ATOMIC ENERGY COMMISSION

DIVISION OF BIOLOGY AND MEDICINE

BIOLOGIC CONSIDERATIONS IN ANATOMIC IMAGING WITH RADIONUCLIDES

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- PROGRESS REPORT -

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This year's Progress Report will follow the outline proposed in last year's proposal, discussing each item as presented in the Renewal Proposal.

I. Regional Space Studies as an Index of Endothelial Integrity.

This could perhaps more properly be termed radioisotopic assessment of microvascular physiology. Our investigations have progressed significantly in this field such that in addition to microvascular transport of ions and macromolecules determined by equilibrium spaces we are also initiating and progressing on studies to appraise endothelial integrity by using dual tracer techniques to estimate microvascular reflection coefficients. As indicated in the renewal proposal, much of the emphasis has been on continued study of various aspects of brain edema. We have in the past year also progressed significantly in our studies involving the tumor microvascular system and in studies involving hepatic endothelial injury seen in radiation damage. Thus, although the outline will follow the renewal proposal, this report will emphasize those areas where most progress has been made.

a) Regional Brain Spaces. The current studies designed to test the effect of dexamethsone on triethyl tin induced brain edema have left us with some questions, particularly regarding what happens to the tin metabolically. The question of whether or not steroids could induce extracerebral alterations of tin effect has not been sufficiently answered yet and current studies

are underway using labeled triethyl tin to ascertain the fate of the tin in triethyl tin induced brain edema. Once this has been completed we should have a clear idea as to whether dexamethsone alterations seen in triethyl tin induced brain edema are direct effects on brain membrane systems or are influenced by the systemic effects of steroids (1).

We have not as yet pursued the study of lead intoxication encephalitis in the experimental animal in as much as our effort with triethyl tin have not been completed. Our previous experiments have shown significant alteration in regional brain spaces with water and tin induced brain edema that is not identified by an increase in the pertechnetate ion space. This suggests that it may be possible to develop radionuclide techniques to measure altered cerebral function where the brain scan remains normal. These studies revealed that there was a moderate diminution of brain vascular volume in these forms of brain edema. More recently, we have come to observe that a more sensitive index of altered regional brain function may be alterations of regional sodium/potassium ratios rather than alteration of vascular volume per se. Although we do not have as yet quantitative evidence on the relative sensitivity of sodium/potassium ratios vs. vascular volume as an index of cerebral edema or altered endothelial integrity in the brain microvascular system our studies to date have suggested that an earlier and more readily detectable correlation with subtle

alterations of brain function can be obtained by the sodium/potassium approach. We fully intend to initiate clinical studies as soon as we have more clearly documented an optimal approach to discerning subtle derangement in brain physiology using tracers and until this is clarified clinical studies do not appear warranted.

b) Additional Studies of Endothelial Dysfunction. Our continued and expanding interest in the microvascular system as an area of emphasis for studies of biologic considerations in anatomic imaging with radionuclides has progressed significantly over the past year. This has resulted in the preparation of a review article on the history of studies of the microvascular system as prerequisite to our more comprehensive understanding of areas for emphasis using tracer techniques. To complement this historic perspective, we have also in the past year been invited to present the New Horizons for Radiologists Lecture at the Radiological Society of North America Meeting. This paper encompasses much of the work which has been supported in the past and is continuing to be supported under the terms of this AEC Contract. It can be seen that much of the emphasis on ascertaining biologic considerations of anatomic imaging with radionuclides depends upon a more clear understanding of microvascular physiology(2).

Our studies on regional vascular volume during plasma volume expansion have now been completed and are in manuscript form, and

have been submitted for publication to the Amer. J. Physiol.

(3). These studies have shown that there is a remarkable regional difference in the amount of increased transvascular transport of macromolecules following plasma volume expansion using albumin in the experimental animal. These studies suggest however, that the difference in regional specificity for macromoleculature transport in the microcirculation is more dependent upon oncotic pressure than upon vascular distension per se with its concomitant increase in the pore size. Thus, we now have a clue toward the mechanism of altered regional microvascular permeability to macromolecules in plasma volume expansion.

Our studies of radiation effect on tumor microvascular permeability have progressed to the phase of publication (4). In essence, the results of our experiments suggest that there is remarkable influence of radiation on tumor microvascular systems which is not necessarily dependent upon a cytokinetic phenomenon. That is, radiation appeared to alter the integrity of the vascular endothelial structures without necessarily being dependent upon endothelial cytokinetics. Here we were able to show an alteration in the microvascular transport of macromolecules when we gave radiation to tumors using a Gardner lymphosarcoma in mice. This has significant implications and therefore continued studies are planned. We will further investigate whether the endothelial alterations could significantly change the nutrients supplied to

tumors, e.g. oxygen, and therefore change the relative radiosensitivity at various times after the initial radiation therapy. In addition to its practical application for radiotherapy, a further understanding of the radiation effect on the tumor microvascular system seems warranted to clarify the utility of tumor scans in patients undergoing radiotherapy.

We have previously hypothesized that a significant mechanism for the positive tumor scan using gallium or many of the other isotopes suggested for tumor scanning is that these agents demonstrate increased microvascular permeability to macromolecules found in tumors. This is related to the new vessel formation which is essential to supply tumor nutrients. Whether or not other factors including tumor cell binding and pinocytosis are related to the positive tumor scan in no way affects the probability that some of the positivity of tumor scanning agents is due to increased macromolecular transport in the microcirculation of tumors. Since we have demonstrated that this can be altered by radiation, it seems reasonable that when one uses scanning agents to estimate change in tumor size and/or function, the knowledge of possible alterations of endothelial permeability seems a prerequisite to understanding the significance of changing scans in the face of radiotherapy. Obviously, one might ask, does alteration of gallium uptake reflect clear cut influence of radiation on tumor viability or does this merely reflect radiation effect on the micro-

vascular system in the tumor? It is anticipated we should have answers to these questions sometime within the next year or so.

c) Hazards Familiar to the Division of Biology and Medicine.

Over the past years we have embarked on a study of noncytokinetic radiation injury as demonstrated by altered microvascular function. The most encouraging aspect of these studies has resulted in the publication of an article entitled "Non-cytokinetic Radiation Injury: Anticoagulants as Radioprotective Agents in Experimental Radiation Hepatitis". Here we were able to show that heparin effectively protected the rat from hepatic radiation injury when given over prolonged periods of time. This has tremendous clinical implications when one appreciates that a major limitation to hepatic radiotherapy for hepatic metastatic disease is the fact that the radiation damages normal liver. Since radiation hepatitis appears to be predominantly a lesion involving the endothelial structure of the central venules, use of anticoagulants to protect the liver against radiation seems a logical sequel. Although our initial studies are very encouraging, it is obviously essential that we define the optimal type of anticoagulation, duration of anticoagulation therapy, and relative radiation effects prior to embarking on the clinical application of these studies in patients with hepatic tumors. While this may not have direct bearing on the biologic characteristics of anatomic imaging with radionuclides it does have direct bearing as radioprotective agents do to the mission of the Division of Biology and

Medicine, Atomic Energy Commission. This project has been dominantly supported thru AEC contract funds.

Finally, in relation to additional models of endothelial dysfunction, we have prepared a review on microvascular physiology and tracer implications for the forthcoming proceedings of the Association of University Radiologists Symposium sponsored by NIH held at Glen Cove Long Island. The report is attached (5).

II. The Measurement of Ventilation Using Radioactive Xenon, and A Scintillation Camera Interfaced to A Small Digital Computer.

The system described in the previous report has now been in operation for 14 months. This consists of a Pho-gamma III scintillation camera (Nuclear Chicago Corporation) fitted with a diverging collimator interfaced to a PDP 12 digital computer. The xenon-133 gas is delivered from a dual-bag box with a wedge spirometer in the circuit, and is used at a concentration of 1 mCi/liter of either air or oxygen, approximately 50 mCi being used for each examination.

Images are collected in a 32 x 32 matrix, temporarily stored in the buffered memory, and transferred to magnetic tape without data loss. Data collected is under program control and consists of the following steps:

- (1) An image of a uniform disc source of Technetium-99m containing 999000 counts is collected and stored, for subsequent correction of the data for the non-uniform

response of the gamma camera.

- (2) A background image, with the patient seated in front of the gamma camera, is collected for one minute, after adjusting the pulse height analyser for the 81 KeV emission from ^{133}Xe .
- (3) The patient then breathes the ^{133}Xe in air mixture for 4-5 minutes, or until the 50 liters are exhausted, for the washin part of the study, and is then switched to air alone for the washout, which may last up to 10.2 minutes.

An option exists in this part of the program to collect an image of a single breath of ^{133}Xe , followed by its subsequent washout, prior to the washin part of the study.

Data frames are collected for varying time intervals, with 6 second frames when the count rate is changing most rapidly - i.e. at the beginning of the washin, or the washouts, followed by 12 second frames and then 30 second frames when the count rate is low, e.g. at the end of the washout periods. In this way the shape of the activity-time curves are accurately reproduced and the data is more reliable during the low count-rate parts of the study.

The patients name, age, sex, and relevant diagnostic problem is stored on the tape together with the study

number and date.

- (4) Posterior and anterior perfusion scans, using $^{99m}\text{Tc-Fe(OH)}_3$ or $^{99m}\text{Tc-MAA}$, are stored on the same tape. The injection of radioactive particles is given with a patient in the same upright position in which the ventilation study was performed, and these scans are obtained within a few minutes of completing the ventilation examination.

When the data tape is completed it is corrected by a general Pre-Processing Program. This corrects for background activity, for the non-uniform response of the gamma camera, for the deadtime loss of the analog-to-digital converters in the interface, and for radioactive decay.

The corrected data tape is then processed by a special calculation program called "H/A program". This requires considerable user interaction and consists of the following steps:

- (1) After data tape identification, a small region (20-25 cells of the matrix) is outlined between and beneath the lungs for tissue background correction. The average counts per cell from this region are used to correct each frame for the ^{133}Xe content of the overlying chest wall.
- (2) Regions of interest within each lung, or more formal subdivisions such as upper, mid, and lower zones are

next outlined.

- (3) The user is then presented with an activity-time curve for the entire study and selects those frames to be used to determine the height of the washin curve and then those frames for the area beneath the washout curve (or above the washin curve), by placing cursors over the appropriate frames.
- (4) Calculation of ventilation is then automatic, and may be repeated from different parts of the study such as the single breath, or washin, or for varying length of the washout.

Ventilation is determined from the relationship:

$$\text{Flow per unit volume, } F/V = \frac{q_0}{\int_0^t q(t) dt} = \frac{H}{A}$$

Where q_0 is the quantity of tracer present represented by H , the height of the curve at the end of the washin, and $\int_0^t q(t) dt$ is the area under the washout curve, A (6). In the case of the lungs, flow per unit volume can be thought of as the fractional exchange of air, and when multiplied by the time for a single breath gives the fractional exchange of air per breath. The results are presented as the numerical values for H , A , and H/A for each region, and can be summed for combinations of regions for each lung and for both

lungs together.

In addition the results are presented as grey-scale images of each of these values, for each cell in the outlined regions, so that detailed functional relationships within each lung may be readily appreciated from these "functional images". Tidal volume and respiratory frequency are determined from the wedge spirometer tracings, and lung volume is determined from the postero-anterior and lateral chest radiographs, using Barnhard's method(7). The calculations for this are done on the same computer.

Results

The examination has now been performed on more than 180 subjects including 22 healthy volunteers, 40 patients with pulmonary embolism, 54 with chronic obstructive lung disease, asthma or bronchiectasis, and 20 with carcinoma of the bronchus. A variety of other pulmonary conditions have also been studied and several patients have had repeated examinations.

Detailed analysis of the results in the patients pulmonary embolism and chronic obstructive lung disease are in progress, while those for the normal volunteers are complete, and are described in the accompanying preliminary draft, which is being prepared for publication(8).

The normal subjects showed the expected gentle gradient of increasing ventilation from apex to base when ventilation was

calculated from the washin, the washout, and from the single breath. The figures obtained for each zone are similar by these methods. The left lung, although having a smaller volume was ventilated slightly more efficiently than the right, and the difference is statistically significant between the lower zones. No significant medial to lateral gradient was observed in either lung.

A good correlation $\gamma > 0.8$ was found between the fractional exchange of air per breath and tidal volume, and also between the calculated exchanged volume (determined from the fractional exchange of air per breath and lung volume) and tidal volume. The difference between the latter measurement amounted to 200 mls. from the washin studies and 250 mls. from the washout studies; - figures which represent anatomic dead-space and, presumably, some physiological dead-space.

The overall figures for the fractional exchange of air are about 8% greater when calculated from the washout compared to the washin values, but tidal volume was also about 8% greater during the washout part of the studies than during the washin.

The tissue background correction thus allows the washout curves to be used for measuring ventilation. This part of the study is better at detecting regions of poor ventilation, than either the single breath or the washin.

With increasing experience, we have abandoned the single breath part of the study. The present examination requires

about 10 minutes to prepare computer tapes, fill the xenon-balloon and collect a uniformity array. The part of the procedure that concerns the patient takes up to 15 minutes for the ventilation study, and another 10-15 minutes for the perfusion scans. Correction of the data tape takes 5-8 minutes, while the calculation of regional figures takes a further 10-15 minutes.

The procedure is currently undertaken by our senior nuclear medicine technicians.

Our current indications for ventilation - perfusion studies are as follows:

- (1) The differential diagnosis of defects in perfusion in patients with pulmonary embolism and chronic obstructive lung disease; and the diagnosis of pulmonary embolism in the presence of obstructive lung disease.
- (2) The preoperative assessment of patients with carcinoma of the bronchus and other conditions requiring pulmonary resection.
- (3) The early diagnosis of obstructive lung disease and the assessment of its severity independent of the patients efforts.
- (4) The assessment of the effects of bronchodilation therapy and radiation treatment.

Future Plans

Ventilation-Perfusion Ratios:

A new calculation program is almost completed which will enable ventilation-perfusion ratios to be determined from a combination of these ventilation figures and the regular perfusion scans. We shall be able to use our present data, which is stored on a magnetic tape, for these calculations.

Transmission Gamma Densigraphy

A new data collection program is now ready for the transmission studies. The wedge spirometer has been interfaced to the PDP 12 and will be used to trigger data collection from the camera throughout each respiratory cycle. ¹³³Xe washin-washout studies will be used to calibrate the transmission system.

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