloride in Human Erythrocytes BY DAVID L. LILIEN AND LESLIE R. BENNETT, Center for the Health Sciences, University of California, Los Angeles, Calif.

During the course of studies comparing ^{111}In-chloride with ^{67}Ga-citrate in tumor localization, it was noted that the indium preparation was distributed within the skeleton in a pattern conforming to the expected normal marrow distribution. Furthermore, in patients receiving local marrow ablative

doses of radiation, the therapy ports were clearly demonstrated with decreased indium localization within the irradiated marrow-bearing areas. Since it is well known that trivalent indium is transported in plasma bound to transferrin, and since it appears to compete with iron for the same binding sites, it was postulated that indium was appearing in bone marrow by entering into at least the early metabolic pathways of iron transport and hemoglobin synthesis. Indium had previously been found by others to be taken up by mature red cells in small amounts and appeared subsequently to be present in the heme moiety of hemoglobin. Accordingly, a study of the characteristics of indium transport by both mature red cells and reticulocytes in comparison to iron was undertaken. Reticulocyte-rich red cells were obtained from patients with various hemolytic anemias and mature cells from type-matched normal donors. Incubations were performed using ^{59}Fe(III)- and ^{111}In(III)-labeled transferrin in normal plasma under various conditions. In all ways studied to date, the characteristics of uptake of both indium and iron are remarkably similar. There is an early rapid (essentially complete within 1 min) association of small amounts of both indium and iron with both mature red cells and reticulocytes, the association being consistently greater with reticulocytes than with mature cells. This association is not temperature-dependent and is not inhibited by a variety of inhibitors of energy metabolism. It would thus appear to represent an adsorption phenomenon, probably of the transferrin-metal complex to the membrane, reticulocytes apparently having a greater number of binding sites. After the first minute, the time course of uptake of both iron and indium are similar, mature cells taking up less than 10% of the label taken up by reticulocytes. This transport phenomenon is both temperature- and energy-dependent, the patterns of inhibition produced by various inhibitors being very similar for both ions. Once cell-associated, neither label is eluted by reincubation in unlabeled control plasma or in protein-free medium containing chelating agents which further indicate transport into the cell rather than membrane binding. Further studies on the intracellular disposition of the labels will be presented. These studies demonstrate that indium may be useful in certain hematological studies as a substitute for iron when the highly desirable imaging characteristics of ^{111}In may come into play, such as in marrow scanning. Further, a new clue as to the mechanism of indium (and perhaps even the chemically similar gallium) localization in tumors may come from these and similar studies which would improve their usefulness in the diagnosis and staging of malignant disease. [Supported by NIH Training Grant No. 5-T01-GM-01920-03 and AEC Contract No. AT(04-1) GEN12.]

Quantification of Left-to-Right Shunts by Radionuclide Angiocardiography in Children BY D. L. MALTZ AND S. TREVES, Children's Hospital Medical Center and Harvard Medical School, Boston, Mass.

A new method for quantification of left-to-right shunts using gamma function fitting of pulmonary time-activity histogram is described. Patients were prepared for the study with oral potassium perchlorate, 6 mg/kg body weight. No sedation was used. It was important that respirations remained regular and quiet. An anterior radionuclide angiocardiogram was obtained by injecting $^{99m}TcO_4^-$ (specific activity, 10–40 mCi/ml) as a bolus into a peripheral vein using 200 μCi/kg body weight with a minimum of 3 mCi. The dynamic information was detected and recorded by gamma scintillation camera (Nuclear-Chicago HP) with a 15,000 parallel-multihole collimator, 2.5 cm deep, and a magnetic tape system. A region of interest was selected over the lung free from extrapulmonary activity. The region was played back into a digital computer (PDP-11/20) which acquired data at a rate of 2 frames/sec. The pulmonary time-activity histogram so obtained was analyzed by the computer using a least-squares fit to the gamma function. The derived histogram represented pulmonary flow without recirculation. It was subtracted from the original one to obtain a second histogram representing multiple pulmonary recirculations due to left-to-right shunting. This was again fitted to the gamma function to obtain a histogram representing the first pulmonary recirculation. The areas under the first and second derived histograms were determined. These represented pulmonary flow and pulmonary flow from which systemic flow had been deleted, respectively. Thus systemic flow could be represented and a pulmonary systemic flow ratio (O_p/O_s) obtained [area 1/(area 1 — area 2)]. Twenty-seven patients ranging in age from 4 months to 21 years who had diagnosis by recent previous cardiac catheterization were studied. Ten had either pulmonic or aortic stenosis without shunt, and 17 had either atrial or ventricular septal defects with oximetry determined O_p/O_s of 1.05–3.0. The only radionuclide studies used were those in which there was a compact bolus as determined by inspection of the time-activity histogram obtained from a region of interest over the SVC or innominate vein. The derived radionuclide data were compared with the catheterization data using a linear regression model: correlation coefficient, 0.91; standard error of the mean, 0.25; $p < 0.001$; regression line slope,

0.87; and intercept, 0.22. Eight of the ten normals by oximetry data were normal by this technique, and two had $O_p/O_s < 1.12$. All of the 17 with left-to-right shunts had values which were close to those obtained from catheterization. Shunts with $O_p/O_s < 1.2$ could be separated from those with $O_p/O_s > 1.2$, and accurate quantitation could be obtained on shunts of O_p/O_s 1.2–3.0. The estimation of the functional size of the shunts by this method would have led to the same clinical management as those values obtained at catheterization. This method appears to provide a simple, rapid, and relatively atraumatic technique of quantifying and detecting left-to-right shunts accurate enough to guide in the clinical management of patients.

Clinical Evaluation of the Carcino Embryonic Antigen Test (C.E.A.) BY E. K. MINCEY, E. L. ARCHIBALD, A. G. RICHARDS, P. COY, D. M. LYSTER, AND R. T. MORRISON, Vancouver General Hospital, University of British Columbia and British Columbia Cancer Institute, Vancouver, B.C., Canada.

Two hundred and fifty persons consisting of health volunteers, patients suspected of having cancer, and patients having other nonmalignant disease had C.E.A. tests as part of the initial investigation. One hundred of the cancer suspect patients were subsequently proven to have carcinoma (gastrointestinal tract, lung, ovary, breast, pancreas, and others). The level of C.E.A. in plasma was measured by radioimmunoassay by the zirconyl gel method of Hansen. Ninety percent of patients with adenocarcinoma of the pancreas or ovary had elevated values. Eighty-five percent of patients with adenocarcinoma of the gastrointestinal tract (stomach, colon, rectum) or lung had elevated values. Higher C.E.A. values were found in patients with extensive metastatic disease. A high incidence of elevated values was found in patients with alcoholic cirrhosis. We have found the C.E.A. test to be a valuable aid to cancer management; its greatest application may be in following postsurgical and postirradiation patients for evidence of recurrence.

Intraocular Capillary and Aqueous Humor Dynamics Studied by Washout of Xenon and Albumen after Ocular Micro-injection BY J. O'ROURKE, J. BRONZINO, C. WILLIAMS, I. SHAFFI, AND C. BENSON, University of Connecticut Health Center, McCook Hospital, Hartford, Conn.

This study aims to develop safe and informative measurements of capillary flow in vascular diseases of the eye and of aqueous humor turnover in glaucoma.

Updated results offered concern about equipment design and clearance rates derived from several hundred animal and 189 clinical studies in low-vision, low-risk human eyes (*Arch Ophth* 81: 526–533, 1969; 84: 415–420, 1970).

Information presented will include:

1. Methods of microinjection with topical, spot anesthesia using a "wet-wall" technique with control pipette cannula plus safety and comfort.
2. Fixed-probe assembly required for eye counting and use with a multichannel analyzer storage unit to provide digital and analog recording of monoexponential ocular clearances. Camera xyz imaging of mixing and transit also shown.
3. Normal xenon clearance in cat eye, 6–13 %/min, slowed by hyperviscosity of blood, restored by infusions of Dextran 40 or surfactins such as pluronio 68.
4. Human clearance of xenon ranges between 5 and 9%/min and is slowed by uveal inflammation, possibly from diffusion barrier affecting xenon partition.
5. Normal albumen clearance reflecting bulk drainage of aqueous humor at about 1.0 %/min in humans, markedly reduced by carbonic anhydrase inhibitor (acetazolamide) administration in both species.

Application of principles of nuclear medicine to a small, complex surface organ is possible by using direct microinjection of tracer rather than systemic administration. Ocular uptake is slow and small and easily obscured by that of bulkier adjacent tissues.

A New Radiopharmaceutical for ^{99m}Tc Bone Scanning BY R. PEREZ, Y. COHEN, R. HENRY, AND C. PANNECIERE, The American Hospital of Paris and the CEA, Paris, France.

The use of ^{99m}Tc is so practical that we have tried to adapt it to bone scanning. The Tc-polyphosphate complex has already been described elsewhere and has demonstrated a very interesting field of use. Nevertheless, the inconsistency in the chemical purity of the commercialized tripolyphosphate mixture available, with a subsequent inequal labeling has led us to adopt a chemically defined salt: sodium pyrophosphate ($P^2O^7Na^4$, 10 H^2O). With this compound we have noted a greater as well as more constant labeling effectiveness: about 90% as compared to 50–70% with Tc-tri-polyphosphate mixture. Also the extemporaneous method of preparation is very simple. There is no chemical toxicity for pyrophosphate with the DL_{50} being 72.5 mg/kg mouse.

Concerning the pathways in the total body of this radiopharmaceutical, its renal passage as well as accumulation is one-third less than that of the polyphosphate mixture, this being an incontestable advantage in the study of the dorso-lumbar spine (the area most frequently examined).

The clinical use of this product is now routine (over 300 cases). It affords us the additional advantage of bone labeling without that of intestinal or soft tissues. Various examples of our explorations will be presented.

Radiotoxicity of Intracellular ^{125}I in Mammalian Cells: Effect on the Survival Curve BY EILEEN W. PRINCE AND S. J. ADELSTEIN, Shields Warren Radiation Laboratory, Boston, Mass.

The radiation hazards attendant to the use of isotopes emitting electrons less than 25 keV in energy, and thus of ranges in the order of cellular dimensions, continues to be problematical because of microdosimetric uncertainties. Because of their high specific ionization, these radionuclides may be a greater hazard than that estimated from conventional dosimetry when they are concentrated in particularly radiosensitive structures such as cell nuclei. The most extreme example in common medical use is ^{125}I, which decays by electron capture with a resulting cascade of Auger and conversion electrons. The incorporation of ^{125}I into DNA would be expected to result in extensive destruction of the genetic apparatus. Here we report on the effects of ^{125}I incorporated into DNA as the thymidine analog, iododeoxyuridine (IUdR).

Survival curves of exponentially growing cultures of Chang liver cells, obtained with 250 Kvp x-rays at a dose rate of 80 roentgens/min, have a D_0 of 170 rads and an extrapolation number of 3.4. Continuous exposure of the cells to extracellular ^{125}I as sodium iodide up to 10 μCi/ml does not change the plating efficiency of the cells. This concentration of ^{125}I results in a dose rate of approximately 0.3 rad/hr to the cell nucleus.

Exposure of the cells to $10^{-6}M$ or less of unlabeled IUdR for one doubling time does not alter their colony-forming ability. Levels of unlabeled IUdR which do not affect the plating efficiency also do not alter the x-ray survival curve when the cells are allowed to incorporate the compound for one doubling time.

With ^{125}I-labeled IUdR, continuous exposure to concentrations above $10^{-10}M$ (2.6×10^{-3} μCi/ml) completely inhibit colony formation whereas exposure to various concentrations of ^{125}I-labeled IUdR for one doubling time yields a survival curve of a D_{37} of $5 \times 10^{-10}M$ ^{125}IUdR. Under the conditions employed for obtaining the dose survival curve for ^{125}IUdR, the cellular uptake at $5 \times 10^{-10}M$ is approximately 4×10^{-10} μCi/nucleus. This results in a dose deposition of about 85 keV/day/cell nucleus. Assuming a uniform distribution of dose, which is probably not justified, the rad-equivalent dose would be less than 1 rad/day. Comparison of this figure with the D_0 of 170 rads for x-rays emphasizes the extreme degree of toxicity associated with the intranuclear decay of ^{125}I when affixed to DNA.

Other investigators, studying ^{125}IUdR incorporation into the DNA of bacteria and phage, have concluded that as a consequence of Auger cascades, the decay of ^{125}I causes lethal double-strand breaks in DNA with a very high efficiency. The low rad-equivalent MLD obtained in our experiments with mammalian cells is consistent with this hypothesis. (Supported by contract AT(11-1)-3229 with the USAEC.)

Use of Low-Lactose Milk or Lactase to Solve the Dietic Problem Associated with Milk Intolerance BY Y. SASAKI, M. LIO, H. KAMEDA, S. MURAO, H. YAMAMOTO, M. IGARASHI, AND T. NAGASAWA, The Second Department of Internal Medicine, University of Tokyo, Hongo, Bunkyo-ku, Tokyo, Japan.

It has widely been recommended that milk is a good nutrient not only for children but also for adults. Milk has also been very often used in hospital meals. A problem with the milk-feeding programs for adults has been the milk intolerance or lactase deficiency, which is prevalent among Japanese as well as other Asian races. With the purpose of making it possible for milk-intolerant subjects to drink milk without ill effects, we have studied two methods: (A) feeding a patient with a low-lactose milk instead of natural milk, and (B) giving lactase with natural milk. The ingredients of low-lactose milk compared with natural milk are as follows: protein, 3.2 gm/dl (3.0 in natural milk); fat, 4.5 (3.2); lactose, 0.3 (4.5); sucrose, 1.3 (0); and the same amount of vitamins as natural milk.

So far 15 Japanese subjects including four healthy volunteers were studied. Milk-drinking habit and history of milk intolerance were surveyed by questionnaires. The subjects were given 500 ml of natural cow milk with 5 μCi of lactose-1-^{14}C after overnight fasting. They were observed for the development of abdominal discomforts such as gas, full-sensation, borborygmus, cramps, and diarrhea. Carbon dioxide in the exhaled breath was sampled serially, and specific activity of $^{14}CO_2$ was measured with the method reported previously. The area under the $^{14}CO_2$ specific activity curve from time 0–4 hr was measured by planimetry and used as an index for ^{14}C-lactose absorption. The test was repeated in the same subject

using 500 ml of low-lactose milk or 500 ml of natural milk plus 5 gm of lactase.

Eleven subjects had history of abdominal discomforts after drinking milk. Indices for ^{14}C-lactose absorption after ingestion of natural milk ranged from 4.0 to 14.8 with the mean of 9.6. Eight of this group developed abdominal symptoms during the test. Three subjects did not develop any symptoms. After ingestion of low-lactose milk, the indices for this group ranged from 8.7 to 24.9 with the mean of 16.3 ($n = 6$) showing the increase of 31–204% ($\overline{m} = 69$) in comparison with those after natural milk intake. After administration of lactase with natural milk the mean index was 18.6 ranging from 14.5 to 24.9 ($n = 5$) with the increase of 69–162% ($\overline{m} = 108$). None of them developed abdominal symptoms after low-lactose milk or lactase plus natural milk.

Four subjects had no history of abdominal discomforts after milk drinking. The index for ^{14}C-lactose absorption after natural milk ingestion was 16.0 in mean with the range of 12.2–18.8. After intake of low-lactose milk ($n = 4$) or lactase plus natural milk ($n = 1$), the indices ranged from 12.2 to 23.7 with the mean of 17.5. The increase of the indices was 24–38% ($\overline{m} = 23$) as compared with those after natural milk intake. They did not develop any symptoms at all during those tests.

Our study suggests that the use of low-lactose milk or lactase with natural milk can solve the dietic problems associated with milk intolerance.

Evaluation of an Instant ^{99m}Tc-Labeled Lung Scanning Agent BY G. SUBRAMANIAN, R. W. ARNOLD, F. D. THOMAS, AND J. G. MCAFEE, Upstate Medical Center, Syracuse, N.Y.

The purpose of this study is to evaluate the preparation, animal tissue distribution, and clinical utility of an "instant" ^{99m}Tc-labeled albumin macroaggregate.

An unlabeled macroaggregate of human serum albumin and stannous chloride with a particle size of 10–60 microns was prepared using an acetate buffer in the conventional manner. This stable macroaggregate was prepared in quantity as a sterile suspension and stored in individual vials under refrigeration. At the time of use this aggregate was labeled with $^{99m}TcO_4^-$ simply by mixing; the labeling yield is quantitative and is stable for more than 36 hr.

To study the biological handling of this material, a double-labeled MAA was used for animal tissue distribution studies; ^{131}I-human serum albumin was macroaggregated with stannous chloride and was subsequently labeled with ^{99m}Tc for simultaneous tissue distribution. This was injected into adult albino rabbits and tissue samples were taken serially from 15 min to 24 hr. These studies showed very comparable distribution results for the two labels: more than 90% of the particles were found in the lungs at 15 min and less than 8% were present at 24 hr. The lung biological half-time was less than 12 hr with both labels, indicating that the macroaggregates are cleared from the lung and not just the label; the primary route for elimination seems to be particle dissolution.

Based on these studies, clinical trials were started and more than 50 cases have been done to date; in some, selected comparison studies were done using ^{131}I-MAA. As expected, ^{99m}Tc-MAA images were of consistently higher quality and information content than the ^{131}I-MAA images. The comparisons were made with the same camera and a divergent collimator. Biological half-time measurements of ^{99m}Tc-MAA in these patients averaged 16–18 hr with an effective half-time of approximately 5 hr. The biological half-time can be modified by altering the heating time for aggregate production.

Because of preparation problems in the older methods, ^{99m}Tc-MAA has not received general acceptance for routine clinical use. In contrast, the present preparation in kit form allows for instant availability on demand of a high-quality ^{99m}Tc-MAA agent. Approximately 500 μg of albumin are injected for a typical human study, although higher specific activities can be used. In comparison to the ^{131}I-MAA, the ^{99m}Tc-MAA produces greatly superior clinical images of very high photon flux with a fraction of the absorbed radiation dose and therefore should find wider clinical acceptance.

Radiopharmaceuticals in Clinical Pharmacology: the Pharmacokinetics of ^{195m}Pt Cis-Dichlorodiammine Platinum BY WALTER WOLF AND RONALD B. INGALLS, Radiopharmacy Program, University of Southern California, Los Angeles, Calif.

One of the major problems in clinical pharmacology is the assessment of the optimal dose of a chemotherapeutic agent to be administered to a patient at each particular stage of his disease. It is the aim of these studies to evaluate whether a drug labeled with a gamma emitter can be effectively used to determine rapidly and in vivo such parameters as target-to-nontarget localization, drug distribution, and rate of compartmental transfer.

Cis-dichlorodiammine platinum has been labeled with ^{195m}Pt obtained by ^{194}Pt(n,)^{195m}Pt to a specific activity of 0.1–1 mCi/mg. The ^{195m}Pt has a half-life of 4.1 days, decays by IT and emits at 99 keV

(12%) and 129 keV (2.4%), as well as Pt x-rays (mostly 77 keV).

The labeled drug, presently in Phase II studies, was administered intravenously to 250–500-gm rats at doses 2–4 mg/kg after the animals had been placed under the Anger camera. Serial pictures at 10–30-sec intervals were taken for the first 3 hr and the kinetics of distribution were evaluated by computer analysis. Rats bearing Fisher 344 Dunning ascitic leukemia and Walker 256 carcinosarcoma were studied similarly.

The data obtained have been subjected to compartmental analysis, and the results will be presented orally. In the nontumor-bearing animals, the results suggest a very rapid phase of excretion, accounting for 60–80% of the injected dose, followed by a phase of high kidney retention of the radiopharmaceutical. The tumor-bearing animals show, at the same dose, a very high retention, with considerably more complex kinetics.

To determine whether the material has metabolized and also to determine intracellular localization, we have labeled the platinum compound with tritium. NMR deuterium exchange studies of cis-dichlorodiammine platinum showed that less than 5% exchange occurred between the product and D_2O, even after 48 hr of contact, suggesting the probable stability of the tritiated material for subsequent biological studies.

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