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LABORATORY OF NUCLEAR MEDICINE AND RADIATION BIOLOGY
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ANNUAL PROGRESS REPORT

for the period ending

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INTRODUCTION

O. R. Lunt

Details of research progress by the Laboratory staff are summarized in the body of this report. Notable advances on an impressive range of problems of both applied and fundamental nature have been achieved.

In the Nuclear Medicine area, significant advances were made in the development of new and useful radioactive, diagnostic test materials and in the application of rapid organ imaging procedures for use in the diagnosis and management of pulmonary embolism and obstructive lung disorders.

on, In the Biochemistry-Developmental Biology area, important advances have been made in the use of cell cultures that retain organ-specific functions. Heart cells, hepatocytes, uterine cells, neurones and glial cells have been used to elucidate controls for the production of enzyme and other proteins.

Research in the Environmental Radiation Division has continued with a natural desert community exposed to low, but continuous, levels of gamma radiation. Six years of exposure have begun to modify the function and composition of this ecosystem. Heteromyid rodents continue to reproduce, but the life span of pocket mice (Perognathus formosus) has decreased slightly. Seed production by the gymnosperm Ephedra nevadensis has been drastically reduced. Leopard lizards (Crotaphytus wislizenii) are disappearing because of radiation-induced female sterility, and this same effect also seems to be appearing among whiptail lizards (Cnemidophorus tigris). Life span appears to be an extremely important factor in determining the response of animals to sublethal, chronic irradiation.

In the area of Radiobiology, major advances have been made in determining the mechanisms by which ionizing radiation alters nucleic acids, the mechanisms of action of radiation modifiers, the conformation of enzymes, the nature of radiation effects in brain cells in vivo and in cultured cloned cells, and the effects of salt stress on tumor incidence.

Construction is in progress on the building to house the Laboratory's biomedical cyclotron. This building is being funded by the Regents, the Chancellor's Office and from funds available to the Dean of the School of Medicine. Installation of the cyclotron is expected about the first of October. This facility will add important, new capabilities to our research in nuclear medicine and other areas. The cyclotron facility is located adjacent to the UCLA Medical Center to facilitate its application in medical care and research.

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Introduction (Cont.)

The research budget has precluded expansion of Laboratory's overall program; however, specific shifts in emphasis of research goals and budgets, agreed upon with the Division of Biology and Medicine of the AEC, have been initiated. The addition of a new staff member in the Developmental Biology area has already had a favorable influence on the total research of the Laboratory. One other, recent, staff appointment in Radiobiology is expected to achieve closer coordination of the Developmental and Radiobiology areas. The programs in Nuclear Medicine, Environmental Radiation, and Biochemistry remain at about previous levels.

The bulk of future research in basic nuclear medicine will be conducted in the 4,000 square feet of space provided at the Medical Center. This move brings our Nuclear Medicine staff into closer physical proximity with similar activities at the Medical Center and facilitates interaction with the Department of Radiology staff and with interested personnel of other departments. With this move, much needed space in Warren Hall is made available.

Within the past year, six of our staff have received appointments in academic departments, making use of the special FTE's provided by the Regents for the Laboratory. The appointments carry with them substantially all of the privileges of professorial series appointments, with the exception that tenure is related to the duration of the Contract.

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NUCLEAR MEDICINE

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Functional Assessment of Canine Lung Transplants by Radioisotope Scanning Procedures

Toyoharu Isawa, J. R. Benfield, J. Castagna, D. E. Johnson, and G. V. Taplin

Thirty-four dogs with left lung allografts, 21 fresh and 13 preserved and 14 dogs with autografts were sequentially studied by radioisotope inhalation and perfusion lung scanning procedures.

Allografts and autografts were found to function well immediately after operation. In autografts, both ventilation and perfusion were well maintained during the period of study. In allografts, ventilation deteriorated sooner and more severely than perfusion. The ventilation-perfusion index decreased more rapidly and more severely in the preserved transplants than in the fresh allografts. Partial bronchial obstruction at the bronchial anastomotic site was indicated on the aerosol inhalation scan as a locus of excessive radioactive deposition ("hot spot"). Such findings occurred first, in allo- and autografts transiently in the immediate postoperative period as a result of edema, next, at the time of rejection (7 to 30 days) in allografts and thirdly, many months postoperatively in autografts as a result of bronchostenosis by scar formation.

It is concluded that the ventilation and perfusion abnormalities which may complicate lung transplantation can be identified in a practical, non-traumatic and reproducible way with radioisotope inhalation and perfusion lung scintigraphy.

Interim Report

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Unilateral Pulmonary Artery Agenesis, Stenosis and Hypoplasia
Functional Disturbances Revealed by Radioisotope Lung Imaging

Toyoharu Isawa and George V. Taplin

Two patients with agenesis, one with stenosis and another with hypoplasia of a pulmonary artery were studied by three types of lung scintigraphy. In pulmonary artery agenesis, perfusion is completely absent and ventilation to the affected lung is reduced but with no evidence of airway obstruction. In pulmonary artery stenosis, perfusion is greatly diminished but ventilation is normal in the affected lung. In pulmonary artery hypoplasia, perfusion and ventilation are both diminished but there are signs of severe airway obstruction in the affected lung. In stenosis and hypoplasia, perfusion to the involved lung can be increased by placing the affected lung in the most dependent position. Differential scan features of these vascular anomalies versus pulmonary embolism and bronchogenic carcinoma are discussed. Lung scintigraphy not only enables regional functional disturbances to be visualized but also reveals specific abnormalities of ventilation and perfusion from which diagnoses of these pulmonary artery anomalies can be facilitated.

Final Report

Submitted to the "American Journal of Roentgenology, Radiation Therapy and Nuclear Medicine" for publication.

Radioaerosol Inhalation Lung Imaging. Its Role In Suspected Pulmonary Embolism

Toyoharu Isawa, Michael Hayes, and George V. Taplin

Seventy-three patients with suspected pulmonary embolism were

studied by combined radioaerosol inhalation and perfusion lung scanning procedure using ^{99m}Tc - or ^{113m}In -albumin aerosol and ^{131}I - or ^{99m}Tc -MAA, respectively. Single breadth radioxenon inhalation studies were also done.

The twenty-eight patients who had single or multiple regions of pulmonary ischemia which were well aerated, were diagnosed pulmonary embolism. The remaining 45 patients had other causes for their perfusion abnormalities. Forty-three had pre-existing, obstructive airway diseases and two had unilateral vascular anomalies.

It is concluded that perfusion and radioaerosol inhalation scanning procedures help distinguish the regional ischemia of pulmonary embolism from that associated with obstructive airways disease. Short-lived test agents, camera equipment and a combined perfusion-inhalation lung imaging procedure promises even greater diagnostic efficiency while providing the necessary information in one hour or less.

Final Report

Unilateral Pulmonary Artery Agensis and Hypoplasia (Functional Disturbances Revealed by Lung Imaging)

Toyoharu Isawa and George V. Taplin

This paper describes the physiological disturbances demonstrable by lung imaging, which help distinguish unilateral pulmonary artery anomalies from other conditions with which they may be confused.

Three different lung-imaging procedures were used: namely, ^{133}Xe -gas inhalation camera studies after the single breadth technique,

radioaerosol inhalation lung scanning with ^{99m}Tc -albumin and perfusion lung scanning using ^{131}I -MAA by intravenous injection. Two patients, each with an absent right pulmonary artery and one with a hypoplastic left pulmonary artery, were studied with lung-function tests, chest films, pulmonary angiography, bronchography and lung scintigraphy as just described.

The two pulmonary artery agenesis patients showed no perfusion to the involved right lung even after the patients were injected with the tracer while in the right lateral decubitus position. Radioaerosol inhalation scans showed diminished but even distribution of radioactivity in the involved lung. Xenon-133-gas distribution was also diminished, but its washout was normal. The patient with left pulmonary artery hypogenesis had a unilateral hyperlucent lung radiographically and greatly diminished perfusion by scanning. When the tracer was injected with the patient in the left lateral decubitus position, the scans indicated a slight increase of perfusion to the involved lung. Radioaerosol scans showed excessive deposition in the left central major bronchus with little in the peripheral lung parenchyma, findings which are characteristic of unilateral emphysema (J. Nucl. Med. 10:345, 1969). Radioxenon lung images showed a diminished radioactivity and extremely slow gas washout from the involved lung. Function tests showed slight-to-moderate restriction of lung volumes and diffusion abnormalities in both agenesis and hypoplasia of unilateral pulmonary artery plus mild airway obstruction in the individual with a hypoplastic left pulmonary artery. Bronchography revealed normal small airways in the agenesis

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n case and bronchiectasis in the hypoplasia case.

Absence of or a great reduction in perfusion to an entire lung is seen in massive pulmonary embolism and bronchogenic carcinoma. In pulmonary embolism, ventilation is not disturbed except in the very early stage. In bronchogenic carcinoma the perfusion defect depends mainly on the extent of hilar node involvement. The history, physical and radiological findings can help distinguish these disorders from unilateral vascular anomalies. Lung perfusion and inhalation imaging procedures have additional value by revealing the underlying functional disturbances of ventilation and perfusion in unilateral pulmonary artery anomalies.

Reference: J. Nuc. Med. 11:330-331, June 1970.

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- Influence of Coronary Arterial Injection of Radioactive Particles on
Cardiodynamics

N. D. Poe

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9). Selective intracoronary injection of radioactive albumin macroaggregates (MAA) would be a suitable method of studying regional myocardial blood flow if cardiac function is not compromised. This hypothesis was tested in 7 open-chest dogs. A flow probe was placed on the anterior descending coronary artery. Myocardial contractility, carotid artery pressure and the EKG were also monitored. One-half ml volumes of substances to be evaluated were injected slowly into the artery through a fine needle. Normal saline or supernatant of MAA preparations does not alter any of the parameters. Meglumine diatrizoate usually produced a

transient flow increase. Contractility was variably affected but the EKG and carotid artery pressure remained stable. MAA suspensions (10-50 micron) were injected in 0.3 and 0.03 mg amounts. With the former, flow and contractility usually decreased with rapid recovery while the latter could frequently be given with no detectible changes. Conclusions: Functional alterations are solely attributable to particle blockade. Flow and contractility are affected in advance of EKG or arterial pressure changes. Sufficient MAA can be injected for external radioscanning detection without demonstrably interfering with cardiac function. Potential clinical applications exist.

Interim Report

Distribution and Clearance of Inhaled Aerosols

N. D. Poe

Originally described for determining regional pulmonary ventilation and airway abnormalities, lung scanning following radioaerosol inhalation is a convenient clinical and experimental method for assessing distribution and clearance of inhaled aerosols. Using positive pressure or ultrasonic nebulizers and saline solutions of ^{198}Au colloid or $^{99\text{m}}\text{Tc}$ technetium albumin, the following observations have been made: (1) aerosol normally is deposited uniformly throughout both lung fields in proportion to ventilation (compared to ^{133}Xe studies). Minimal activity is observed in the trachea and major bronchi. Clearance half-time is about 21 days; (2) decreased deposition is seen in regions of parenchymal

disease but not embolism without infarction; (3) rapid irregular respiration or severe obstructive disease reduces peripheral deposition and enhances tracheobronchial deposition. A second, more rapid clearance phase ($T_{1/2}$ about 5 hours) becomes apparent. This represents clearance by the ciliary mechanism. Scans performed 6 to 24 hours after inhalation show only peripheral activity remaining; (4) in the lateral decubitus position, aerosol deposition is relatively greater in the dependent well-ventilated lung. The reverse is found in anesthetized animals with poor expansion of the dependent lung; (5) sites of partial airway obstruction can frequently be identified as localized "hot-spots" due to increased aerosol deposition; (6) 75 percent or more aerosol is lost in the tubing and the exhaust with only 5-15 percent ever reaching the lower respiratory tract. Inhalation lung scanning offers a unique method for qualitatively and quantitatively studying aerosol administration and deposition. It is a practical and available technique for evaluating medicinal aerosol therapy.

Reference: Dis. Chest 56:264 No. 3, Sept. 1969.

The Influence of Pulmonary Arterial Ischemia on the Distribution of Inhaled Radioaerosols

N. D. Poe

The present study was undertaken to further explore certain factors influencing alveolar deposition of radioaerosols and determine the relationship between aerosol deposition and ventilation in chronic arterial ischemia. Both radiogas ventilation and radioaerosol inhalation techniques

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have been advocated as a means of differentiating pulmonary ischemia of embolic origin from other causes of ischemia by demonstrating persistence of substantial air exchange in primary vascular occlusion in contrast to poor exchange in parenchymal disease. The reliability of this distinction has not been fully established.

Permanent vascular occlusion was effected in dogs with plastic sponge emboli or surgical division of the left pulmonary artery. The latter produced total pulmonary arterial ischemia while autopsy observations indicated the possibility of incomplete interruption of flow in the embolized group. Ultrasonically generated ^{99m}Tc albumin aerosols were administered to the embolized group by positive pressure (28 cm H_2O) or negative pressure (15 cm H_2O). The high pressure group showed no significant decrease in aerosol deposition during 2-12 months follow-up. The negative pressure group demonstrated little initial decrease but decrements of 30% or more were seen within 2 months in 3 of 4 animals.

In the group with sectioned pulmonary arteries the average reduction of aerosol deposition in the ischemic lung was 73% at one week with negative pressure breathing. Subsequent observations were quite variable, but at 6 months the average reduction was only 34%. At no time was there a total absence of aerosol deposition in the ischemic lung. A limited number of comparisons of spontaneous, positive and negative pressure breathing were made beyond one month. No consistent differences were noted..

Distribution of ^{133}Xe ventilation and radioaerosol deposition correlated almost perfectly in normal animals. After left pulmonary arterial

of division, reduced radioactivity in the ischemic lung was evident with
ence either technique, but the aerosol values tended to be lower. Although
to the two methods are not directly comparable, the results suggest that
c- aerosol inhalation scans may be a more sensitive qualitative approach in
detection of poorly ventilated regions.

va- The data support previous observations that ischemic lung continues
the to undergo air exchange even in the chronic stage. However, ventilation
reduction may be marked at any time diminishing the clinical usefulness
of ventilation studies under these circumstances. The variations in
altered ventilation may be related to the completeness of the vascular
or obstruction.

Reference: J. of Nuc. Med. 11:351, No. 6, June 1970

Determination of in vivo Persistence of Tantalum Dust Following Broncho-
graphy, Using Reactor-Activated Tantalum and Total Body Counting

ion T. Upham, S. Graham, R.J. Steckel and N.D. Poe

g- Tantalum has recently been recommended by Nadel and others, as a
promising bronchographic contrast agent. Strong points in these recom-
mendations have been the non-reactivity of metallic tantalum in biolog-
ical media and its rapid clearance from the bronchi following bronchography.
Using low-level gamma irradiation from neutron activated tantalum dust,
and several different particle sizes, to assay the thoracic retention of
tantalum following experimental bronchography in dogs, we have demon-
strated long-term retention, of the order of 20% of the administered

tantalum dose. This result was totally unexpected, and although direct extension of these data to the clinical situation is not possible, caution is urged in the clinical use of this new agent, because of possible long-term effects of a particulate contrast material retained in the lungs, bronchi and/or regional lymph nodes.

Interim Report

Diagnostic Evaluation of Brain Scintigrams in Comparison With Neuro-radiological Procedures

G. H. Wilson and N. D. Poe

One-hundred children from the newborn period to sixteen years of age have been studied by brain scintigrams and cerebral angiography. The work-up in many cases has also included pneumoencephalography. The brain scintigrams were performed using ^{99m}Tc . In children under five years of age, the scintigrams were obtained using the Anger camera. Cooperative older children were scanned with a rectilinear scanner. The cerebral angiograms were done selectively following percutaneous catheterization of the femoral artery. The pneumoencephalograms were done on a Mimer with laminography where indicated.

The results of this comparative study indicate good correlation between the scanning and radiographic procedures in most tumors, excluding midline basal and posterior fossa tumors which the scan cannot readily identify. For most degenerative and congenital defects, the scan is of little value.

Interim Report

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Effects of Short-Term Epithelial Reticular Cell and Whole Organ Thymus Grafts in Neonatally Thymectomized Mice

Esther F. Hays and Paul F. Alpert

Neonatally thymectomized mice were implanted with thymus grafts composed of epithelial reticular cells for periods of 7 and 14 days. Regardless of whether the grafts were placed immediately after thymectomy, or at 3 weeks of age, there was little recovery of the lymphocyte depletion and impaired immunologic responsiveness, characteristically found in a neonatally thymectomized host. The findings were similar in animals studied at 2 months or 2 weeks after graft removal. Many of the short-term remnant grafts were populated with lymphocytes and had attained the morphologic appearance of thymus by 14 days.

A lesser degree of lymphocyte depletion and impaired responsiveness to SRBC occurred if thymectomy was delayed until 7 days of age, if remnant grafts were removed after 2 months, and if intact neonatal thymus was used for the short-term grafts. Complete normality was found in some of the animals in all of these groups.

These observations suggest a direct role for mature thymus lymphocytes in reconstituting the neonatally thymectomized host and indicate that epithelial cell function is to direct the maturation of cells that ultimately behave as thymus lymphocytes.

Reference: Journal of Experimental Medicine 130:847-857, No. 4,
October 1, 1969

Effect of Antilymphocytic and Antithymocytic Sera on the Development of Mouse Lymphoma

Donna L. Vredevoe and Esther F. Hays

Injections of antisera to lymphoid tissues of C3H/HeJ mice significantly increased the incidence of (a) lymphoma in normally resistant C3H/HeJ adult mice injected 4 times with Gross leukemia virus and (b) growth of allogeneic lymphomas in C3H/HeJ and AKR mice when compared to similarly treated animals injected with normal rabbit serum. The same antilymphoid cell sera were able to suppress sheep red blood cell hemagglutinin responses in parallel sets of mice.

Immunosuppressive drugs, 6-mercaptopurine (100 mg/kg of diet) and azathioprine (100, 150, or 200 mg/kg of diets or 150 mg/kg mouse injected intraperitoneally), did not increase the incidence of lymphoma in C3H/HeJ adult mice receiving multiple injections of Gross leukemia virus or depress the hemagglutinin response to sheep red blood cells.

There was a tendency towards prolongation of latent periods of spontaneous lymphoma in AKR mice and virus-induced lymphoma in C3H/HeJ mice injected with C3H/HeJ antithymocytic serum prior to development of lymphoma. Incidence and latent period of virus-accelerated lymphoma in AKR mice was not altered by administration of the antithymocytic serum during the latent period of lymphomagenesis.

Reference: Cancer Res., 29: 1685-1690, September 1969.

Immune Response in Preleukemic Mice

Manuel Frey-Wettstein and Esther F. Hays

Humoral and cellular immunity was assessed serially in preleukemic AKR and Gross virus-injected C3H/HeJ mice over a period of 10 to 12 months as measured by quantitative γ globulin determination, hemagglutinin and hemolysin titers following immunization with sheep red blood cells, and macrophage migration inhibition. Normal production of γ globulins as well as humoral antibodies was found in both of these experimental strains, while macrophage migration inhibition, which is believed to be a correlate of cellular immunity, appeared to be abnormal throughout the life of these two groups of animals, which were destined to develop a high incidence of lymphoma. Some aspects of this apparent dissociation between humoral and cellular immune response are discussed with regard to the mouse virus lymphoma system, primarily involving the thymus, which was used in these studies.

Interim Report

Studies with Heterologous Antithymocytic Serum

Donna L. Vredevoe and Esther F. Hays

AKR or C3H/HeJ transplanted mouse lymphomas originally induced by Gross virus have been shown to be neutralized by in vitro incubation with an immunosuppressive rabbit anti-mouse thymus cell serum (ATS). Neutralization was measured by significantly increased latent periods or decreased incidence (at 60 days post transfer) of lymphoma in syngeneic

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recipients of ATS-incubated cells when compared to NRS-incubated cells. Although ATS was shown to neutralize lymphoma cells by in vitro incubation, when it was administered in vivo to adult C3H mice during a course of 1 to 4 weekly intraperitoneal injections of cell-free filtrates of Gross virus induced lymphoma, the incidence of lymphoma was significantly greater in mice receiving ATS and virus than in mice receiving virus alone. The latent period to lymphoma development ranged from 119 to 290 days post initiation of treatment. The incidence tended to increase as the number of injections of cell-free filtrate was increased with a maximum incidence reached at 3 injections. These studies illustrate a dual action of the antithymus cell serum i.e., a direct action on tumor cells and cells to prevent their replication in syngeneic hosts, and an immunosuppressive action in animals given lymphomagenic virus which promotes the development of lymphoma.

Interim Report

Regeneration and Morphologic Changes in Thymic Grafts Exposed to a Lymphomagenic Virus

Esther F. Hays

Thymic grafts composed of epithelial reticular cells placed under the renal capsule were found to regenerate to the morphology of normal thymus with a characteristic sequence of cellular events. Exposure of such grafts in AKR mice to a lymphomagenic virus (Gross) resulted in no visible change in this regeneration pattern, yet lymphoma was found to

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cells. develop in high incidence in these grafts. Intact thymic grafts placed
incuba- subcutaneously or under the kidney capsule and biopsied at intervals in
course the prelymphomatous period were found to be identical to grafts unexposed
of to virus when examined microscopically. These findings suggest that
i- exposure of grafts to lymphomagenic virus does not alter the function of
ing the epithelial reticular cells which is that of directing lymphoid re-
m 119 population of the grafts with stem cells derived from the host bone
in- marrow. When lymphoma does develop in the thymus, it occurs as a trans-
ased formation of a lymphoid cell or cells without any prior alteration of
illus- the morphological appearance of the graft, implying a direct thymus
tion cell-virus interaction in the malignant change.

Interim Report

Dynamic Kidney Function Studies in Renal Transplant Recipients

Michael Hayes and George V. Taplin

der The renogram and sequential kidney scans supplement each other and
nal have distinct diagnostic value in a variety of renal problems. This
of study was undertaken to determine the usefulness of combining these two
i no procedures in the management of renal transplant patients. A secondary
to purpose was to compare ^{99m}Tc DTPA, an inulin substitute with ^{131}I Hip-
purate which is cleared primarily by tubular excretion as test agents
for dynamic kidney imaging.

Using a large crystal scintillation camera, twelve kidney trans-
plant recipients were studied, with a total of 38 examinations. Serial

1-1/2 minute kidney images were obtained for as long as 20 minutes post-injection, following a single intravenous injection, containing 300 u Ci of ^{131}I Hippurate and 2 mCi $^{99\text{m}}\text{Tc}$ DTPA. Images were made with the patient in the supine position so that both the transplanted kidney and the bladder could be included in the camera's field of view. Renograms and cystograms were obtained from magnetic tape data for both agents by area of interest quantification: a method which accepts only counts from selected areas, and rejects surrounding background counts.

Renocystograms derived in this manner were found to be more reliable than those obtained with external probes for two reasons. First, accurate organ localization is obtained by direct visualization and radioactivity from nearly all surrounding tissue can be excluded by the area of interest device and, second, the depth response of the scintillation camera is less affected by the inverse square law than that of an external collimated detector. Kidney to background ratios at two minutes, and renal transit times can be determined accurately and were found to be more responsive to daily variations in function than visible changes in sequential scans. The amount of radioactivity in the bladder 20 minutes post-injection could be estimated and was found to be a reliable index of function in the absence of urinary obstruction. The quantified renocystogram was found to augment the anatomical and functional information derived from serial scans. In general, functional changes in the transplanted kidney were reflected by the scan-renocystogram examination before the development of either clinical signs and symptoms or laboratory

findings indicative of the rejection phenomenon.

^{99m}Tc DTPA provided better scan statistics and lower patient radiation exposures than ^{131}I Hippurate as the test agent. Both agents seemed equally sensitive to moderate changes in function. However, when overall function was severely depressed, ^{131}I Hippurate was the more sensitive agent. In some cases, the use of both agents in combination gave valuable information regarding selective depression of either glomerular filtration or tubular excretion, but, in most instances, the functional disturbances registered by each of the two agents were similar and ran in parallel directions.

It is concluded that ^{99m}Tc or ^{113m}In chelates may be used as satisfactory ^{131}I Hippurate substitutes for evaluating the transplanted kidney when overall function is fair to good. If a single radiopharmaceutical must be used in all cases, ^{131}I Hippurate remains the agent of choice.

Interim Report

The Physics of Radionuclide Imaging Made Easy With a Three Dimensional Phantom

Michael Hayes

Much of the knowledge on organ imaging of radionuclide distribution is in a form which is difficult for the clinician to understand and apply to everyday scan interpretation. This report is the result of an effort to bridge the gap between physicist and physician by presenting information on the physical properties of scanning in a way which requires neither expertise in mathematics nor the study of complex graphs and

charts.

The 3-dimensional phantom has been used to illustrate the following facets of radionuclide imaging.

1. Increasing the density of surrounding media decreases depth response.
2. Increasing collimator to organ distance decreases changes of detecting radionegative lesions.
3. Background subtraction or contrast enhancement decreases the changes of imaging deep-seated radiopositive areas.
4. High discriminator or narrow analyzer window settings improve detection of radionegative defects at a cost of greatly increased scanning time.
5. Increasing radionuclide energy improves the chances of detecting radionegative lesions.
6. The scintillation camera introduces no significant image distortion with a parallel hole collimator, moderate distortion with a divergent collimator and severe distortion with a pinhole collimator.

In conclusion, the 3-dimensional phantom is useful in studying variables which affect nuclide imaging. Its two main advantages are simplicity of use and ease of data interpretation. The desired information is revealed directly by inspection only without the need for mathematical analysis.

Interim Report

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Delayed Brain Scanning With ^{99m}Tc Pertechnetate for Improved Tumor Detectability

G.F. Gates, E.K. Dore, and G.V. Taplin

This investigation describes the results of ^{99m}Tc pertechnetate brain scans performed during the first hour following tracer injection and of rescanning selected patients one to twenty-four hours later. Eighty brain tumors were found among the nearly 1500 patients who had brain scans performed during the two year period 1968-69. Seventy-four had a tissue diagnosis and in the remaining six, diagnoses were established by clinical, scan, and neuroradiological findings. Forty had both early and delayed scan examinations and in 15 the early scans were normal or equivocal. Fourteen of these 15 became positive upon delayed examination. Twenty-six nondiagnostic to moderately positive early scans increased in their degree of abnormality upon delayed examination. The detectability of brain tumors improved from 80 percent with routine early scanning to 93 percent by rescanning selected patients later. The optimal time for delayed scan examination is three-four hours following tracer injection.

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Final Report

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Magnacamera Studies of the Liver's Dual Circulation

Hideo Yamada, Parameswaran Ramanathan and George V. Taplin

The dynamic aspects of the liver's dual circulation were studied with the Magnacamera and the video quantifier following rapid intravenous injection of ^{99m}Tc albumin solutions or microaggregates. Studies were

made in normal subjects, in patients with space occupying lesions and in liver cirrhosis. Areas of normal versus abnormal liver (cold lesion) were identified during replay of the video tape. Analogue tracings from each of these two areas were obtained with the "cursors" during the first sixty seconds and again at five minutes following injection. Polaroid pictures were made at intervals determined from the tracings of changing radioactivity levels in the areas of interest (normal versus abnormal liver and liver versus heart).

Normally the hepatic arterial curve starts to rise 1-2 seconds after the peak of the left heart curve. It reaches a plateau in about 5 seconds and is followed by a more gradual rise which represents the portal venous component. In the tumor region, the arterial component rises to a plateau quickly but is not followed by a further increase in radioactivity during the usual portal phase, thereby indicating greatly diminished or absent portal flow. In advanced cirrhosis, the arterial component is more prominent than in normal subjects but the portal venous phase is reduced and sometimes absent.

With this capability one can study alterations in the arterial and venous components of the liver circulation, both in parenchymal disease as well as in localized liver lesions such as cysts, abscesses, primary and secondary tumors. The procedure deserves further investigation because of its potential usefulness in the management of cirrhosis and its possible diagnostic value in distinguishing malignant from benign lesions of the liver.

Interim Report

Placental Transfer of ^{113}Sn Contamination in $^{113\text{m}}\text{In}$ Generator Eluates

Norman S. MacDonald, Martin Hackendorf and Anne Flesher

Traces of ^{113}Sn appear in acidic eluates from tin-indium generators. In view of the growing use of 100-min $^{113\text{m}}\text{In}$ in placental scanning, it is desirable to estimate the additional radiation exposure to the fetus arising from this moiety of 115-day ^{113}Sn . Pregnant rabbits (16) received 10 mCi, intravenous injections of $^{113\text{m}}\text{In}$, either as the raw eluate or with added albumin adjusted to pH 7. Tin contaminations were too low for detection with hematoxylin, but samples of injected solutions after 3 days showed residual activities from 0.2 to 0.05 $\mu\text{Ci/ml}$ with gamma spectrum and decay time of ^{113}Sn - $^{113\text{m}}\text{In}$ equilibrium mixtures. Radiotin retention was measured in the maternal rabbits and the litters taken 1-2 days after injection by Caesarian section or delivered 7-11 days after injection. After 1 day, 33-52% of the ^{113}Sn injected was recovered in the maternal body but less than 4% was in the liver, spleen, GI tract and kidneys. After 2 days, however, 23% was in these excretory organs. Between 1-3% of injected ^{113}Sn was in the fetuses at 1-day postinjection. This decreased to 0.1-0.5% by the time of normal delivery 7-11 days later. The burden of tin in the fetuses decreased faster than the maternal burdens. For placental scanning in humans a 1-mCi dose of $^{113\text{m}}\text{In}$ might contain 0.05 μCi of ^{113}Sn . Calculated mean integrated radiation dose to the fetus, using MIRD data, would be 0.08-0.8 mrad for effective half-times between 20 and 115 days or roughly 1/100 to 1/10 the dose received from the $^{113\text{m}}\text{In}$. This small additional

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radiation exposure can be completely avoided by passing the raw eluate through a 2-cm column of ZrO_2 just before sterilization by membrane filtration. This also provides protection against accidental massive tin breakthrough.

Reference: J. of Nuc. Med. 11:344-345 No. 6, June 1970.

The Radiation Dose to a Human Adult Population From a Decade of Caesium-137 Internal Body Contamination

N. S. MacDonald, I. Ban, A. Flesher and M. Hackendorf

This report presents the results of 1052 measurements of the ^{137}Cs burden in 454 persons during the decade 1960-69. These individuals, men and women, were all over 20 years old and lived in or near Los Angeles, California. The quantitative measurements of ^{137}Cs , together with naturally-occurring potassium-40, were made by analyses of the gamma spectra obtained with a "total body counter" consisting of four sodium iodide crystal scintillation detectors in a steel-lined room, and a multichannel pulse height analysis system. The accuracy of the technique ($\sigma = \pm 4\%$ for ^{40}K and $\pm 10\%$ for ^{137}Cs) agreed closely with the accuracies reported for 15 other "body counters" during a nationwide interlaboratory comparison. The trend of individual values, expressed as picocuries of ^{137}Cs per gram of potassium ($Ci \times 10^{-12}/gm K$) over the ten year span showed an easily discernible peak of bodily contamination during 1964-65 occurred about 12-15 months after the cessation of detonations of nuclear devices in the atmosphere by the USA and USSR. The highest mean value observed for men was $115 \pm$ pCi/gm K during

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the third quarter of 1964. Subsequent nuclear testing programs conducted in the atmosphere by Great Britain, France and China have not reversed the downward trend since 1965, but have significantly slowed the rate of decrease, particularly in 1968-69. This effect of recent injections of ^{137}Cs into the environment was seen clearly in the flattening of the curves after late 1967 in charts which presented the mean values of $^{137}\text{Cs}/\text{gm K}$ for men and for women, tabulated by quarterly periods. In fact, if the quarterly mean values were replotted on semi-logarithmic graph paper, the points from mid 1965 through 1967 could be described quite well by a single declining exponential function, with a slope corresponding to a "half-time" of about 17 months. Since early 1968, however, the decline in body burdens departed from this exponential rate and, indeed, values of $^{137}\text{Cs}/\text{gm K}$ for early 1970 remained at about the same level as in 1969. The consistently higher concentrations of ^{137}Cs observed in men, compared with women, has previously been reported by a number of other investigators. The reported concentrations of ^{137}Cs in 7 day, pooled, regular diets obtained bimonthly from a local hospital were also collected for comparison. The $^{137}\text{Cs}/\text{K}$ ratios in people were about 3 times greater than the ratio in these dietary samples. Whether or not they truly represented the diets of the persons we measured is, of course, unproven, but the finding agreed with the threefold difference in $^{137}\text{Cs}/\text{K}$ ratio reported for people and their diets by Gustafson. It is interesting that the plots of the ^{137}Cs body burdens in each of 8 individuals measured periodically over a span of

6-10 years had essentially the same shape and salient features as the curves of quarterly mean values for the population.

What has been the radiation dose sustained by members of this particular population as a result of the continued presence of ^{137}Cs in their bodies during the last ten years? A reasonable estimate can be had by calculating the absorbed radiation dose to an hypothetical "standard man" whose body burden of ^{137}Cs fluctuated according to the curve for quarterly mean values for males. A total body mass of 70 kg with a potassium content of 135 g was assumed. The concept of "absorbed fraction" introduced by Ellett, Callahan and Brownell and developed in detail for target body organs in the MIRD pamphlets was used together with the equilibrium absorbed dose constants for ^{137}Cs and ^{40}K . The total body concentration of ^{137}Cs , integrated over the ten-year period, was obtained by planimeter measurement of the area under the mean curve for males. The calculated absorbed doses to total body, to marrow, and to the gonads were between 8 and 10 millirads for the 10 year period. These values include the doses delivered by all beta particles, primary photons, conversion electrons and X-rays attending the disintegration of ^{137}Cs nuclei. To place this radiation dosage in perspective, the total dose delivered simultaneously by the natural ^{40}K continually present in the body, calculated by the same method, came to 156 mrad. Now, in our population sample, no single individual ever had a ^{137}Cs burden greater than twice the quarterly mean value, from which we infer that very few persons in the area received as much as 20 mrad internal dose from ^{137}Cs . We conclude that the average dose attributable to

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¹³⁷Cs internal contamination was about 10 mrad, or about 6% of the radiation received from the body potassium. This is close to the United Nations Scientific Committee estimate of the long term ¹³⁷Cs commitment, which amounted to 15 mrad absorbed dose to worldwide populations as a consequence of nuclear explosions carried out through 1965. Although the major part of this dose commitment has now been delivered, ¹³⁷Cs will be with us, literally, for many years to come. Programs to monitor it must therefore continue.

Interim Report

Altered Immunoglobulin Metabolism in Systemic Lupus Erythematosus and Rheumatoid Arthritis

J. Levy*, E.V. Barnett*, N.S. MacDonald, and J.R. Klineberg*

Immune globulin G and immune globulin M metabolism was evaluated in 10 patients with systemic lupus erythematosus (SLE), 10 patients with rheumatoid arthritis (RA), and in seven normal volunteers. The biological half-lives of purified IgG and IgM, labeled with ¹³¹I and ¹²⁵I, respectively, were determined by serial measurements of radioactivity in the blood and urine with a gamma well counter, and by serial counts of total body radioactivity in a total body counting chamber.

The mean survival half-life for IgG in patients with SLE was 8.2 days as compared to an average of 18 days in normal controls. An average of 10.1% of total body IgG was catabolized daily compared to a mean

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of 3.9% in normal controls. Turnover of IgM in patients with SLE was, with very few exceptions, normal. In contrast, patients with rheumatoid arthritis revealed a milder abnormality of IgG metabolism, but markedly abnormal IgM catabolism with a mean half-life averaging 5.9 days as compared to 9.3 days in control subjects. An average of 14.2% of total body IgM was catabolized daily in patients with RA as compared to 8.1% in normal controls.

Our data suggest that there are basic differences between patients with RA and SLE in the synthesis and catabolism of IgG and IgM not readily apparent from a single measurement of serum IgG and IgM concentration. Abnormal IgG and IgM metabolism may be related to underlying immunological mechanisms in these diseases. Immunoglobulin turnover studies appear to be an additional means for the characterization of rheumatic diseases.

Reference: J. of Clin. Invest. 49:708-715, (1970)

Biomedical Cyclotron Facility

N.S. MacDonald and Benedict Cassen

During fiscal year 1970 the construction documents for the small, one story building to house the cyclotron were drawn up, approved, submitted to bidders, and a contract awarded. Funds for this structure are being provided by the University of California Regents, and the UCLA School of Medicine, Department of Radiology. Construction began May 4, 1970, and should be completed by the end of October, 1970. Purchase of

the accelerator itself and annual operating costs are covered with funds provided by the Division of Biology and Medicine of the AEC. The Cyclotron Corporation (Berkeley, California) was the successful bidder for constructing the accelerator. It is a model CS-22, compact AVF, fixed frequency cyclotron, capable of providing 22 MeV protons, 11 MeV deuterons and 29 MeV helium-3 beams, with external target beam currents in the neighborhood of 50 microamps. The machine will be completed and ready for shipment in July 1970. We hope to take delivery and move the machine into the massive concrete vault during August, before the rest of the building is complete.

Planning and acquisition of ancillary equipment for operation of the facility was well under way. For example, the systems for electro-mechanical safety interlocks and for radiological safety monitoring were designed and are being assembled. This included a mechanical device for transporting solid-target holders from the cyclotron vault into the hot lab by remote control.

Interim Report

Radioactive Diagnostic Agent Development

N.S. MacDonald, G.V. Taplin, M. Hackendorf, and L. Griswold

Efforts to improve the ease, efficiency and reliability of labeling human serum albumin with Technetium-99m for preparing radioactive agents for organ scanning procedures were continued. A compact, completely closed and lead shielded system for conducting the labeling operations

with pH control under sterile conditions was developed and is undergoing "field-testing" for routine use at Harbor General Hospital. An All-glass and Teflon system for extracting radioactive Tc-99m pertechnetate from alkaline solution of its parent Molybdenum-99 with methyl ethyl ketone was devised and is undergoing tests. The apparatus minimizes manual handling by rapid evaporation of the organic solvent, permits making up saline solutions of very high activity per unit volume needed for "bolus-type" injections.

Experimental data on the characteristic distribution in tissues and organs of several radioactive pharmaceutical agents in rabbits and rodents were obtained. This information was needed to support applications for State licensing of these agents for human usage on an "investigative new drug" basis at Harbor Hospital. They included EDTA chelates of Indium-111 and Technetium-99m with ethylene diamine tetra acetic acid (EDTA) primarily for rapid sequential scanning of kidneys; In-111 chloride and In-111 albumin complex for blood pool scanning; and Fluorine-18 as carrier free fluoride for bone scanning.

Interim Report

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Fluorine-18 for Bone Scanning

L. R. Bennett, et al.

Research in this project is centered around several isotopes and several forms of these isotopes. Continuing evaluation of F-18 is progressing, indicating that it has very good potential for demonstration of metastatic bone disease. The very great advantages of being able to perform the study shortly after injection of the tracer and with speed rapid enough to include large areas of the body, are very encouraging. It appears that the use of F-18 on a routine clinical basis for bone scanning is soon to become common practice.

Interim Report

Galium-67 for Tumor Localization

L. R. Bennett, R. C. Small, et al.

Investigation of Ga-67 citrate based upon the work reported by Edwards and Hayes of the Medical Division of Oak Ridge associated universities is in progress. This material shows uptake in certain types of malignancies, especially Hodgkin's disease, some epitheliomas, and some adenocarcinomas. Patients having known disease which is being evaluated as to its extent are being studied with the use of Ga-67. So far results are highly suggestive that certain tumors do show dramatic uptake of this radiotracer.

Interim Report

Demonstration of Vascularity of the Femoral Head

M. M. Webber and M. D. Cragin

Continuing study of the vascularity of the femoral head is underway, with effort during this last year to evaluate variations of the normal vascularity of the femoral head as shown by uptake of phagocytes within the bone marrow of the femoral head. The ultimate applicability of this technique is to demonstrate avascularity of the femoral head following fractures and other pathology, in order to determine whether or not healing can be expected. It is hoped that a conjoined study using both F-18 and Technetium-labeled particles of sulfur for demonstration of bone marrow phagocytic activity can be carried out. It would appear that information of great prognostic significance might be obtained.

Interim Report

Demonstration of Clots Within Veins

M. M. Webber and W. K. Victory

Continuing studies of clot localization have been carried on with special emphasis on development of an in vitro system to demonstrate the affinity of various radiotracer agents for clots in vitro and evaluation of these systems as to whether they have a true relationship to what happens in vivo. Numerous microscopic studies have been done in addition, documenting the fact that particles of albumin attach themselves to clots formed in vitro.

Interim Report

Cerebral Blood Flow Studies

M. M. Webber, et al.

ay, Evaluation of flow of bolus injections of pertechnetate prior to
brain scanning procedures was done on a routine basis over a several
n month period, in an effort to determine whether or not such flow studies
is demonstrating the initial entrance of radioisotope into the vascular
system of the brain would lead to significant improvements in our diag-
al- nostic abilities. Although this study has not yet been completed, it
18 appears that only in exceptional cases is there additional information
gained from such studies. In the case of vascular tumors or strokes
n- information gained may be valuable.

Interim Report

Radioautography of Human Brain Tumor Cells

J. C. Kennady and M. Kim

Radioautography of human brain tumor cells cultured in the laboratory
has been carried out with 99m Technetium pertechnetate in an effort to
e determine whether the tumor cells, per se, show an uptake of the isotope.
n This agent, commonly used in brain scanning, accumulates in the tumor
region thus creating the brain:tumor ratio. The mechanism responsible
on, for this ratio has never been elucidated.

ts Autoradiographs have been made from surgically excised brain tumor
grown in culture: glioblastoma (3), meningioma (5), ependymoma (8), and
neurofibroma (3). The cultures contain both tumor cells (astrocytes, etc.)
and brain stroma cells (mesenchymal cells, microphages, macrophages,

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fibroblasts). To date, our results indicate that autoradiographs are best obtained from those cultures which have been growing in the laboratory not longer than 15 days. Also, brain stroma cells show a high affinity for the radioisotope, particularly the small basophilic cells which may be microphages. These results raise the question as to whether the supportive stroma of the tumor plays an active role in the brain scan picture.

Reference: J. of Clin. Res. 18:45, Jan. 1970

Dynamic Assessment in Differential Diagnosis of Brain Lesions

J. C. Kennady, R. Cole, M. Hayes

In our first 100 patients with clinical evidence of intracranial pathology studied by carotid angiography, brain scanning and the scintillation videocamera (Ter-Pogossian type), the camera provided a dynamic assessment of the following brain lesions.

Meningioma vs. Arteriovenous malformation: The routine 99m Tc-pertechnetate brain scan shows the involved region as an area of increased radiodensity. By virtue of the rapid shunting of blood away from normal brain tissue and draining into enlarged veins, the videocamera visualizes the dynamic difference between the A-V malformation and the meningioma.

Avascular tumors vs. Acute cerebrovascular occlusions: The routine brain scan shows the former as a region of increased radiodensity and the latter is usually not visualized during the initial 7-10 days. The videocamera demonstrates both of these lesions as areas of decreased vascularity and no delayed filling of the avascular tumor.

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Vascular tumors vs. Chronic cerebrovascular occlusions: Variable

regions of increased radiodensity are seen in routine brain scans for both lesions. The videocamera shows the radiopharmaceutical entering the vascular tumor region more rapidly, in higher concentration and with transient retention compared to adjacent brain. In chronic vascular occlusions, the involved region is distinguished from normally perfused brain by the prolonged retention of the test agent indicating a loss of autoregulation in the pial arteries.

The videocamera has the added feature of measuring the amount of radioactivity in any two identically sized regions of the cerebral hemisphere simultaneously. Hence, semilog plotting of this activity provides T 1/2 values for selected regions of the brain and confirms the visual impression obtained from the videotape.

Interim Report

Comparative Assessment of Cerebrovascular Disease by Angiography, Scanning and Image Intensifier Camera

J. C. Kennady, B. J. Miller, W. B. Anderson and M. Hayes

In 100 patients with clinical evidence of intracranial pathology studied by carotid angiography, brain scanning and the image intensifier videocamera, 34 had cerebrovascular disease. Brain scanning was performed with the 10-probe scanner; serial angiography was followed by the camera studies using the same indwelling internal carotid catheter.

The videoquantifier is initially calibrated using a 90 mCi ^{57}Co standard source placed flush to the 3-mm-hole collimator in a 1.5 cm²

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area. Phantom studies show that the videocamera resolution of a static field is 3 mm and can delineate coils of tubing (1.5 mm dia) spaced 5 mm apart through which a $^{99m}\text{TcO}_4$ solution is flowing. The videocamera sensitivity studies show a linear incremental dose response in the sensitivity range used in these patients. Technetium-99m-labeled albumin microaggregates ($^{99m}\text{Tc-AA}$), 1-8 microns in size, are used primarily because the material is a nondiffusing intravascular test agent with an optimal energy range for the videocamera.

Five patients had acute vascular disease with neurological symptoms ranging from 12 hr to 7 days and angiographic evidence of anterior or middle cerebral artery trunk or branch occlusions. The routine ^{99m}Tc -pertechnetate brain scans were within normal limits. The occluded regions had a decreased $^{99m}\text{Tc-AA}$ concentration in contrast to adjacent brain areas in the videopolaroid pictures. The rate removal curves from these areas showed a 0.5-1.5-sec delay in the appearance and a lower peak radioactivity of the test agent compared with other regions of the hemisphere. This would indicate slow collateral perfusion of the microvasculature distal to the occlusion.

Twenty-five patients presented a history of cerebrovascular disease of several months to 4 years duration. These patients had definite anterior or middle cerebral artery trunk or probable distal branch involvement by angiography. The routine brain scans showed a region of variable increased radiodensity in the majority of the patients. The videocamera studies showed clearly delineated regions of increased $^{99m}\text{Tc-AA}$ concentration

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in the areas indicated by the neurological deficit. Rate removal curves of these regions demonstrated an earlier appearance, higher peak activity and delay in the disappearance ($T_{1/2}$ 2.2-4.4 sec) of $^{99m}\text{Tc-AA}$ than observed elsewhere in the hemisphere. These results would indicate an increase in the microvasculature, possible loss of autoregulation and a delay in the capillary venous drainage from the involved regions.

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Four patients had A-V malformations that were well outlined by angiography. The routine brain scans were positive in three and equivocal in one close to the midline vertex. The very rapid appearance, high-peak radioactivity and disappearance ($T_{1/2}$ 0.8-1.2 sec) of $^{99m}\text{Tc-AA}$ in the region of the malformations was seen and quantified.

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In conclusion, the image intensifier camera presents a dynamic assessment of the macro- and micro-vasculature within and surrounding cerebrovascular abnormalities.

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Reference: J. of Nuc. Med. 11:333 No. 6, June 1970