CEREBROSPINAL FLUID SCANNING WITH ^{111}In

Philip Matin and David A. Goodwin

Veterans Administration Hospital and Stanford University School of Medicine, Palo Alto, California

The study of cerebrospinal fluid flow using radionuclides requires scanning periods up to 48–72 hr. The most commonly used radiopharmaceutical, ^{131}I-iodinated human serum albumin (IHSA), has the disadvantages of beta emission and longer than optimum half-life. In addition, ^{131}I emits a series of gamma rays that are not useful for scanning. A radionuclide is now available that has more ideal characteristics for CSF scanning. Indium-111 has a half-life of 2.8 days, no beta emission, and emission of 2 gamma photons/disintegration. The photons have energies of 171 and 247 keV with yields of 89% and 94%, respectively. This combination of useful photon energies and high yield is extremely desirable for scanning.

By performing minor alterations in the electronics of the gamma scintillation camera (*1*) or by using a "wide window" in a rectilinear scanner, both photons can be used simultaneously. Counting both photopeaks simultaneously makes available approximately 1.8 gamma photons/disintegration. This permits a larger number of disintegrations to be counted in a significantly decreased scanning time.

This paper describes the use of ^{111}In as a label for the scanning of cerebrospinal fluid in humans.

METHODS AND MATERIALS

Indium-111 is a cyclotron-produced radioisotope which is available as the trichloride in 0.05 *N* HCl. It is produced carrier free with activities ranging from 5 to 10 mCi/cc.

Indium-111 decays by electron capture with a 67.5-hr physical half-life (Fig. 1). This physical half-life is ideally matched to the observed optimum scanning time of 48–72 hr. It emits two gamma rays in cascade in very high abundance: 171 keV—89%, and 247 keV—94%. Both of these photons are in the desired energy range for use with rectilinear scanners as well as with the Anger gamma camera system. Indium-111 decay provides approximately 180 useful photons per 100 disintegrations with the dual spectrometer system (*1*) of the Anger gamma camera or a rectilinear scanner with a sufficiently wide window.

A dual-channel spectrometer system improves instrument sensitivity by 40–60% for ^{111}In. This sensitivity for ^{111}In is 30–40% higher than for equal amounts of ^{99m}Tc with the camera. Similar increases in sensitivity may be obtained with rectilinear scanners by including both photopeak within the window.

A colloid of ^{111}In as well as indium transferrin complex, described in more detail later, were used as radiopharmaceuticals for cerebrospinal fluid scanning (*2*). Standard CSF scans (*3–7*) were obtained following lumbar intrathecal injection of the ^{111}In compounds using either a Nuclear-Chicago Pho/Gamma III scintillation counter or an Ohio-Nuclear dual 5-in. rectilinear scanner. The activity of ^{111}In varied from 0.2 to 1 mCi in a volume of 3 cc or less.

Received Jan. 18, 1971; original accepted April 8, 1971.

For reprints contact: Philip Matin, Roseville Community Hospital, 333 Sunrise Ave., Roseville, Calif. 95678.

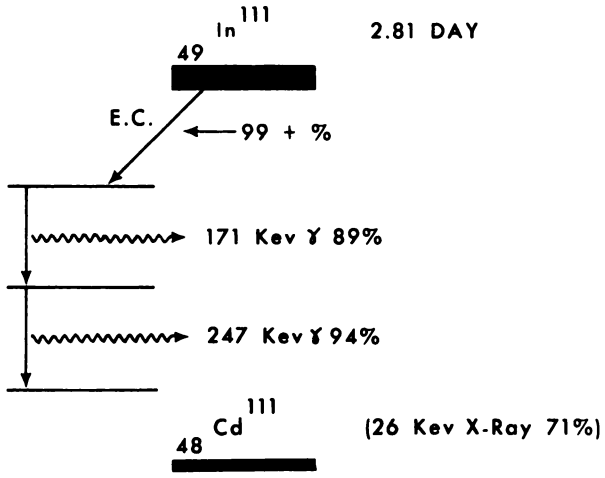

FIG. 1. Decay scheme of ^{111}In.

The indium transferrin complex was formed by slowly titrating the ^{111}In-HCl solution into a sterile test tube containing a small predetermined volume of the patient's own serum. Although pooled transferrin, a β_1 globulin, is commercially available, the use of transferrin in the patient's own serum avoids the introduction of a foreign protein.

The binding of transferrin to the indium is decreased if buffers are added or the pH of the 0.05 *N* HCl solution is raised.

It has been reported that the transferrin in 1 ml of human plasma can bind 4 μg of indium (*8*). However, to determine the amount of total protein required for injection, we performed an analysis of the binding of the ^{111}In-HCl solution to plasma.

The amount of plasma required was determined by performing serial dilutions of plasma in ^{111}In 0.05 *N* HCl solution with specific activity of 5 mCi/ml. The dilutions were deposited on cellulose acetate electrophoresis strips, and the electrophoresis was accomplished in a barbital buffer. The protein fractions were isolated, separated, and counted in a gamma well counter. The results are shown for ^{111}In in Fig. 2. This figure shows that at a ratio of two volumes of serum to one volume of indium there is approximately 98% binding.

We found that the serum of patients with iron deficiency anemia had greater indium binding capacity since there were more available transferrin binding sites.

There is approximately 3 mg of transferrin per milliliter of normal serum (*9*). When the activity of the ^{111}In approached 10 mCi/ml, only 0.15 mg of transferrin and 3.5 mg of total protein (0.5 ml serum) was required to bind the standard dose of 250 μCi of ^{111}In (0.025 ml ^{111}In solution). The pH of this ratio of serum to indium was in the range of 6.6–6.8, obviating the need for additional buffers.

The stability of the indium-transferrin complex, made as described, was tested by immunoelectrophoresis using antihuman transferrin and by cellulose acetate electrophoresis. This radiopharmaceutical was used to perform CSF scans in dogs, a monkey, and an adult male patient.

Five mongrel dogs and one Macaque monkey were studied. The material was injected in the lumbar region in the monkey and into the cisterna magna of the dogs. Peripheral blood samples were obtained at 4, 24, 48, and 72 hr to determine plasma radioactivity. The animals were observed for changes in temperature and behavior. Followup intrathecal punctures were performed to observe possible changes in the composition of the cerebrospinal fluid.

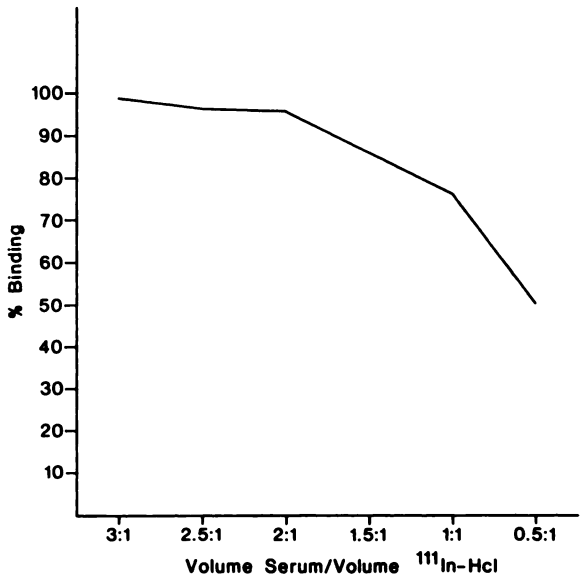

FIG. 2. Binding of ^{111}In-HCl to serum transferrin determined by serial dilutions of ^{111}In-HCl (5 mCi/cc) in normal human serum.

The patient was studied in the usual manner with a lumbar intrathecal injection of 0.50 mCi of the ^{111}In-transferrin complex in less than 2 cc. He received a simultaneous injection of 0.5 mCi of ^{111}In-transferrin and 0.1 mCi of ^{131}I-IHSA. At each scanning session, he was studied at both the ^{131}I photopeak and the ^{111}In dual photopeak. The time for each study and the counting rates for the two isotopes were compared.

An ^{111}In-phosphate colloid (*2*) was used to obtain CSF scans in five male patients with ages ranging from 48 to 62. This colloid was identical to the ^{113m}In-colloid used for routine liver scanning except that ^{111}In was substituted for ^{113m}In, and the material was carrier-free (no added Fe^{3+}). In all of the patients there was a suspicion of subarachnoid adhesions, and all were studied by lumbar intrathecal injection of 0.2–1.0 mCi in a volume of 3.0 ml or less. Three patients had subsequent IHSA cisternography using 200 μCi of ^{131}I-IHSA.

RESULTS

Cerebrospinal fluid scans with ^{111}In-phosphate colloid were performed on five patients. In all five patients the PO_4 colloid ascended normally to the region of the basal cisterns, but the passage around the cerebral convexities was both delayed and sparse. There was an accumulation of the colloid in the basal cisterns which persisted for several days after injection as seen in Fig. 3.

The IHSA CSF studies were performed in three of the patients to rule out the possibility that the failure of the colloid to ascend around the convexi-

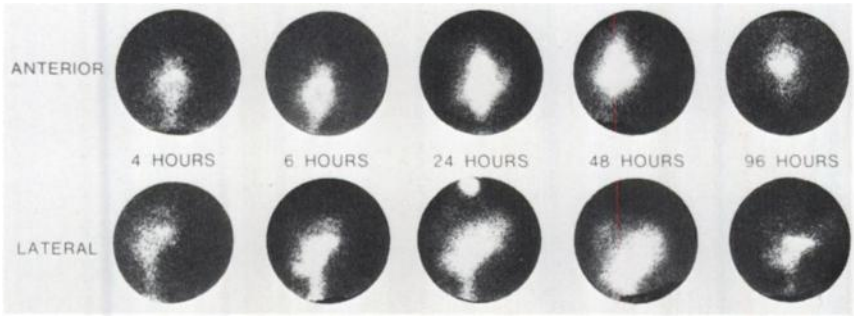

FIG. 3. Cerebral cisternography with ^{111}In-phosphate colloid showing accumulation of colloid in basal cisterns. Marker at top of 24-hr lateral views locates vertex.

ties was due to cerebral pathology. In two of the three IHSA studies there was passage around the cerebral convexities with concentration at the region of the superior sagittal sinus. This indicated that the flow of the colloid was not identical with the flow of IHSA and therefore not identical with natural CSF flow. This suggested that the ^{111}In-PO_4 colloid might be used for myelography but not cisternography.

The results using a ^{111}In-transferrin complex have been more promising.

After intrathecal injection in the monkey, the complex ascended normally through the basal cisterns and passed around the cerebral convexities. It concentrated normally at the vertex and appeared to be reabsorbed normally at the region of the superior sagittal sinus. In the dogs it followed the typical canine pathway demonstrated by IHSA (*10*).

After testing the complex for stability, sterility, and pyrogenicity, it was used in an adult male human patient. Figures 4A and B are the anterior and lateral views, respectively, of a 52-year-old male studied simultaneously with 500 μCi of ^{111}In-transferrin complex and 100 μCi of ^{131}I-IHSA.

The scintiphotos at 4, 24, and 48 hr were taken in sequence by changing the spectrometer of the scintillation camera from the single 364-keV ^{131}I "window" to the dual ^{111}In windows at 171 and 247 keV. The study shows an almost identical pattern of flow of the indium-transferrin complex and IHSA around the cerebral hemispheres. This patient was suspected of having subarachnoid adhesions with a delay in passage of CSF around the cerebral convexities. The ^{111}In appeared to demonstrate the delay more effectively because of the greater amount of information provided by collecting more counts in a given time.

The high counting rate provided by small doses of ^{111}In greatly reduced scanning time when compared with IHSA cisternography performed in the same manner. In most cases, a greater number of counts were collected to give better detail of the cerebral cisterns. The actual counting rates were over three times greater with equivalent doses of ^{131}I and ^{111}In. However, larger doses of ^{111}In can be given with safety.

The replacement of 10% of the spinal fluid of monkeys with the ^{111}In-transferrin complex (3 ml, 14 gm protein or 2 mg/kg) produced no discernible changes in temperature, behavior, or spinal fluid chemistry. There were no ill effects in the patients secondary to lumbar intrathecal injection of up to 500 μCi of ^{111}In-transferrin complex (7.0 mg protein).

The peripheral blood levels of ^{111}In following lumbar or cisternal intrathecal injection in the animals remained low until the ^{111}In-transferrin complex ascended around the cerebral convexities. The maximum activity was found between 24 and 48 hr.

Samples of the indium-transferrin complex which had been at room temperature for a week or longer were tested for in vitro stability. A qualitative test was performed by immunoelectrophoresis using anti-

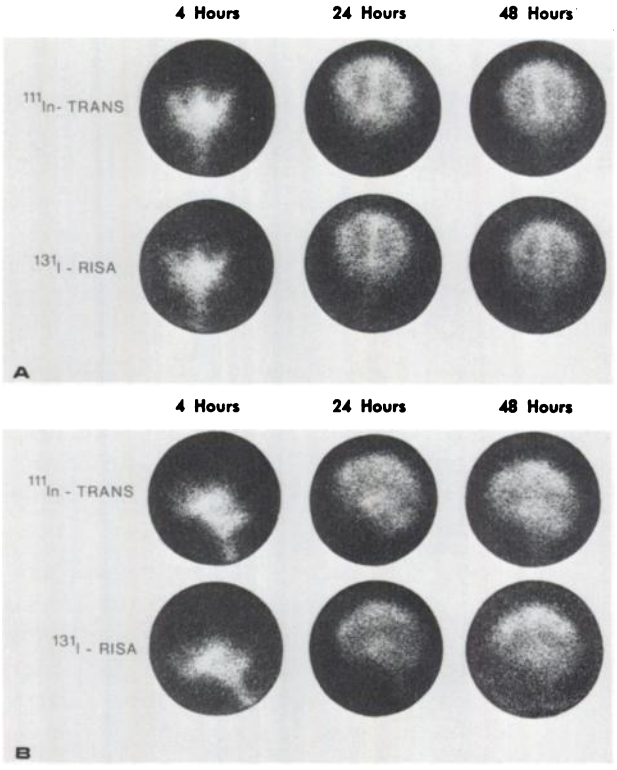

FIG. 4. Comparison between ^{111}In-transferrin and ^{131}I-IHSA cisternography at 4, 24, and 48 hr in patient with suspected hydrocephalus. Figure 4A is anterior view and Fig. 4B is lateral view.

human transferrin against ^{111}In-transferrin. The line of binding was autoradiographed to see if the ^{111}In remained bound to the transferrin. In all cases it was. A quantitative test was performed on cellulose acetate electrophoresis strips where the migrating transferrin fraction could be removed and counted. This method was also used to confirm the stability of the complex in blood samples drawn from the dogs and humans at 4, 24, and 48 hr.

The dosimetry of ^{111}In when instilled intrathecally as the indium-transferrin complex has been calculated. The total beta and gamma dose from 500 μCi of ^{111}In to brain tissue is approximately 0.8 rads. The dose to the spinal cord is 0.2 rads, and to the spinal column marrow 0.13 rads. The brain tissue within the range of the internal conversion electrons (0.05 cm) would receive a significantly higher dose. Since the half-life of ^{111}In is only 2.8 days, patients in whom there might be a complete blockage of the CSF pathway would still not receive a prohibitive dose.

DISCUSSION

In early studies of cerebrospinal flow using radionuclides the need to use a radiopharmaceutical incorporating a normal constituent of CSF or an agent behaving similarly to normal CSF became apparent (*3–7*). For example, unless large volumes of CSF were replaced, ^{198}Au-colloid did not appear to follow the course of CSF to the parasagittal region (*11*). However, ^{131}I-IHSA, a labeled normal component of CSF protein, followed the natural pathways.

To evaluate the early reports concerning the use of colloidal gold, we initially used ^{111}In colloids since these were easy to synthesize. After a lumbar intrathecal injection, the material flowed only to the region of the basal cisterns. In human subjects, in whom ^{131}I-IHSA had been shown to flow normally, very little colloid flowed around the cerebral convexities.

The binding of indium to albumin can be difficult. However, indium binds strongly to transferrin, the endogenous beta globulin known best for its iron-binding capacity. It was decided to attempt to produce a ^{111}In-transferrin complex which would be suitable for intrathecal injection. The considerations included the source of the transferrin, the amount of transferrin required to bind millicurie amounts of ^{111}In, the total amount of protein which would be injected, and the stability of the complex. In addition, since the preparation of ^{111}In requires solutions of dilute HCl, the final pH of the complex would have to be within a suitable range for intrathecal injection.

We found that using the patient's own serum as a source of transferrin was satisfactory for binding and safe for use. At the optimum binding concentration of two volumes of serum to one volume of ^{111}In eluate, the pH was in a desirable range for intrathecal injection. Approximately 98% of the indium is bound at this concentration.

The total amount of protein was less than the amount generally accepted as safe for IHSA CSF studies in outlining the spinal canal and cerebral cisterns. The transferrin label followed the CSF pathways as shown by IHSA scanning and was apparently reabsorbed in the region of the superior sagittal sinus along with the CSF. Since these are the desired properties of a radiopharmaceutical for CSF scanning, the advantages of ^{111}In appear to be available for use in humans in the form of ^{111}In-transferrin.

In addition to exploring further uses of ^{111}In-transferrin, other radiopharmaceuticals such as ^{111}In-DTPA and EDTA will be evaluated in our subsequent studies (*12*). If ^{111}In can be bound successfully to albumin, its use as a CSF scanning agent will be explored.

SUMMARY

Indium-111 is now available for radionuclide procedures in humans. This cyclotron-produced radionuclide decays by electron capture with a half-life of 2.8 days. There is no beta emission, and 1.8 gamma rays useful for scanning are emitted per disintegration.

Radiopharmaceuticals using this nuclide have been developed for cerebrospinal fluid scanning because of the almost ideal half-life and decay scheme. An indium-transferrin complex, using the patient's own serum, has been used in animals and in one human. This benign radiopharmaceutical has been shown to follow the natural CSF pathways delineated by ^{131}I-iodinated human serum albumin (IHSA) and therefore appears to be useful for routine CSF scanning.

Colloids such as indium phosphate colloid collect at the region of the basal cisterns and are unsatisfactory for cisternography.

The use of ^{111}In in chelates such as EDTA and DTPA will be evaluated in future studies. If ^{111}In can be successfully bound to albumin, its use as a CSF scanning agent will be explored.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Roland A. Finston for his assistance in performing dosimetry calculations and to Chung H. Song for excellent technical assistance. Connie Murphy patiently prepared the manuscript.

This work was supported in part by Veterans Administration Part I Research Grant #3204.

REFERENCES

1. GOODWIN DA, MENZIMER D, DEL CASTILHO R: Dual spectrometer system for high-efficiency imaging of multi-gamma-emitting nuclides with the Anger gamma camera. *J Nucl Med* 11: 221–223, 1970

2. COLOMBETTI LG, GOODWIN DA, HERMANSON R: ^{113m}In-labeled compound for liver and spleen studies. *J Nucl Med* 10: 597–602, 1969

3. DICHIRO G, REAMES PM, MATTHEWS WB: RISA-cisternography. *Neurology* 14: 185–191, 1964

4. DICHIRO G: Observations on the circulation of the cerebrospinal fluid. *Acta Radiol* (diag.) 5: 988–1002, 1966

5. TATOR CH, FLEMING JFR, SHEPPARD RH, et al: Studies of cerebrospinal fluid dynamics with intrathecally administered radioiodinated human serum albumin (^{131}IHSA). *Canad Med Ass J* 10: 493–503, 1967

6. TATOR CH, FLEMING JFR, SHEPPARD RH, et al: Radioisotopic test for communicating hydrocephalus. *J Neurosurg* 28: 327–340, 1968

7. MATIN P, GOODWIN DA, DENARDO GL: Cerebrospinal fluid scanning and ventricular shunts. *Radiology* 94: 435–438, 1970

8. HOSAIN F, MCINTYRE PA, POULOSE K, et al: Binding of trace amounts of ionic indium-113m to plasma transferrin. *Clin Chim Acta* 24: 69–75, 1969

9. SCHULTZE HE, HEREMANS JF: *Molecular Biology of Human Proteins.* New York, Elsevier, 1966

10. YARNELL P, MATIN P, CUNNINGHAM J: Canine radioisotope cisternography. *Neurology*, in press

11. RIESELBACH RE, DICHIRO G, FREIRICH EJ, et al: Subarachnoid distribution of drugs after lumbar injection. *New Eng J Med* 27: 1273–1278, 1962

12. WAGNER HN, HOSAIN F, DELAND FH, et al: A new radiopharmaceutical for cisternography. *Radiology* 95: 121–125, 1970

ACCEPTED ARTICLES TO APPEAR IN UPCOMING ISSUES

Radiostrontium Localization in Metastatic Osteosarcoma (Letter to the Editor). Accepted 4/28/71.
L. D. Samuels
Authors' Reply by Gerald L. Schall and Louis S. Zeiger

Optimizing the Window of an Anger Camera for ^{99m}Technetium. Accepted 4/29/71.
Theodore P. Sanders, Toby D. Cohen, and David E. Kuhl.

Parathyroid Scanning with ^{75}Se Selenomethionine and Glucagon Stimulation (Case Report). Accepted 5/10/71.
Fuad S. Ashkar, Juan L. Naya and Edward M. Smith

Further Observation on ^{131}I-BSP Clearance in the Dubin-Johnson Syndrome (Letter to the Editor). Accepted 5/10/71.
Masahiro Iio

Metastatic Extraosseous Osteosarcoma to the Liver: A Case Demonstrated by ^{85}Sr and ^{99m}Tc Colloid Scanning (Case Report). Accepted 5/10/71.
Murray K. Dalinka, Arlie E. Fiveash, and James K. Aston

Scintigraphic Demonstration of Cerebral Infarction in a "Watershed" Distribution (Case Report). Accepted 5/13/71.
Bassett B. Kilgore and Frederick J. Bonte

Unidirectional Versus Bidirectional Scanning (Letter to the Editor). Accepted 5/13/71.
R. Sear
Authors' Reply by G. H. Simmons and J. G. Kereiakes

Accumulation of ^{131}I-Labeled Albumin in a Subdural Hematoma Demonstrated by Cisternography (Case Report). Accepted 5/13/71.
Naomi P. Alazraki, Samuel E. Halpern, Roger N. Rosenberg, and William L. Ashburn

^{99m}Tc Human Serum Albumin. Accepted 5/13/71.
W. C. Eckelman, G. Meinken, and P. Richards

Phagocytic Activity of the Liver as a Measure of Hepatic Circulation—A Comparative Study Using ^{198}Au and ^{99m}Tc-Sulfur Colloid as a Radioactive Material. Accepted 5/13/71.
H. Mundschenk, A. Hromec, and J. Fischer

Erythrocytic Production in Anemias. I. The Use of the Survival Curve for Estimating Production in the Non-Steady State (Concise Communication). Accepted 5/13/71.
L. Sanchez-Medal, A. Loria, and E. Juarez-Badillo

Elimination of Salivary Gland Uptake by Lemon (in Vertex View of Brain Image) (Letter to the Editor). Accepted 5/18/71.
En-Lin Yeh

In Vitro ^{51}Cr and ^{32}DFP Labeling of Granulocytes in Man. Accepted 5/18/71.
C. Dresch, Y. Najean, and J. Beauchet

Use of ^{13}Nitrogen in Studies of Airway Closure and Regional Ventilation. Accepted 5/19/71.
Reginald Greene, Bernard Hoop, and Homayoun Kazemi

The Effects of Coronary Arterial Injection of Radioalbumin Macroaggregates on Coronary Hemodynamics and Myocardial Function. Accepted 5/26/71.
Norman D. Poe

Inhalation Lung Scanning Using Carrier-Free ^{113m}Indium (Preliminary Note). Accepted 5/26/71.
David J. Cook and Harry Lander

Intranasal Pledgets and Cerebral Spinal Fluid Leaks (Letter to the Editor). Accepted 5/26/71.
Eugene T. Morita, David L. Fore, Anthony Trippi, and Richard W. Seaman

Obstructive Jaundice Caused by Hepatic Artery Aneurysm—Demonstration by Radionuclide Imaging Techniques (Case Report). Accepted 5/26/71.
Peter J. Mehnert and Leonard M. Freeman

Sources of Gamma-Camera Image Inequalities. Accepted 5/27/71.
L. M. Morrison, F. P. Bruno, and W. Mauderli

Correlation of Pulmonary Photoscan and Angiogram as Measures of the Severity of Pulmonary Embolic Involvement. Accepted 5/27/71.
Kevin M. McIntyre and Arthur A. Sasahara

Brain Scan in Hyperparathyroidism (Case Report). Accepted 5/27/71.
Fred Mishkin and Klaus Weber

Analytic Approach to Dynamic Radioisotope Recording. Accepted 5/27/71.
Yasushi Ishii and William J. MacIntyre

Fast Neutron Activation Analysis of the Major Body Elements. Accepted 6/2/71.
H. C. Biggin and W. D. Morgan

Relationship of the Thyroid Scintiscan to the Therapeutic Effects of ^{131}I in Hyperthyroidism with Diffuse Goiter. Accepted 6/2/71.
Soen L. Tjoe, Bennett Levine, Ralph G. Wieland, and Jeffrey C. Chen.

Serial Pulmonary Perfusion Scanning in Radiation Therapy for Bronchogenic Carcinoma. Accepted 6/2/71.
Kenneth R. McCormack, Simeon T. Cantril, and Stephen Kamenetsky

Thyroid Hemagenesis or Thyroiditis? (Letter to the Editor). Accepted 6/7/71.
Elliot Liff
Author's Reply by Joseph A. Russotto

Estimation of the T_4 Binding Capacity of Serum TBG and TBPA by a Single T_4 Load-Ion Exchange Resin Method: Comparison to Two Unrelated Methods, Survey of the Population, and Abnormalities in Various Diseases. Accepted 6/9/71.
Samuel Refetoff, Swen R. Hagen, and Herbert A. Selenkow

Cyclotron-Produced ^{157}Dy Compared with ^{18}F for Bone Scanning Using the Whole-Body Scanner and Scintillation Camera. Accepted 6/9/71.
Y. Yano, D. C. Van Dyke, T. A. Verdon, Jr., and H. O. Anger

Production of ^{99m}Tc on a Medical Cyclotron: A Feasibility Study (Concise Communication). Accepted 6/9/71.
J. E. Beaver and H. B. Hupf

Analysis of the Fissure Sign. Accepted 6/14/71.
Raymond Gize, Miguel Dizon, and Fred Mishkin

Rectilinear Transmission Scanning of Irregular Bones for Quantification of Mineral Content. Accepted 6/15/71.
John M. Vogel and Jerome T. Anderson

Hemangioma of the Liver Treated by Irradiation (Case Report). Accepted 6/15/71.
A. Robert Kagan, Henry L. Jaffe, and Rexford Kennamer

Lower Normal Values for ^{131}I Thyroid Uptake not Related to the Ingestion of White Bread (Concise Communication). Accepted 6/22/71.
Manfred Blum and Ramesh Chandra

Placental Scanning Using ^{99m}Tc Albumin and Ionic ^{113m}In (Concise Communication). Accepted 6/22/71.
Jan Urbanek and Miroslav Graf

A "Technetium-99m Clock" for Calculation of Individual Patient Doses (Concise Communication). Accepted 6/22/71.
Howard A. Anderson, Michael G. Alexander, and C. Craig Harris

Thyroid Uptake Studies in Infectious Hepatitis (Concise Communication). Accepted 6/22/71.
K. B. Desai, R. D. Ganatra, S. M. Sharma, M. C. Patel, and F. P. Antia

Method for Reducing the Energy Dependence of the Resolution of Focused Collimators. Accepted 7/8/71.
D. J. Wyper, F. C. Gillespie, and Irene Hall

Use of Magnifying Multihole Collimators in the Gamma-Ray Camera System (Concise Communication). Accepted 7/9/71.
S. Rudin, P. A. Bardfeld, and H. Hart

Absorbed Dose Calculations (Letter to the Editor). Accepted 7/9/71.
M. F. Cottrall, D. M. Taylor, and K. Unnikrishnan
Reply by John U. Hidalgo

Use and Interpretation of the Lung Scan (Book Review)

Nuklearmedizin Szintigraphische Diagnostik (Book Review)

Gallium-67 for Tumor Scanning. Accepted 7/10/71.
Heinz Langhammer

Measurement of Cardiac Shunting with Technetium-Labeled Albumin Aggregates (Concise Communication). Accepted 7/10/71.
Gary F. Gates, Harry W. Orme, and Earl K. Dore

Radioisotopic Angiocardiography: Findings in Congenital Heart Disease. Accepted 7/16/71.
Joseph P. Kriss, Lee P. Enright, William G. Hayden, Lewis Wexler, and Norman E. Shumway