

Report of the
Visiting Committee for the Medical Department
Of
Brookhaven National Laboratory
To the
Board of Trustees, Associated Universities, Inc.
Spring, 1963

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The Visiting Committee for the Medical Department of Brookhaven National Laboratory met at the Laboratory May 21 and 22, 1963. Members of the Committee who were present were: A. Baird Hastings, Chairman, Louis H. Hempelmann, C. Phillip Miller, Shields Warren, Maxwell M. Wintrobe and W. Barry Wood. Members absent were: Bronson S. Ray and Joseph E. Smadel. Dr. William H. Sweet, a member of the Board of Trustees of Associated Universities, Inc., also attended all meetings of the Committee, except its executive session.

The first session of the Committee was held in the office of Dr. Victor P. Bond, Chairman of the Medical Department. Also present were Dr. Maurice Goldhaber, Director of the Laboratory, Dr. C. Williams, Deputy Director, and Dr. C. E. Falk, Associate Director.

Dr. Goldhaber welcomed the Committee and expressed the hope that the Committee would be of assistance to Dr. Bond in seeking needed personnel, as well as in reviewing the scientific activities of the department on behalf of the Trustees.

Dr. Bond reviewed the present status of suggestions made by the Visiting Committee in 1962, which had been transmitted to him. These were: (1) On relations with hospitals and physicians in the area and on availability of patients for study; (2) on steps taken to strengthen the clinical research program; (3) on steps taken to engage in cooperative activities with the Biology Department; (4) on the progress toward construction of needed additional facilities. The Committee feels that Dr. Bond has made as much progress as could be expected toward solving these problems. (The specific status of these four points as reported by Dr. Bond, is appended as Annex I.)

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Dr. Bond reported the following changes in senior personnel:

(1) Dr. W. L. Hughes, Head of the Division of Biochemistry, is leaving to head the Department of Physiology, Tufts Medical School.

Until a new Head of the Division of Biochemistry is appointed, Dr. W. W. Shreeve will serve as Acting Head.

(2) Dr. Irving L. Schwartz, Head of the Department of Physiology, University of Cincinnati, has been asked to join the staff of the Medical Department to develop research activities in the field of biochemical aspects of hormone action.

(3) Dr. W. Johnson, a pathologist at the University of Utah, will be appointed as Scientist, in June 1963.

Dr. Bond also asked the Visiting Committee for assistance in recruiting able, young, American medical scientists.

The Chairman of the Visiting Committee requested specific members of the Committee to prepare brief statements on the several scientific presentations they were about to hear and which were in their field of interest and experience. (These statements are appended as Annex III.)

The Committee then adjourned to the Conference Room to hear reports by the staff of the Medical Department on the present status of their research activities.

(The program of the scientific sessions, which continued until noon of the second day, is appended as Annex II.)

Following luncheon on May 22, the Committee again met with Dr. Goldhaber, Dr. Williams, and Dr. Bond, and reviewed in more specific terms the problems of the Department of Medicine.

The Committee then met in executive session and adjourned at 3:00 P. M. The conclusions reached by the Committee, together with both general and specific comments on the program of the Medical Department follow.

INTRODUCTION

The Medical Department of the Brookhaven National Laboratory, like its other departments, has both general and specific responsibilities. It has a responsibility to advance medical knowledge in general and it has a responsibility to utilize the techniques and facilities which are unique to Brookhaven, to advance knowledge on the effects of ionizing radiation. These two categories of responsibilities cannot be discharged separately.

The Brookhaven Laboratory is an academy in the ancient sense, where a society of scientists of widely different interests, meet and work together. All aspects of science from mathematics to the study of man are here represented.

It is fortunate for the advancement of science that the Brookhaven National Laboratory is not a service laboratory either to a government agency, or to a single university, but is a research and teaching arm to both, born of a partnership between universities and the Atomic Energy Commission.

By research in the Life Sciences, we hope to gain knowledge, both basic and applied, that will contribute to the health and longevity of man in an age with new environmental hazards.

To this end, the Department of Medicine is directing its research efforts.

It is the considered opinion of the Visiting Committee that in the 15 years of its existence, the Medical Department of BNL has established itself internationally as a source of important new medical knowledge, it has pioneered in research on the medical uses of nuclear energy, and it has been an important training ground for medical scientists. In other words, it is fulfilling with distinction its responsibilities in relation to its several missions.

1. Administration

The Committee wishes to record that the appointment of Dr. Victor Bond as Chairman of the Medical Department is proving to be highly successful. His rapport with the staff is excellent and the spirit of cooperation which pervades the department is highly commendable.

He has firm knowledge of the research activities which are underway and his plans for future development of the department are sound.

It is to be especially hoped that he will be successful, at an early date, in the identification and appointment of a highly able biochemist of the first rank to head the Division of Biochemistry.

The plans to increase the present roster of 39 scientists to 44 or 45 is regarded as a sound and reasonable rate of growth.

2. Collaboration with Universities and Educational Activities

a. There have been a total of 112 individuals from universities listed as Collaborating Scientists with the Department of Medicine. Of these, 60 have been at Brookhaven for part or all of their work.

This summer, it is anticipated that there will be 12 Research Collaborators and 19 students. Such collaboration is desirable and should be encouraged.

b. It has been customary for some years to hold two day conclaves on nuclear science in medicine. These have been attended primarily by medical scientists for the purpose of acquainting them with the opportunities to apply nuclear science to medical problems and to study the harmful effects of radiation.

It is the opinion of the Visiting Committee that such conclaves for medical scientists are not needed as much today as they were previously, and that they should be discontinued.

In their place, it is suggested that symposia on timely topics in the field of nuclear medicine be held, and that in addition to the experts in their several fields, a number of active medical scientists not working directly in

nuclear medicine be also invited to attend.

3. Hospital

It was the opinion of the clinically experienced members of the Visiting Committee that the Hospital of the Medical Department is well administered, the patient care is excellent, and the clinical studies on patients are well carried out.

The problem of patient acquisition has improved during the past year and the availability of suitable patients for clinical study is not a problem at present.

4. Medical Reactor

Dr. Bond reviewed the history of the medical reactor and its use in the study of neutron capture therapy.

The studies undertaken this year are the result of decisions reached by a committee of the Medical Department. The problems undertaken have been: (1) To provide an epithermal neutron beam which would be more penetrating into tissue, (2) to make a systematic study of factors which alter the effects of equivalent radiation of cells in tissue culture, and (3) to study the nature of the reactions that radiation produces in tumor tissue in animals.

The Visiting Committee regards as sound the problems being undertaken with the reactor this year, and ones which need to be solved before further studies on human cancer are undertaken.

5. Research Activities

The research activities of the Medical Department can be grouped under the following headings:

I. Effects of ionizing radiation:

a. On blood radiated outside the body -- recirculated in the body.

b. Exposure of mice to neutrons of discrete energies (Van de Graaff generator).

c. Radiation by "Bragg effect" on animals, their tissues and tumors. (Joint study with Physics Department.)

d. Radiation of animals, tumors and tissue cultures by the medical research reactor.

II. Tumor Detection:

a. Development of Differential Multidetector.

III. Studies on skeletal tissue:

a. Rates of turnover of strontium and calcium.

b. Factors affecting growth and aging of skeletal cells.

c. Effect of irradiation on bone growth.

IV. On immune mechanisms:

a. Following transfusion of homologous and heterologous marrow cells.

V. On nucleic acids:

a. DNA and RNA synthesis and metabolism.

b. On lethal action of H^3 -thymidine (high concentrations) on HeLa cells.

c. On fate of labelled blood cells in body.

VI. Protein metabolism:

a. Collagen -- the role of hydroxylysine and its formation.

b. Tryptophan -- its metabolism in normals and neoplastic disease.

VII. Carbohydrate metabolism:

a. Studies on animals and patients to determine pathways of hydrogen metabolism in relation to carbon metabolism, and as modified by hormone action.

IX. Inorganic metabolism in animals and humans:

a. Salt intake in relation to hypertension.
b. Genetic factors in relation to salt induced hypertension.
c. Trace metal metabolism by neutron activation analysis.
d. Interactions of transition group trace metals with free radicals in biological systems.

X. Computer analysis of tracer kinetics (with Mathematics Department).

Reports were made to the Visiting Committee on most of the topics listed above, and discussions were held with the investigator making the report, in each instance. (Annex III contains the written comments prepared by individual Committee members on individual reports. It is obvious that, in a day and a half, it is impossible to become adequately acquainted with each research activity to permit a critical evaluation.)

GENERAL COMMENTS ON RESEARCH PROGRAM

1. The Committee is in agreement that the overall research program of the Medical Department is sound, is oriented toward the objectives of BNL as a whole, and is adequately diversified to provide advances in medical knowledge on the important frontiers of medicine in general, and of nuclear medicine, in particular.

2. The hospital, the laboratories and the medical reactor, housed in one unit, provide a unique facility for the conduct of the Medical Department's research program.

3. The senior and junior personnel engaged in the several research activities are well qualified and, for the most part, enthusiastic about their work.

4. The close proximity of the other departments of Biology, Chemistry, Physics and Mathematics makes collaboration with members of these departments readily possible. It is the impression of the Committee that more such collaborative research is underway than ever before. This is regarded by the Committee as a highly desirable development.

SPECIFIC COMMENTS

1. The Committee commends Dr. Bond and his staff for the thought that was given in organizing the scientific program. The first seven presentations were given by senior personnel, each of whom had a half hour to describe the research activities of his unit, and put his research in its perspective. This made more meaningful the subsequent sessions with the individual research workers.

For these sessions with individual scientists, the Committee was divided into three groups, each of which met for half an hour, alone, with a particular scientist. This permitted a total of 30 of the Medical Department staff to discuss their work with at least two members of the Visiting Committee in an atmosphere of informality.

2. After dinner, on the evening of the first day, the members of the Visiting Committee met in the sitting room of the Guest House for informal discussion. This proved to be of great benefit, particularly to the new members of the Committee. It also provided an opportunity to discuss the problems of the Medical Department much more thoroughly than was possible in the time formally allotted to the Committee.

For these reasons, it is suggested that in the future, the evening of the first day be kept free in order that the Visiting Committee may meet informally, if it so desires.

3. The suggestion was also made that it would be highly desirable for new members of the Visiting Committee to be invited to spend three days at the Brookhaven Laboratory on the occasion of their first meeting. The extra day, preferably after the official meeting, could be well employed in familiarizing themselves with laboratories and hospital of the Medical Department, and with the special facilities of the other departments.

4. The Committee records its appreciation to Dr. Goldhaber and his staff, and to Dr. Bond and his associates for their time and for the arrangements they had made to provide the Committee with a maximum of information in the time available. The Committee is also appreciative of the presence of Dr. William Sweet at the scientific sessions.

Respectfully submitted,
A. Baird Hastings, Chairman
Louis H. Hempelmann
C. Phillip Miller
Shields Warren
Maxwell M. Wintrobe
W. Barry Wood

Visiting Committee members not present at the meeting:

Bronson S. Ray
Joseph E. Smadel

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A N N E X I.

Present Status of Recommendations
Made in Visiting Committee Report, 1962
(Data supplied by Dr. Victor Bond)

1. Relationships with hospitals and physicians in area; patient acquisition.

a. A notice indicating types of disorders currently under study has been sent periodically to all physicians in Suffolk and Nassau Counties. This procedure has recently been extended to include Chiefs of Medicine of major New York City Hospitals, and all Professors of Medicine in New York City Medical Schools.

b. Specific liaison has been established by individual investigators with other investigators in New York and elsewhere, and patients are referred here as maybe indicated. Institutions involved include, e. g. , Memorial Hospital, Sloan-Kettering, Mt. Sinai, Montifiore, South Nassau County Hospitals, and the Suffolk Home Infirmary at Yaphank.

c. Long-range plans are being discussed in several circles with regard to a large county hospital situated in this area, and a new medical school affiliated with/or part of the new State University at Stony Brook, near BNL. These plans are being actively investigated here, since these developments would aid materially not only in realizing the full potential of the BNL Medical Department, but of the proposed new hospital and medical school as well.

d. Acquisition of suitable patients is not a problem at present in the conduct of the clinical research program at BNL. Excellent rapport is enjoyed with physicians and medical institutions in the local and New York areas.

2. Strengthening of clinical research program.

a. With changing staff, programs have been encouraged that are felt to be of fundamental importance.

b. Attention has been given to acquiring more clinically, yet basically oriented personnel in the next FY.

c. With Dr. Schwartz joining the staff, expected in FY '64, certain current programs very probably will receive additional fundamental and biochemical orientation through collaborative efforts.

d. Hospital utilization for clinical investigative purposes has been greater in FY 1963 than ever before.

e. For the past year, a rotational program providing a resident in hematology from Mt. Sinai at BNL has been in operation. This has been quite successful. Attempts are underway to establish similar residencies in other disciplines.

3. Cooperative endeavors with the Biology Department.

a. Mutual seminars have been held.

b. Previously separate orientation programs for new personnel are now combined.

c. Certain talents have been acquired for joint support of both departments, e. g. , biology has engaged a statistician available to Medical Department personnel; our Veterinarian is called upon to aid the Biology Department.

d. Usually, the Chairman of the other Department is contacted informally prior to acquisition of senior personnel in either department.

e. A facility for large animals has been requested and approved for joint use of the two departments.

4. Construction.

a. The Low-Level Counting Facility is in the FY '64 congressional budget. Detailed plans for its location and construction are well advanced.

b. A new animal isolation facility will be ready for occupancy in the next several weeks, partially replacing structure in old Medical complex that is being abandoned.

c. A new facility for large animals for joint Medical Department-Biology Department use has been planned and approved. Ground clearing has begun.

d. The animal facilities requested with the Low-Level Counting Facility in the FY 1964 budget presentation as an addition to the present Medical Research Center, were not approved but are being re-requested in the FY 1965 presentation.

e. The new quarantine building nearing completion will actually result in an appreciable net decrease in space, since the presently-used larger Bldg. 338 will be destroyed on occupancy of the new facilities. The new facility for large animals will not at all compensate for this loss, since this represents an almost entirely new program (extracorporeal irradiation using bovines). Thus, additional facilities are again being requested in the FY 1965 presentation, to include the much needed additional facilities, and additional quarantine space. Detailed plans and justification are attached.

A N N E X II.

MEDICAL DEPARTMENT VISITING COMMITTEE

PROGRAM

May 21 - 22, 1963

Tuesday, May 21, 1963

| | | |
|-----------------------|---|---|
| 9:00 - 9:45 A.M. | - | Discussions with Dr. Bond |
| <u>Presentations:</u> | | |
| 9:45 - 10:15 A.M. | - | Dr. Dahl - Etiologic Studies on Hypertension |
| 10:15 - 10:45 A.M. | - | Dr. Cronkite - Clinical Studies on Cell Turnover |
| 10:45 - 11:10 A.M. | - | Coffee / Tea Break |
| 11:10 - 11:40 A.M. | - | Dr. Cotzias - Studies on Homeostasis Neutron Activation Analysis |
| 11:40 - 12:10 P.M. | - | Dr. Robertson - Computer Applications in Medical Research |
| 12:10 - 12:40 P.M. | - | Dr. Bond - Present Status of Neutron Capture Therapy |
| 12:40 - 1:50 P.M. | - | Lunch |
| 1:50 - 2:20 P.M. | - | Dr. Popenoe - The Biosynthesis of Collagen Hydroxylysine, Studied with Doubly Labeled Lysine |
| 2:20 - 2:50 P.M. | - | Dr. Shreeve - Oxidations of CHO Intermediates in Diabetes and Obesity, Studied with C ¹⁴ and H ³ |
| 2:50 - 3:10 P.M. | - | Coffee / Tea Break |

MEDICAL DEPARTMENT VISITING COMMITTEE

PROGRAM

May 21 - 22, 1963

Tuesday, May 21, 1963 (Continued)

Informal Discussions:

A.

B.

C.

Visiting Committee and Trustees

| | | | |
|------------------|--|---|---|
| | Dr. Miller Dr. Wintrobe <hr/> (Conf. Rm. 9-31) | Dr. Hastings Dr. Rhoads Dr. Wood <hr/> (Conf. Rm. 5-1) | Dr. Hempelmann Dr. Sweet Dr. Warren <hr/> (Dining Rm. 8-112) |
| 3:15 - 3:45 P.M. | Dr. Tonna | Dr. Borg | Dr. Clifford - Dr. Bozzo |
| 3:45 - 4:15 P.M. | Dr. Feinendegen | Dr. Drew | Mr. Fairchild |
| 4:15 - 4:45 P.M. | Dr. Cuttner | Dr. Delihias | Dr. Archambeau |
| 5:15 P.M. | Cocktails and Dinner | | |

Wednesday, May 22, 1963

Informal Discussions:

| | | | |
|--------------------|---|--------------------------|---------------------------------|
| 9:00 - 9:30 A.M. | Dr. Odartchenko | Dr. Hess - Dr. Stoner | Dr. Bateman |
| 9:30 - 10:00 A.M. | Dr. Schultze | Dr. Commerford | Dr. Conard - Dr. Hammerstrom |
| 10:00 - 10:30 A.M. | Dr. Fliedner | Dr. Hanks | Dr. Jesseph - Dr. Tisljar |
| 10:30 - 10:50 A.M. | Coffee / Tea Break | | |
| 10:50 - 11:20 A.M. | Dr. Keiser | Dr. Stoner | Dr. Cohn - Mr. Gusmano |
| 11:20 - 11:50 A.M. | Dr. Papavasiliou - Dr. Sakamoto | Dr. Aronson | Dr. Schackow - Dr. Lax |
| Noon | Staff Picture | | |
| 12:10 - 1:15 P.M. | Lunch | | |
| 1:15 P.M. | Executive Session and, as designated by Chairman, Visiting Committee | | |

A N N E X III.

Comments made by individual members of the Visiting Committee, based on the presentations of staff and informal discussions with staff.

The comments are arranged approximately according to the program, Annex II. When two comments were available, they are designated "a" and "b".

PRESENTATIONS TO WHOLE COMMITTEE

Dr. L. K. Dahl's presentation of his experimental studies on hypertension were well received by most of the Committee. They were all favorably impressed with his interesting observations that a high salt intake begun early in life is an important factor in the development of hypertension in animals with an hereditary predisposition to this disturbance. Hope was expressed that with the addition of Dr. Irving L. Schwartz to the staff of the Medical Department, clinical investigation under Dr. Dahl will be strengthened.

It was agreed that Dr. Dahl is an able clinician and that the care of patients in the Hospital is excellent.

Dr. E. P. Cronkite and his associates are exploiting the tritiated thymidine technique developed by Hughes, have studied toxicity in animals and have employed the procedure in humans to study cell proliferation. The data presented offer valuable and comparatively precise information concerning the life span of granulocytes in various stages of development; also, they suggest that segmented forms are released at random. Interesting studies are being made on rate of release from the bone marrow in different disorders. The work is imaginative and competent.

Dr. G. C. Cotzias: Melanogranules and Extrapramidal Tract Disease

Instead of reviewing "Studies on Homeostasis Neutron Activation Analysis", as scheduled on the program, Dr. Cotzias presented an interesting hypothesis concerning the possible relationship of the concentrations of trace

metals in the melanin-containing cells of the basal ganglia to the functioning of the extrapyramidal tracts of the brain. Its relevance to the pathogenesis and drug therapy of such extrapyramidal disorders as Parkinson's disease, Wilson's disease, and Huntington's chorea was discussed. The basic hypothesis involves the assumption that the "traffic" of impulses through the basal ganglia is somehow controlled by the state of the melanogranules. Data published by others supporting the thesis were cited, but no new experimental evidence was reported.

Dr. J. S. Robertson: Computer Applications

Dr. Robertson presented a general description of the application of computer techniques to problems of the Medical Division. Many of these applications appear to be routine, e. g., computation of standard deviations and standard errors, least squares, semi-log and power function fits of data plots and information retrieval. Special problems are concerned with extracorporeal blood doses for Cronkite's calves, computation of neutron isodose curves, kinetics of equilibrium reactions involving multicompartiment systems (using analogue computers), gamma spectrum stripping techniques (using a Los Alamos program). The most complex problem involves the conversion of signals from a multidetector positron-scanner to locate the position of positron-emitting substances concentrated in brain tumors.

Dr. Robertson is obviously a competent physicist whose main interest, I suspect, lies in the field of electronic engineering. He seems to be knowledgeable in the applications of computers to problems of the Division, and does not seem to be interested in computer science as such. In the subsequent individual discussions, it became evident that there are a number of people in the laboratory familiar with computer techniques -- Dr. Bozzo from Chile, Mr. Gusmano, Dr. Lax and Dr. Cohn.

Dr. V. C. Bond: Present Status of Neutron Capture Therapy

(See previous section in Report entitled "Medical Reactor".)

Dr. E. A. Popenoe: Biosynthesis of Collagen Hydroxylysine

Collagen is the primary structural protein, synthesized by connective tissue and comprises 1/3 of body's protein. The steps involved in the biosynthesis of hydroxylysine are of importance in understanding the synthesis of collagen. The question of whether hydroxylysine was formed from lysine before, during, or after the protein molecule was synthesized was studied by Dr. E. A. Popenoe. When he fed C^{14} labelled lysine to rats for a total of 15 weeks, isolated the lysine and hydroxylysine of the collagen and determined their specific activities, he found that the ratio : hydroxylysine/lysine = 1.0. This demonstrates that hydroxylation of the lysine takes place at some early stage of collagen synthesis and does not continue after synthesis is complete.

Dr. Popenoe has also used lysine doubly labelled with tritium and C^{14} to obtain information on the mechanism of hydroxylation of lysine. He has found that collagen, formed in implanted polyvinyl sponges, contains hydroxylysine that has only 75% as much tritium per C^{14} , as has lysine. This indicates that a step of dehydrogenation probably precedes one of hydration in the synthesis of hydroxylysine from lysine during synthesis of collagen.

This work on hydroxylysine, which began with its discovery by Van Slyke and Hiller in 1921, is of great importance and is being elegantly carried out.

Dr. W. W. Shreeve: Carbohydrate Metabolism in Diabetic and Obese Patients

By combining double labeling of metabolizable substances with C^{14} and T, it has been possible to measure on patients for the first time, the relative ability of human organisms to convert these substances into fat, to carbohydrate, and CO_2 . Such information is basic to our understanding of the true nature of diabetes and why some people get fat whereas others do not.

It could be extended to studies on why some people make relatively more cholesterol than fat from carbohydrates.

Dr. Shreeve is attacking the basic problem of what happens to the hydrogen of a metabolizable substrate, which are the source of our energy, rather than what happens to the carbons, which are only the carriers of the hydrogens.

This work is of basic and practical importance and should be encouraged.

Informal Discussions with Drs. Miller and Wintrobe

GROUP A

a. Dr. E. A. Tonna is studying the skeletal system with a view to gaining some understanding of the aging process. Attention is focused on periosteal proliferation in response to fracture or saline injections into tissue outside the periosteum. The studies suggest that a stimulus to proliferate is transmitted widely along the whole periosteal layer of the bone. The nature of the "messenger" calling forth proliferation is obscure. The possible relationship to pulmonary osteoarthropathy is raised but unanswered.

He is also developing a microscanning stage for microspectrophotometry.

b. Dr. Tonna has been making some interesting histological observations on the reaction of the periosteum which follows fracture of one of the long bones, as an example of tissue repair. He uses the femur of mice of different ages. After fracture, the periosteum reacts throughout the whole length of the bone.

Repair is much more rapid in young mice -- 5-8 weeks old -- than in older ones. He has observed similar periosteal changes by the injection of 0.25 ml saline just above, but outside of, the periosteum.

Dr. L. E. Feinendegen, by double labelling techniques, is studying the source of precursors of DNA in bone marrow and has measured DNA and RNA in developing erythroblasts and granulocytes. Evidence has been found to indicate reutilization of RNA, derived from dead cells. The studies suggest that H^3 -thymidine is not a good measure of DNA turnover except perhaps for the first two or three days.

In tissue cultures, observations have been made on RNA synthesis in chromosomes and show that, after mitosis, about 25% remains in the chromosomes, the remainder passing into the cytoplasm.

The studies appear to have been well done.

Dr. J. Cuttner has used the whole body counter for studies of iron absorption. The studies are incomplete and the data show great variation

as well as many surprises. In normals, absorption has ranged from 5 to 25%. Mostly male subjects have been used. In polycythemia vera, absorption has ranged from 20 - 95%. Most of the subjects seem to have been iron deficient as judged by serum iron, iron-binding capacity and bone marrow hemosiderin. In women with menorrhagia, iron absorption has ranged from 53 to 90%.

In patients with malabsorption, extremely low values were found (1.16, 2.5%) and yet at least one of these two subjects had little anemia and no iron deficiency as judged by serum iron, serum iron-binding capacity and bone marrow hemosiderin.

In other instances, unexpectedly high or low values and poor correlation with the clinical picture or with the parameters of iron deficiency was noted.

Although the results may be valid, considerably more work needs to be done, particularly in defining the normal and its physiological variations.

Dr. N. Odartchenko, by means of H^3 -thymidine, has labelled late erythroblasts and those with extruding nuclei to measure the duration of mitosis and the premitotic gap, and to observe the effects of 150 r of x-ray. This work has been carefully done and is very impressive.

Dr. B. Schultze is studying the breakdown of serum proteins by autoradiographic means and, interestingly enough, has found Cr^{51} useful for this purpose. The observations on the breakdown of ribonuclease in the kidney are most interesting.

a. Dr. T. M. Fliedner reported his careful and extremely valuable observations on the bone marrows of radiation casualties. The observation concerning the possible difference in the effects of nitrogen mustard and x-ray is very much worth pursuing and his ideas concerning the "resting" stem cells are very intriguing.

b. Dr. Fliedner has made a careful systematic study of the cytology of bone marrow smears of all the patients exposed to radiation during the accident in 1958 at the Argonne National Laboratory. He showed us beautiful micro-photographs demonstrating early abnormalities in the red cell precursors.

Of the people I saw in the informal discussions, Drs. Schultze and Fliedner made the best impressions. These two seemed to me very intelligent, well-trained investigators who were able to describe their work intelligibly and with enthusiasm.

a. Dr. Keiser reported tagging of lymphoid cells and plasma cells with H^3 -thymidine, H^3 -cytidine and H^3 -leucine with a view of determining the role of these cells in antibody production. Studies of germinal centers have also been carried out. The findings are not so clearcut that they can be interpreted easily, but this is probably due to the fact that many events take place within a brief period of time.

b. Dr. Keiser has been immunizing mice to tetanus toxoid, injecting the initial dose into the inguinal region of 4-week old mice and a booster dose into the foot pad at 6 months of age. During the next three or four days when antitoxin is being actively produced, he injects tritiated thymidine, cytidine and leucine and examines the cells of the popliteal lymph nodes to determine which cells are probably concerned with antibody formation.

a. Dr. P. S. Papavasiliou and Dr. Sakamoto discussed studies on trace metals, their regulation, function and excretion. Manganese served as the main example. The work appears to be in the early stages and is not easy to evaluate.

b. Dr. Papavasiliou told us that manganese is excreted by the gastrointestinal tract, a little by the pancreas but most of it by the liver in the

bile. Secretion by the liver is accelerated by surgical operation and other kinds of stress, and especially by administration of steroids.

Informal Discussions with Drs. Hastings and Wood

GROUP B

Dr. D. C. Borg: Role of Free Radicals in Hormone and Drug Actions

Dr. Borg reported on his studies of free radical transfer in biological oxidations. It has developed that univalent electron transfer, which was formerly regarded as unusual and a rarity, occurs in many types of enzyme catalyzed oxidations. Free radicals may occur in substances which are known to modify the course of these oxidations, such as certain hormones (thyroxine and estradiol), certain metals (Mn, Fe), certain substrates (ascorbic and DPNH).

The availability of modern techniques which permit Dr. Borg to detect free radicals in biological reactions (ESR) makes this work possible.

This work is regarded of basic importance, and appears to be leading toward an explanation of hormone action in certain instances, and the mode of action of certain drugs. It is highly desirable that such studies be continued and supported.

Dr. R. Drew: Effect of Neutron Capture Radiation on Survival of HeLa Cells in Tissue Culture

After B_{10} (as sodium pentaborate) had been added to the medium supporting the growth of HeLa cells in plate cultures, the plates were exposed to a neutron beam and the survival of individual cells was scored after 12-14 days incubation. The concentration of borate in the medium ranged from 2 to 10 $\mu\text{g}/\text{ml}$. If the cultures were treated early, i. e., at circa 22 hours when each plated cell had divided only once, many of the cell pairs failed to proliferate further, suggesting that irreversible damage had been caused by the radiation. Occasionally abortive colonies, not visible macroscopically after 12-14 days incubation, were formed by partially damaged cells. When treatment was delayed until colonies containing approximately 80 cells had formed from the individually plated cells, the effect of the irradiation was much less striking. Whether the borate ions are in or on the cells when they exert their damaging effect as a result of neutron capture is not known.

Dr. N. Delihias: Effect of Rous Sarcoma Virus on Nucleotide Sequences of Cellular RNA Molecules

An attempt is being made to compare the sequences of nucleotide bases in the known forms of RNA molecules extractable from normal chorioallantoic membrane (CAM) chick embryo cells with those of comparable RNA molecules derived from CAM cells infected with Rous sarcoma virus. Following treatment of the extracted RNA with ribonuclease, the resulting nucleotide fragments are compared chromatographically. No differences were noted in the ribosomal RNAs from normal and uninfected cells. Preliminary data suggest, however, that the nucleolar RNAs may be different.

Dr. M. W. Hess: Effect of Thymectomy on Immune Response of Mice to Tetanus Toxoid

Mice were thymectomized 1, 2, 4 and 8 days after birth and were given a primary immunizing dose of tetanus toxoid at 4 weeks and a secondary injection at 7 weeks. Antitoxin response after primary injection was only slightly depressed in the thymectomized group as compared to controls, whereas the secondary response was markedly depressed. This result is exactly the opposite of that observed following acute irradiation injury. Certainly it needs to be confirmed by further experiments. Results obtained thus far are only preliminary. "Wasting syndrome" observed in some animals 40-60 days post-thymectomy is also being studied.

Dr. S. L. Commerford: Effect of Ionizing Radiation on the Assembly of Nucleotides into DNA

Dr. Commerford has continued his studies on the metabolism of DNA isolated from the mouse intestine. He has used I^{131} labelled deoxyuridine (IDU) to label the DNA and to study the effect of ionizing radiation on cell death. His data show that as little as 5 rads. radiation are detectable.

Dr. L. V. Hanks: Metabolism of Tryptophan

Dr. Hanks has continued to explore protein metabolism in disease

states by the isolation of metabolic products of tryptophan from the urine of patients suffering from various anemias or multiple myeloma. This work requires a sound knowledge of organic chemistry as well as the ability to devise new methods for the isolation and identification of new compounds.

He has also observed that giving the patient C^{14} labelled tryptophan in minimum amount, results in 2% of the C^{14} appearing as $C^{14}O_2$, whereas if he gives the patient an "overload" of 2 grams of tryptophan, as well, results in 25% of the C^{14} of the tryptophan appearing as $C^{14}O_2$. This observation is of great importance to all studies in which a labelled, metabolizable substance is given, and has not been sufficiently taken into account in the past.

Dr. Hanks' expertness in organic aspects of biochemistry, and the high quality of his work impressed those who heard his presentation, very favorably.

Dr. R. D. Stoner: Enhancement of Immunogenicity of Antigens
Resulting from Complex Formation with Antibody

Meticulous experiments done in mice have resulted in the following observations:

- (1) that the immune responses to both tetanus toxoid and bovine serum albumen are enhanced if the antigen is first complexed with specific antibody;
- (2) that the enhancement is just as great when the antibody in the complex is of mouse origin (homologous) as it is when the antibody is obtained from another animal species (heterologous);
- (3) that acute irradiation injury inflicted four days after a secondary antigenic stimulus does not stop the continued synthesis of antibody, as evidenced by incorporation into the serum antibody of labelled histidine given after the exposure to irradiation.

Dr. R. B. Aronson: (working with Dr. D. D. Van Slyke) On the State of Hydroxylysine in Collagen

It has been observed that only 65% of the hydroxylysine of collagen is capable of reacting. This raises the question of whether the hydroxylysine residue may not be partly bound and partly free. This problem is being studied by determining the kinetics of the reaction of hydroxylysine in collagen from bone and from soft tissue.

This problem has special importance because of the relation that the exact structure of collagen may play in initiating calcification in bone, and for the role that collagen formation plays in aging.

Informal Discussions with Drs. Hempelmann and Warren

GROUP C

Dr. D. Clifford: A very competent veterinarian who is working particularly with Dr. Cronkite. He has been largely concerned with making plans for improvement of the animal quarters and does special surgery for some of the staff, both in medicine and biology. He is at present preparing the extracorporeal loops for irradiation in cattle. He is also interested in the bone lesions of pulmonary osteoarthropathy, a disease which occurs spontaneously frequently after pneumonia in dogs and manifests itself as a general periosteal thickening of long bones. He believes the lesion is related to pulmonary decompensation and is producing fibrosis in lungs of dogs by intrajugular injection of microspheres of cold and radioactive yttrium 90. He is an alert and competent man.

Dr. S. Bozzo: A postgraduate student from Chile working with Dr. Clifford. His special interest is in renal physiology, particularly the energetics of urine secretion and the composition of the urine. His system is to use the bladder of the dog and the guinea pig, washing the bladder with a standard suspension of India ink and distilled water and obtains by photometry the curve of secretion of urine. In addition, continuous conductivity studies are made of the urine for its sodium and water content. He is also very much interested in computers and spends about 80% of his time at present on the computer problem. I gained the impression that his real interest was much more in mathematics than in renal physiology and that he was as much intrigued with the apparatus by which he hoped to obtain his results as he was in dog problems of renal physiology.

Mr. Fairchild and Dr. Robinson: Robinson discussed the problems concerned with monitoring alpha particles in biological systems. The water medium cuts down on the range of the particles and the electrolytes interfere with the electrical signals. In this connection, Brownell claims that a commercially available solid state detector works in water but not in electrolytic solutions. It looks like the problem of monitoring alpha dosage

in tissues is far from solution. Robinson, an older physicist with considerable experience in tissue monitoring, has just begun to work on the problem.

Fairchild discussed the properties of the epithermal neutron beam separated from the slow neutrons by means of lithium filters placed as far from the irradiated target (tumor tissue) as possible. Apparently there is a build-up of the dose by a factor of 4 at a depth of 3-4 cm. and the neutron-to-gamma ratio is increased. This looks much better than the thermal beam which largely dissipates its energy at the surface.

I was very impressed by Robinson. He is intelligent, enthusiastic and seems to know his field.

Dr. J. Archambeau: Archambeau is basically a radiologist, trained first by Dr. Simeon Cantrol at Seattle and then at the Curie Institute in Paris. (He is an energetic man with a large family whose hobby is the 2-mile run.) At present he is radiating HeLa cells by neutron capture and is determining the augmented effect obtained when boron is present in the culture medium. Apparently, the boron is chiefly in the medium. He is carrying on studies to determine whether it passes the cell membrane or whether it is promptly excreted after absorption. He found that boron, like a number of other compounds, enters the red blood cell rapidly. This is at pH 7.4. He stated that boron tends to equilibrate with body water. He finds that for the first two hours a concentration of boron in the blood is higher than that in the brain and, in fact, much of the boron in the brain may still be present in the blood stream. He is using a preparation of molar glucose pentaborate in the dog.

Dr. J. L. Bateman discussed his experiments with Dr. Bond on the biological effect of moderately fast neutrons (0.5 - 2 mev.) from the Van der Graaf of the Physics Department. He has a nice physical set-up for studying monoenergetic neutrons of different energies. He is determining the RBE for various biological end points (spleen-thymus weight, incorporation of nucleic acid precursors, spermatogonia depletion, etc.). He also studies

the effect of dose rate on chromosome bridges in rat livers (exposed when normal, sacrificed some time later following hepatectomy). He is investigating cataract formation after neutron irradiation as a function of age.

This sort of work is essential to an understanding of the hazards of neutron exposure. Bateman seems to be a versatile, careful worker who understands Dr. Bond's mathematical treatment of the data.

Dr. R. Conard presented an excellent account of his recent trip to the Marshall Islands, which was carried out skillfully and well in spite of many difficulties, the chief of which was the fact that the key ship was grounded on a reef for a month and that there was a serious epidemic of Type 1 polio in the Islands, which made it very difficult to do other than emergency work for patients. However, he noted that there was a lag in complete recovery of the blood cells to normal levels. The problem arose as to whether there might be a slightly higher death rate: of 86 exposed patients, 8 had died since 1954; or 175 controls, 7 had died. Some chromosomal preparations were obtained from bone marrow and will be studied by Dr. Moloney. The skin chromosomal studies were not satisfactory, owing to the great extent of contamination of the culture media. One of the members of the group, Dr. Suto, worked on problems of bone age. He had found there was a little transient slowing of bone growth in males 15 to 18 months of age at the time of exposure. Dr. Conard has shown great skill in organizing these expeditions which have proved to be of outstanding value.

Dr. J. E. Jesseph is working together with Dr. Tisljar on the dosimetry of charged particles from the accelerator with the hope that they may ultimately be of value for the therapy of neoplasia. They are particularly interested in pi mesons. They are using a dose of 1,000,000 pi mesons per second. The pi mesons can be deflected by means of a magnet. They react with normal carbon, oxygen and nitrogen. It is Dr. Jesseph's hope to use the high efficiency of the peak of the Bragg effect in treatment of neoplasms.

He has also used 2.2 BEV protons for the treatment of an osteogenic sarcoma in a dog with temporary regression.

Drs. S. H. Cohn and Gusmano described three types of experiments involving internal emitters of practical interest: (1) Short term experiments of the kinetics of the distribution of radiocalcium and strontium in a four-compartment system. (2) Long term experiments on the kinetics of cesium, zinc and scandium metabolism. Using a mathematical model involving a power function, they can extrapolate retention to the far distant future. (3) "in vivo" radioactivity of large populations of normal subjects using a whole body counter with a 400 channel analyzer. They are interested in radionuclides occurring normally or in fall-out. Using gamma stripping techniques involving the "gamstrip" program from Los Alamos, they are able to discover and quantitate the presence of radionuclides which would, otherwise, be lost in the complex mixture of gamma ray spectra.

Cohn obviously knows this field well and Gusmano seems well informed about the complicated gamma ray stripping techniques. Important work!

Dr. E. Schackow is working with Dr. Lax. Dr. Schackow was trained as a radiologist in central Europe and is a straightforward and alert person. His interest is in turnover of potassium and sodium in rats highly sensitive to salt and on a high salt (8%) diet. These rats have been inbred for 6 to 7 generations. The project appears to be in an early stage of development and evaluation is difficult.

Final Comment by the Chairman

As a result of the experiment of obtaining written comments from individual Committee members, following our meeting, the Chairman is personally impressed with the great value that would have been derived, had we been able to have had a three day meeting instead of a two day meeting.

Ideally, the formal presentations and informal discussions would have ended at noon of the second day (as they did), then the afternoon of the second day be left free for (1) preparation of individual reports, and (2) a discussion of those reports by the Committee as a whole, in executive session.

The morning of the third day would then have been available for a considered and unhurried discussion of just what the final report should contain, and what constructive recommendations should be made.

If a three day meeting is out of the question, then I think that scientific presentations should be limited to one day and the second day devoted entirely to a meeting of the Committee in executive session.

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