MASTER

ATOMIC ENERGY COMMISSION
DIVISION OF BIOLOGY AND MEDICINE

BIOLOGIC CONSIDERATIONS IN ANATOMIC IMAGING WITH RADIONUCLIDES

AT(11-1)-1653

CO#1653-107

- PROGRESS REPORT -

September 1970 - August 1971

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St. Louis, Missouri

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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.

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

This work has progressed very well over the past year. We have developed models designed to study the tracer permeability and regional microvascular function in the brain and lung. This is directed toward clinical application using dual tracers as discussed in our Renewal Proposal. The specific results include:

- a) Regional brain spaces. We have studied multiple simultaneous brain spaces in the experimental animal and have clearly identified our ability to identify various forms of brain edema, e.g. triethyl tin and water induced brain edema. This has resulted in the publication of an article entitled "Radioisotopic Assessment of Cerebral Edema" (1). We are now studying the electron microscopic changes using horseradish peroxidase. This aspect of the work has not yet been completed and there are no results yet available. As stated in the Renewal Proposal, we intend to compare transport of various size macromolecules in the microvascular system in an effort to define the pathophysiologic mechanisms and the potential clinical discernability of subtle brain swelling. This has included a study of radiation induced brain swelling.

We have also studied the effect of drug therapy on brain spaces in the tin induced brain edema. This has resulted in a manuscript entitled "The Effects of Dexamethasone on

Triethyl Tin Induced Edema in the Rat" (2). In our studies on regional brain spaces, we have developed an experimental model to assess brain spaces in ischemic brain injury. This has direct application to brain scanning in stroke, both in understanding the pathophysiologic mechanisms of stroke and directing more meaningful therapy based on radionuclide approaches. In addition, it may be possible to diagnose early brain swelling where the standard brain scan may be entirely normal. Here we have injected microspheres suspended in sucrose medium of similar density such that a quantitative amount of microspheres can be deposited in the rat brain. Serial space estimations have been used to document the delayed increase in technetium brain space with cerebral ischemic injury and the early diminution of vascular volume as evidenced by the decrease in red cell-albumin space (3). Most interestingly, we have observed the time dependent sequence of altered brain spaces in ischemic injury. Immediately after injury, the brain spaces are normal, four hours later there is diminished blood volume, at 16 hours there is increase in the per-technetate space, and at 24 and 48 hours there is increase in the albumin space suggesting a progressive increase in microvascular permeability, ultimately allowing large macromolecules to transit from the intra- to extravascular spaces.

We have used this model to assess the effect of steroid therapy on early brain swelling, and our initial results (4) are sufficiently encouraging to suggest that this model may be useful to define optimal therapeutic approaches,

toward the pathophysiologic aberrations in acute ischemic injury.

- b) Additional models of endothelial dysfunction. We have studied an additional model of endothelial dysfunction, the tumor microvascular system. We hypothesize that most tumor positive scanning agents depend upon increase in the microvascular transport of macromolecules into the interstitial spaces of tumors in comparison with normal surrounding tissue. This has been the subject of a review article entitled "Pathophysiologic Basis of Soft Tissue Tumor Scanning" (5).

Currently, Dr. Jeannie Kinzie of the Radiation Therapy Department has been devoting full time to working with us on this project. She is studying macromolecular transport in tumor microcirculation, similar to our previous efforts in normal animals as described in our article "Macromolecular Transport in Microvascular System" (6). These tumor microcirculation studies will be continued during the forthcoming year in an effort to more clearly define the pathophysiologic basis of tumor localization of radionuclides, and these tracers will be used to assess the pathophysiology of selected experimental tumors. We also hope to define their ability to discern potential response to radiation therapy. A preliminary report describing our methods is enclosed (7).

2. Regional Pulmonary Function Studies.

We have continued our investigation of regional pulmonary function using the camera and computer system discussed last year. Dr. Roger Secker-Walker, from the University College Hospital in England, is now with us and is devoting 100% of his time to the assessment of regional pulmonary function with radionuclides. As described in last year's proposal, we are investigating the regional change in lung density as an index of regional ventilation. Prior to more widespread clinical application of the regional change in lung density study, we felt it was necessary to obtain a more quantitative assessment of ventilation in order to appraise how closely the respiratory change in lung density correlates with quantitative ventilation. Thus, we appraised the regional ventilation methods using inert radioactive gases. Initially, we have studied the washin, equilibrium and washout methods with single breath and constant inhalation techniques to identify their variance and seek the most efficacious method to define regional ventilation in cc's of air per unit lung. This is the subject of a preliminary report enclosed (8).

Regional lung water studies. We have developed a computer program interface for regional lung water studies using the transit difference of multiple tracers as an index of regional lung water space. Initially, we have used antipyrine and labeled plasma protein as dual tracers in an experimental animal in which we have induced regional pulmonary edema by the intrabronchial injection of hyperosmotic radiocontrast material.

We have been able to identify an increase in regional lung water (pulmonary edema) by this technique (9). It is envisioned that in the forthcoming year we will continue to develop this in experimental animals and hopefully appraise its clinical utility by using a dual tracer assessment of regional lung water in patients with pulmonary vascular congestion. The major limitation in developing the technique for more widespread application has been the time it has taken to obtain and program a computer interface for this specific parameter. We are most encouraged by our initial foray into this area, but have not yet obtained sufficient clinical information to warrant the conclusion that it will be widely applicable.

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