

Work performed under AEC Contract No. AT-(40-1)- Title I.
The Bowman Gray School of Medicine of Wake Forest College.

Distribution and turnover of sodium and potassium in acute infections.

Dr. George T. Harrell, Jr., Project leader

July 1, 1949 to March 15, 1950

Facilities: The actual construction of the Isotope Laboratory on the fifth floor of the Medical School, built in part with funds from the preceding contract with ONR, was completed and the lab turned over to us June 20, 1949. It was discovered that the weight of the fume hood, delivered about June 30, was greater than the supporting girders of the old roof of the medical school could support and hence the floor plan of the laboratory had to be revised after construction was completed in order to relocate the hood over a major structural girder. This relocation involved moving of a wall and installation of additional shielding in the form of boiler plates. These alterations were completed and the remainder of the equipment purchased under this year's grant was installed by September 15, 1949. Shipments of sodium 24 were begun September 26, 1949.

Personnel: Dr. Jerry K. Aikawa, one of the AEC fellows assigned to us, has been working full time on the project since the completion of his training course at Duke.

Miss Eloise Rhoades, a technician, began work May 1, 1949, but had to be trained from scratch in techniques being utilized. She and Dr. Aikawa were sent to the Oak Ridge Institute of Nuclear Studies in March, 1950, for a short period of observation in refinement of techniques.

It has been impossible to find another satisfactory girl to add as a second technician to expedite the experiments. It was decided that much of the work now being done by Miss Rhoades could be better done by a man who would be primarily responsible for the handling of animals. Accordingly, Claude Taylor - a negro college graduate who has served as a farm agent, has been hired to begin work April 1, 1950. The school is underwriting from other funds any deficit in the salary of this negro technician which may be incurred in the three months remaining under the present grant.

Dr. Ernest Yount has assisted part time, chiefly in the design of experiments, monitoring, health physics, and in the few human experiments - which often have not been directly related to the primary research project - simultaneously performed.

Dr. Kingsley Stevens, our second AEC Fellow, transferred to Chicago in September 1949, just as he was becoming useful to us.

General plan of experiments

July to September 1949: In order to standardize techniques and to train the technician, determinations of plasma volume and thiocyanate space were done in rabbits in which serum sickness had been induced 1) by injection of human plasma fractions and 2) by passive transfer techniques utilizing immune serum previously prepared in other rabbits. During this interval, the flame photometer,

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spectrophotometer, and the counters were installed and standardized but no isotopes were employed.

September to November 1949: Similar experiments in rabbits with serum sickness and with passive transfer techniques were repeated and observations made on the sodium 24 space. Tissue analyses were done for sodium 24 and total sodium in an attempt to localize the area in which the fluid and electrolyte changes were taking place.

November 1949 to February 1950: The variation in the results in the experimental animals in the preceding groups necessitated determination of normal control values for rabbits. No such data were available in the literature.

March 1950: Preliminary experiments were begun utilizing the above techniques with a pneumococcal skin infection ("dermal pneumonia").

As suitable cases were available on the ward, the facilities and personnel of the isotope laboratory were utilized. No systematic attempt was made to study infectious disease in human beings at this time. Scattered observations have been made using ^{131}I in thyroid disease and ^{24}Na in Addison's and other problems in doses authorized for peripheral vascular studies here by Dr. Harold Green of the Department of Physiology.

Results

The results in repeat serum sickness in experimental rabbits were more variable than similar experiments performed the preceding year. In general an increase in the thiocyanate space at the time of the development of precipitins was observed. In the passive transfer experiments, simultaneous injection into previously unsensitized rabbits of antigen and antibody, prepared in another rabbit against that same antigen, was found six and 24 hours later to elevate significantly the thiocyanate space, which presumably measures extracellular fluid. Such changes were not found when either antigen or antibody alone was injected into control animals. The changes were interpreted as indicating an abnormal increase in membrane permeability directly or indirectly attributable to the immunologic reaction. No significant changes were found in the blood volume in either group.

Utilizing the radiosodium technique, rabbits were passively sensitized with anti-human gamma globulin and were actively sensitized with 10 cc. per kilogram of human plasma intravenously. The increase in the radiosodium space over the base line values was only about 1 to 5 per cent of the total body weight; the errors in the technique were in a comparable range, hence it was not possible to draw a definite conclusion from the study.

Statistically accurate data were obtained in over 50 normal rabbits for plasma volume, hematocrit, thiocyanate space, radiosodium space, serum sodium and serum potassium concentration.

Tissue analyses for radiosodium space were obtained on six control animals.

In the preliminary pneumococcal experiments, satisfactory local edema has been produced, but in the present stage of the experiments bacteremia is developing too rapidly. It is hoped that a better experiment can be designed which will permit longer survival with slower invasion of the blood stream by the organism so that more marked edema and greater alteration in permeability will develop.

Critique of the experiments

Considerable time was lost due to the vagaries of air transport. In the animals with serum sickness it is necessary to start injections 10 days before the expected arrival of the shipment of radioisotope. Due to the weather, several shipments did not arrive on schedule. Because of the short half-life of the sodium and the fact that the animals had passed the peak of the immune response by the time the shipment could be retrieved by surface transportation, at least four weeks' work was completely futile. These very disheartening experiences led us to change to surface transportation entirely and to arrange with the Department of Physiology and the Isotopes Division for joint use of each shipment. The isotope is now arriving weekly rather than bi-weekly and is coming by truck with much greater regularity in the time of arrival.

We encountered great variability in the response of animals this year; in preceding years, the variability has not been so marked. Review of the data indicate that the age, weight, and breed of the animals are all factors which affect their response in our type of experiments. A trip was made to Oak Ridge to consult with Mr. Jacob Furth of the Biology Division, Oak Ridge National Laboratories, in an attempt to devise means for reducing these variables. We discovered that Dr. Furth has encountered much the same problem and had arrived at the same ultimate solution as we. It would appear that we must plan in the future to raise our own animals from an inbred strain utilizing groups of the same age and weight. The negro animal technician has been hired with this end in view, but it may be a year before the full benefits of the animal breeding program can be achieved. It is not clear how much additional expense this program may incur and how it can be borne.



SUMMARY OF PROJECT

Distribution and Turnover of Sodium and Potassium in Acute Infections

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Patients recovering from infections or serum sickness have a diuresis during recovery; water and chloride are lost. In the acute phase of Rocky Mountain spotted fever and trichinosis, edema develops and the blood chlorides and proteins drop; no data are available on sodium and potassium.

It is not known from blood volume and thiocyanate studies whether the extravasated fluid is found between cells or within them. The increase in permeability can be visualized as a graded series of pores. In mild disease only crystalloids leave the blood stream; in more severe instances small protein molecules such as albumin, or larger ones such as gamma globulin will leak out. A small defect should be detectable by radioactive ions, a larger one by tagged protein molecules. An antigen-antibody reaction may be responsible for the defect.

If the mechanism by which increased amounts of electrolytes are passed across capillary and cell membranes can be established, it may be possible to correct the physiologic abnormality. Eventually it may be possible to induce an increase in permeability so that radioisotopes could enter certain tissues and exert a radiation effect.

Some tumors may be caused by filterable viruses; others can concentrate viruses such as vaccinia. If a virus could be introduced into a cancer and immune serum administered, an antigen-antibody reaction should take place only on parasitized cells and circulating radioisotope be concentrated in cancerous tissue. If, through application of the auto-antibody technique, an antiserum against cancerous tissue can be made, a similar reaction would take place and only on malignant cells.