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ATOMIC ENERGY COMMISSION

Division of Biology and Medicine

A PROGRAM FOR THE
STUDY OF TRANSPLANTATION OF TISSUES AND ORGANS
AND
RELATED TOPICS IN SURGICAL RESEARCH

FINAL TECHNICAL PROGRESS REPORT
TO END OF CONTRACT TERM WORKING INTERVAL
January 1, 1973

Department of Surgery of the Harvard Medical School at the
Peter Bent Brigham Hospital, Boston, Massachusetts

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MASTER

This is a technical Final Report covering work over several years through to the official contract terminus 30 June, 1972, and thereafter a terminal six months for final expenditure of unexpended budgetary allocation to:

January 1, 1973

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FINAL TECHNICAL REPORT

Work Completed to January 1, 1973

Submitted January 1, 1974

Responsible Investigator: Dr. Francis D. Moore

Department of Surgery, Harvard Medical School, Peter Bent Brigham
Hospital, Boston, Massachusetts —

CONTRACT NUMBER AT(11-1) - 3424

(Formerly NY CONTRACT NO. AT(30-1) - 2265)

1. HISTORICAL

This work was originally commenced by Dr. Moore under contract with the Office of Naval Research about 1946. The original focus was on the application of radioactive and stable isotopes to a variety of medical problems, including the study of body composition by isotope dilution.

In 1948, this contractual relationship was taken over by the Atomic Energy Commission and the work was broadened to include a variety of parameters of surgical metabolism, physiology, and endocrinology bearing on the care of the critically ill or injured patient.

During the years 1948-1965 the study of injury, acute illness and its care was "programmatic" for the Atomic Energy Commission and this remained the central focus of the work.

Starting about 1960, the Atomic Energy Commission began to have an interest in tissue transplantation because of the possibility of treating massive radiation damage by bone marrow transplantation. Thus, this area of work became a feature of the contract study of critical illness and surgical convalescence.

About 1966 or 1967 the programmatic interest of the Atomic Energy Commission changed so that there was little or no interest in the general care of human injury but the main focus was on tissue transplantation.

By 1971, it became evident that the Atomic Energy Commission was no longer interested in work in this general area and, on advice from Washington, we were told that the entire medical orientation of the Atomic Energy Commission would be towards certain types of radiation injury. It was thus inevitable that this contract would be phased out.

This phasing out process has now been completed and these laboratories have sought support from other sources.

2. GENERAL SUMMARY OF AREAS COVERED (1946-1973)

In this section no effort will be made to recount in detail the studies undertaken, publications made, clinical procedures instituted, or educational impact of this contract. The reader is referred to the extensive files available in the New York Operations Office or in Washington (Division of Biology and Medicine) where, on an annual basis, extremely detailed and carefully drawn reports will come readily to hand. Instead, we will simply list the areas that have been under investigation during these years with a

referenced bioliography.

A. Body Composition as Measured by Isotope Dilution

1. Definition of principle.
2. Establishment of methods from multiple isotope dilution.
3. Definition of human normals throughout the age standard for both sexes.
4. Definition of changes characteristically seen in disease. Reference is made here to the book published in 1963, "The Body Cell Mass and Its Supporting Environment; Body Composition in Health and Disease" by Moore et al. (Saunders, W.B., Philadelphia).
5. Autoregulation of body composition with particular reference to restoration after bleeding.
6. The physiology of hemorrhage as an example of body compositional distortion and self-regulatory restoration by transcapillary refill; endocrine response; oxygen transport kinetics.
7. The human skeleton as a feature of body composition; methods for estimating its weight in the living.
8. Body composition in the normal dog; distortion of canine body composition with chronic heart failure.
9. Isotope kinetics; definition of kinetic models and establishment of prototypic mathematical analysis formulations. Reference is made here to the article "Reference Models for Clinical Studies by Isotope Dilution" by Moore, F.D., et al. (Ann. Surg. 168:671, 1968).

B. Metabolism and Endocrinology in Surgical Care in Critical Illness

1. Definition of normal post-traumatic metabolism in man.

2. Application in clinical and metabolic care in trauma, burns, heart disease, and shock.

3. Basic surgical nutrition; definition of calorie: nitrogen ratios required for tissue synthesis.

4. Metabolic care of the surgical patient in a variety of clinical situations. Reference is made here to the two books on this topic. First (1950) "The Metabolic Response to Surgery" by Moore and Ball (Thomas, C.A. 1950), and the more complete text "Metabolic Care of the Surgical Patient" by Moore (Saunders, W.B., 1958).

C. Post-Traumatic Pulmonary Insufficiency

1. Definition of the problem as principal cause of death under critical care.

2. Definition of the syndrome; description of phases of patho-physiologic development and treatment.

3. Publication of summarizing book "Post-Traumatic Pulmonary Insufficiency" (Moore et al., Saunders, W.B., 1969).

4. Development of oxygen mixing equipment to standardize oxygen delivery.

5. Initial bioengineering development of a new extracorporeal oxygenator for prolonged extracorporeal support.

6. Definition of muscle surface cationic electrometry for definition of changes in muscle surface pH in the low flow states, anoxia, pulmonary insufficiency, and postoperative cardiac patients.

D. Transplantation of Tissues and Organs

1. Laboratory and clinical transplantation of the kidney; early phases; first reported series in man.

2. Transplantation of kidneys in identical twins.

3. Definition of drug immunosuppression using azothioprine; initial application in patients.

4. Commencement of continuing series of kidney transplantation between unrelated donor-recipient pairs, as well as within family groups. Establishment of kidney transplant routines now used widely throughout the world and based on azothioprine and related drug immunosuppression.

5. Laboratory and clinical transplantation of other tissues and organs: bone marrow, parathyroid, ovaries, thyroid, liver.

6. Use of whole body irradiation and local tissue irradiation in transplantation of tissues and organs.

7. Exploration of antilymphocyte sera and antilymphocyte globulin for use in laboratory and clinical transplantation of tissues and organs.

8. Exploration of the newer, less toxic methods for establishing transplanted tissues; thoracic duct fistula; active and passive enhancement by pretreatment either with antigen or antibody.

9. The procurement, preservation, and viability assessment of tissues and organs.

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Final Progress Report - AT(11-1) - 3424

Bibliography of Work Supported Wholly or in Part

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- b. Post-Traumatic Pulmonary Insufficiency; Oxygen Toxicity; Clinical Management
- c. Extracorporeal Support; the Membrane Oxygenator; Bioengineering Design
- d. Oxygen Transport and the Oxyhemoglobin Dissociation Curve

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- c. Immunologic Studies and Other Tissue Models
- d. Organ Procurement and Preservation
- e. Legal and Ethical Aspects; Historical Accounts

Bibliographic Outline

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