JOINT MEDICAL RESEARCH COMMITTEE MEETING
30 March 1972

The 105th meeting of the Joint Medical Research Committee (of the Office of the Director of Defense Research and Engineering) was held on 30 Mar 72 at the Armed Forces Radiobiology Research Institute (AFRRI). A series of short presentations was made covering the collaborative program of research begun during the past six months at the AFRRI.

(Cf: Attachment 1: Agenda of Meeting)

The meeting was chaired by Dr. Chris J. D. Zarafonetis, M.D. of the Simpson Memorial Institute, Ann Arbor, Michigan, and was attended by representatives from Headquarters, DNA, the offices of the three Surgeons General, and a variety of military and federal medical facilities and agencies.

(Cf: Attachment 2: Attendee List)

The collaborative work presented is summarized below in abstract form.

1. Development of Clinical Nuclear Medicine Technology, 1970-1980

M. C. Johnson, COL, MC, USA
Chief, Nuclear Medicine Service
Walter Reed General Hospital

The numbers and types of isotope diagnostic procedures are increasing at a remarkable rate, but, at present, are still limited to determinations of static structural changes in certain major organ systems. Dynamic studies are not yet possible, and the resolution of structural detail is still not comparable to the best x-ray techniques.

In the future, improvement of resolution will become possible utilizing solid state detection now being developed, and dynamic studies utilizing computers tied in with imaging systems will also become available. This latter will be an extremely valuable contribution to clinical nuclear medicine.

In the meantime, there is a critical need for research in the utilization of isotopes in diagnostic systems. The development of new radiopharmaceuticals is a particularly appropriate area for collaborative work and has already started with AFRRI as the core laboratory for the necessary basic work. The present status of this program will be outlined by MAJ George Dunson, MSC.

2. Development and Production of New Radiopharmaceuticals

G. Dunson, MAJ, MSC, USA
Chief, Radiopharmacy Section
Walter Reed General Hospital

Two years ago, collaboration began between Walter Reed and Bethesda using ^{18}F. Since then, this program has expanded to include a large number of institutes, both military and civilian. It now includes:

Armed Forces Radiobiology Research Institute
Walter Reed General Hospital
Walter Reed Army Institute of Research
U.S. Naval Hospital, Bethesda
Naval Research Laboratories Cyclotron Facilities
Fairfax Hospital
Georgetown University Hospital
Johns Hopkins Medical Institution
Prince Georges General Hospital
Northern Virginia Pathology Laboratories
Washington Hospital Center.

AFRRI's contribution is planned to include both research and development of new radiopharmaceuticals and production of those agents which would not be available commercially, or which would be prohibitively expensive. Projects involving ^{99}Tc (POLYPHOSPHATE) and ^{123}I have already been set up at the AFRRI.

A collaborative effort with the cyclotron facility at the Naval Research Laboratory utilizing alpha spectroscopy techniques in an effort to develop a tumor specific agent has been started.

A wide variety of diagnostic lists are now being produced and soon will be in the AFRRI laboratories at a cost which is far below those available commercially, and with increased quality.

The pig has been tested as a potential experimental animal for isotope research and appears so far to be an ideal animal.

AFRRI has become the central and critical laboratory for the development and production of these radiopharmaceuticals.

Comments by Captain Varon

The use of ^{99}Tc (POLYPHOSPHATE) as a bone scanning agent has great promise as a scanning test in patients with suspected breast malignancy to determine prior to

biopsy whether osseous metastases were present or not. The simplicity, low cost, and safety of this procedure lends itself to becoming a reasonable pre-operative screening test.

3. Therapy of Radiation Injury by Marrow Transplantation

K. E. Kinnamon, LTC, VC, USA
Assistant Chief of Biology
Medicinal Chemistry Division
Walter Reed Institute of Research

Bone marrow transfusions in man have a high incidence of graft vs host reactions or secondary disease. The timing of secondary disease is unfortunate, because it coincides with the ability of the bone marrow to recover.

In animals recovering from GvH, a reversal to original cell types has been seen. Antibodies against the graft bone marrow would suppress that tissue, prevent the GvH reaction, and allow regeneration of the normal cell types.

Crude antilymphacy-to-serum has been tried in an attempt to suppress the graft marrow without success, although problems of purity and timing still require study.

Comments by Captain Varon

The following two abstracts are of special importance because they demonstrate how the AFRRI can collaborate with and contribute to residency and post graduate medical training programs.

4. Neurosurgical Research Utilizing the Microsurgical Research/Teaching Laboratory: Conception - Development - Projection

B. L. Rish, CDR, MC, USN
Neurosurgery Services
National Naval Medical Center

Clinical microsurgery was originally developed by otologists in order to do middle ear surgery. During the past two years, neurosurgeons have turned to this technique more and more as a solution to their basic

problems of small field intracranial surgery, particularly neurovascular surgery.

The adoption of a new technique requires a whole new training program which will be based here at the AFRRI and open to a variety of surgical specialities.

Currently, a combined research and training program is being established at the AFRRI in conjunction with the inception of a neurosurgical training program at the U.S. Naval Hospital, Bethesda.

Two research projects have been started:

1. Management of vascular spasm: with spasmolytic agents applied directly to vessels exposed through microsurgical approach.

2. Development of autogeneous shunts in the management of hydrouphalus, to eliminate foreign body reactions using autografts are being tried now.

5. AFRRI's Contribution to the U.S. Navy's Neurology Residency Program

W. L. Brannon, CDR, MC, USN
Chief, Neurology Service
National Naval Medical Center

During the past 25 years, the field of neurology has expanded tremendously, but the U.S. Navy has lagged behind. In July of 1971, the clinical training program in neurology at the NNMC was tentatively approved by the AMA. The one part lacking was the basic science and research base. This was initially provided by liason with Georgetown University, but in the past several months we have substituted an extensive basic new science program at the AFRRI. This joint program has been approved by the American Board of Psychiatry and Neurology.

6. The Hippocampus and Voluntary Movement

H. Teitelbaum, Ph.D.
Associate Professor, Psychology Department
University of Maryland

We have been studying what takes place in the brain when an animal initiates movement, using EEG electrodes in various locations.

Electrodes in the hippocampus have demonstrated that there is hippocampal involvement in voluntary movement. This is an area which heretofor had not been thought to be involved in movement. These observations have been repeated and correlated with biochemical changes by Dr. Catravas of the AFRRI.

7. Effect of Opiates on Central Nervous System Enzymes

G. N. Catravas, Ph.D.
Project Director, Experimental Pathology Department
Armed Forces Radiobiology Research Institute

In the experiments presented today the morphine-induced changes in the activities of the following brain enzymes were studied: a. Choline acetyl transferase (acetyl choline synthesis), b. Acetyl cholinesterase (acetyl choline hydrolysis), c. Monoamine oxidase (deamination of biogenic amines), and d. RNA polymerase (brain RNA synthesis). The following brain areas were selected: a. Cerebellum (synergic action of voluntary movement), b. Cerebrum (motor expression), c. Hippocampus (learning - memory), d. Hypothalamus (emotional expression), and e. Thalamus (sleep-wake states, relay station for pathways from receptors to cerebrum).

Rats were made tolerant to morphine by injecting the drug twice a day for 7 days and sacrificing them at predetermined intervals of time following the last injection. Most important results thus far:

a) Choline acetyl transferase: a very pronounced increase in activity during the first 15 minutes (when the animals become superactive) followed by decrease and then an increase. These activity changes are much more pronounced in the cerebellum.

b) Acetyl cholinesterase activity increases in all brain areas studied, but not to the extent that Choline acetyl transferase does. This indicates net acetyl choline synthesis.

c) Monoamine oxidase activity decreases in all areas with maximal values at approximately 30 minutes after last morphine injection.

d) RNA polymerase activity in the thalmus decreases. However, in the Hippocampus after an initial drop, a very pronounced activity increase has been observed.

8. Glycoprotein Profiles in Tumor Diagnosis

M. F. Dolan, CDR, MC, USN
Head, Research Branch
Laboratory Service
National Naval Medical Center

Since July 1971, the Naval Hospital, Bethesda, Maryland, has been pursuing a collaborative effort with Mr. Evans and Dr. Sobocinski of the Radiation Biology Department of AFRRI, directed toward critical assessment of the value and limitations of the serum concentration of the various classes of protein-bound carbohydrates as an aid in differential diagnosis of neoplastic diseases from "non-malignant processes".

Despite the relatively small numbers to date, 273 blood serum samples from 176 individuals, the results are very promising not only for the primary objective, but as a tool to estimate tumor activity and as a prognostic tool in tumor therapy.

Thus, 93.7% of some 25 different malignant tumor types, in varying stages of proliferation were objectively selected from controls with no clinical disease, normal pregnancies, benign tumors, non-neoplastic diseases, and malignancies which had achieved a "5-year cure". Only one case each of ulcerative colitis and Crohn's disease, both in the acute phase, fell in the metastatic malignant tumor area, and those returned rapidly to normal with treatment.

Where prediagnostic or pretreatment specimens were available, all the estimates of the status of the tumor (benign or malignant) and the activity of malignant tumors proved to be correct. When pre- and post-treatment sera were tested, changes in the glycoprotein profile appeared to be of significant prognostic value.

9. Using Changes in the Visual Acuity of Primates as a Tool to Assess Retinal Damage

C. R. Curran, Capt, USAF, VC
Principal Investigator, Behavioral Sciences Department
Armed Forces Radiobiology Research Institute

In the last few years, the most common method of evaluating damage to the visual mechanism has involved exposure of primates to the conditions which may cause visual damage and then analysis of any changes in the

animals' visual acuity. Visual acuity in primates is currently tested with Landolt "C" rings. The testing procedure essentially determines the smallest gap in the rings, expressed as 20/20, 20/15, etc., which the animals can detect at a level significantly greater than chance.

Recently a collaborative effort was established between the Navy Medical Research Institute and AFRRI pooling the relevant expertise of each laboratory to study the location of lesions produced in the area of the fovea by irradiation with a Q-switched neodymium laser and the extent of the resultant visual decrement. Particular attention will be devoted to the large spot case in which a series of laser pulses at energy levels below the threshold for damage from a single pulse will be directed at the fovea. Emphasis will be on exposure parameters which simulate possible exposure conditions in the operational environment.

Similar evaluation of the visual acuity of primates will be conducted following exposure at AFRRI to pulsed doses of 43 MeV electrons from the linear accelerator at or above 2000 rads. In this case, the Naval Medical Research Institute will also participate in evaluation of any resulting observable retinal damage.

A collaborative effort is also in the planning stages with the Armed Forces Institute of Pathology. Until recently, all evidence strongly indicated that, once a lesion had been produced on the retina, the damage and its resultant visual decrement were permanent. Preliminary data collected at AFIP suggests that at some energy levels there may in fact be a reversal and some recovery may actually occur. The objective of a collaborative effort would be to inspect more deeply into the relevant parameters that may be implicated in such recovery.

10. Leucogenenol on the Site of Antibody Formation

F. A. H. Rice, Ph.D.
Professor of Chemistry
American University

It has been found that daily injection of leucogenenol into rats that have been previously injected with sheep erythrocytes leads to an earlier formation of peak titers. Using the hemolysin-N-gel technique it has been found that leucogenenol causes an increase in the concentration of antibody-forming cells in lymphatic tissues and in the bone marrow which presumably results in the formation of peak titers.

Splenectomized rats, injected daily with leucogenenol and 3 days after splenectomy with sheep erythrocytes, reach normal peak titers in 7 days. Again, leucogenenol increases the concentration of antibody-forming cells in lymphatic tissues and in the bone marrow which presumably accounts for the splenectomized rats' ability to respond to the injection of sheep erythrocytes with the formation of a normal titer of hemolysin.

11. Enhancement of Navy Operational Toxicology Programs Through Collaborative Biomedical Research

T. A. Hill, LCDR, MSC, USN
Officer in Charge, Navy Toxicology Unit
National Naval Medical Center

The Navy Toxicology Unit (NTU) is currently concerned with four programs in operational toxicology. These are material toxicity, emergency exposure toxicity, hyperbaric toxicology, toxicodynamics. To gain additional expertise in support of these programs, collaborative studies are being developed with the AFRRI in the areas of performance evaluation, absorption, distribution, metabolism, and elimination.

A performance evaluation study is currently in progress with trained Rhesus monkeys to determine the behavioral effects of continuous inhalation of sulfolane. Sulfolane is a heterocyclic sulfur compound with potential for use in the CO_2 scrubbing system of nuclear submarines. Through the liaison to AFRRI established via the behavioral studies, protocols are also being established for the conduct of pharmacologic studies and, when appropriate radio labeled toxicants are available, complete metabolism and distribution studies. It is anticipated that the first of these studies will begin with tricyclomethylene trinitrate (a toxic ordnance waste) in approximately 30 days.

12. Effects of Anesthetics on Atrio-ventricular Conduction in Dogs

J. L. Atlee, LCDR, MC, USN
Staff Anesthesiologist
Anesthesiology Department
National Naval Medical Center

Up to 61% of patients undergoing anesthesia may have periods of cardiac arythemnia. The severity and frequency of these arythemnias are a function of cardiac conductivity. Anestheti: effects on cardiac conductivity have not been studied adequately. We have instituted a collaborative

research effort with the staff of the AFRRI in this area, employing relatively new techniques of catheter electro cardiography, monitoring electrical activity of the bundle of this directly.

Analysis of the electrical activity requires fairly sophisticated recording and analytic systems and the ability to precisely locate the catheters.

This system allows study of a wide variety of drugs as well as anesthetic agents, and we have done a preliminary study on halothane alone and halothane combined with other drugs.

13. Bone Marrow Transplantation Following Whole Body Irradiation

J. L. Curry, LCDR, MC, USN
Head, Tissue Bank
Naval Medical Research Institute

A bone marrow transplantation program is being established at the National Naval Medical Center, using the facilities and staff of the Tissue Bank of the NMRI and the U.S. Naval Hospital, Bethesda making up the Transplantation Service, NNMC. Renal transplants and bone marrow transplants are proposed.

Patients with aplastic anemia, certain rare types of immune deficiencies, and leukemia, will be candidates for bone marrow transplantation. The leukemia patients are by far the most common, but represent the greatest difficulties in management because of the need to ablate the abnormal marrow completely either with cytotoxic chemicals or whole body irradiation.

At the present time, improvements in available techniques have made engraftment possible in over 90% of patients, but have not made it possible to overcome graft vs host disease. Comparison between cytotoxic drugs and whole body irradiation indicates that whole body irradiation has a modest but definite theoretical advantage. Proper radiation sources are difficult to find, but the ^{60}Co source at the AFRRI is ideally suited for uniform whole body irradiation.

Comments by Captain Varon

The use of the AFRRI ^{60}Co source for this program and a similar one planned by Drs. Graw and Herzig of the National Institutes of Health will be on the agenda of the AFRRI Board of Governor's meeting on 13 Apr 72.

Following the presentations, Dr. Zarafonetis made the following remarks:

Captain Varon, I want to thank you and all the essayists for a very splendid series of presentations, and also, to apologize to you and them for putting you under the tight pressure of the time limitations. This has been necessitated by the fact that I am due to meet with Secretary Wilbur and the Surgeons General at 1230 today. I will be very happy to convey to them some of the impressions I have of this morning's discussions; in particular, the great amount of collaborative work that is going on, not only within the services but also with our civilian federal agencies and our universities. As you are well aware, we are under the gun to make maximum use of our facilities and capabilities in cooperation with all members of our medical brotherhood.

We must continue to do the type of thing that has been displayed here this morning. Aside from the inherent value of the research itself is the fact that we have an institute here that is open to all. This is what all institutes are going to have to be. Society is demanding it of us, and you all are showing really great leadership in this connection. I am sure Colonel Huycke and the rest of us that are on the Joint Medical Research Committee are delighted and pleased with the rapid progress that has been made in this direction through your efforts here at AFRRI. Thank you all very much for a most enjoyable morning.

The meeting closed at 12:30 p.m..

MYRON I. VARON
Captain MC USN
Director