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Report of the Medical Division Advisory Committee

January 22-23, 1968

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The members of the Committee met with Dr. W.G. Pollard and Dr. G.A. Andrews briefly on the evening of January 21, 1968. The history of ORINS and ORAU was reviewed and broad matters of policy and financing were discussed.

The newly formed Committee then held a short organizational meeting. By lot B.E. Billingham and W.C. Moloney were chosen for three year terms, F.J. Bonte and D.B. Zilversmit two years, and R.E. King and W.H. Langham for one year terms. Using the same method, W.C. Moloney was designated chairman of the Committee. It was agreed that all members of the Committee would participate in the overall review of the research programs and other activities of the Medical Division but each member would assume particular responsibility for programs related to his special field of interest.

On Monday, January 22, 1968, at 8:30 a.m. there were formal presentations in the Medical Division Conference Room. The first general topic, Radiation Effects, included presentations on total body x-ray irradiation in man, clinical and hematological effects and cytogenetics. In reviewing this portion of the program Dr. Langham emphasized the need for more and better data on the effects of radiation in man and contributed the following comments: "There is an urgent need for more and better data on radiation effects in man, especially in the range of 25 to 300 rads delivered at dose rates of from about 1 to 10 rads/hr. This type of information is needed for military operations, civil defense, manned space flight, nuclear emergency, whole-body therapy of diffuse malignant disease and radiation suppression of immune response in bone marrow therapy of early radiation disease and in organ transplantation, which is becoming a popular endeavor.

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The retrospective study financed by NASA and done by the Medical Division of ORAU has made a contribution beyond expectation and should be continued.

The low level total-body exposure facility (LETBI) is now making prospective contributions and should be used for this purpose to the fullest ethical extent. The dosimetry, which is always a major problem, is being exhaustively and meticulously investigated which is essential to meaningful dose-response correlations. The monitoring of patients during exposure may result in much needed indicators of early radiation response to supplement hematological observations which, at best, leave much to be desired." Dr. Langham pointed out that while observations would be carried out on sick individuals, some extrapolations could be made to well people. This may furnish more meaningful data than extrapolation of observations from experimental animals to man.

Dr. Langham also pointed out the inadequacy of present day routine hematological studies in following irradiated individuals and voiced the hope that more sensitive methods would be developed. In this regard histochemical studies and investigations on leukocyte lysozymes may provide useful information on the effect of radiation.

The Committee was impressed by the volume and quality of work produced in cytogenetics by Dr. K.O. Goh. Developments in this field have clearly established the presence of chromosomal damage due to radiation. Much remains to be learned concerning the nature and importance of chromosomal injury in relationship to leukemogenesis and carcinogenesis in man. Cytogenetic studies, especially in those individuals exposed to low level total body radiation, would seem particularly valuable in this program.

The investigations carried out on the relationship of radiation to infection and the role of marrow depression, suppression of the immune mechanism, injury to the gastro-intestinal tract, etc. are of great theoretical and practical importance in this era of organ transplants and radiation therapy. However, the question arises concerning the advisability of extending research into a field which will require sophisticated micro-biological techniques especially in regard to fungal

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and viral infections. In discussing experimental radiotherapy. Dr. King expressed the following misgivings about the present programs:

"I see no reason why they would consider a diagnostic radiologist. In fact I doubt very much if Dr. Comas has enough to do as a clinical therapeutic radiologist to fill his time and since he does have a talent for investigative radiation therapy, I feel that what funds would have gone into a diagnostic radiologist should be given to Dr. Comas to strengthen his own experimental work. As I understand it, he has one technician and a minimum laboratory space, which is hardly enough for a person with his capabilities and the material which is available for study."

A tour of the Main Building and Annex was undertaken at 11:30 a.m.. Most members of the Committee felt that more time should have been allotted to visiting the various laboratories and facilities and "on the spot" discussions with the staff.

During the afternoon, from 2p.m. until 4:30 p.m. the second and third portions of the program were presented. Dr. Frederick J. Bonte submitted the following assessment of Section II, Medical Radioisotopes:

"One of the most interesting projects now being carried out by Dr. Hayes and his group is reflected in the paper "Factors Affecting the Distribution of Hydrrous Ferric Oxide Colloid." Apparently this colloid has the property of trapping certain ions, while retaining the properties of the primary ion colloid. Several methods of influencing the distribution within the reticuloendothelial system to favor bone marrow deposition are described and could actually result in the development of an agent for selective bone marrow scanning, with increased photon information and decreased patient marrow dose. This phase of the work should be continued.

In several papers Dr. Hayes and his associates discuss the relationship between Gallium and Indium ions which are transported throughout the body on plasma protein binding sites. Gallium has the property of saturating some of the primary binding sites for Indium, and unbound Indium will then go selectively to

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bone, and even more interestingly, to kidney. Iron has the property of blocking Indium binding sites on transferrin. I feel that this work, too, should continue in the direction of developing a more suitable agent for renal scanning. The best available compound for this purpose is chlormerodrin labelled with mercury 197, which produces a family of photons of unfavorable energy for present-day rectilinear scanners and scintillation cameras. Gallium 67 produces several photons of considerably more favorable energy. I would like to see the results of early clinical trials with this emitter, which are apparently about to get underway.

Another program concerns the development of scanning techniques for determining the location of emitting sources in depth. There are a number of other programs of this sort going on in other departments throughout the country, and this one is not unique, nor does its approach to the problem seem to be.

I am not in an especially good position to evaluate the work contained in the paper "Correlation of Erythropoiesis and Reticuloendothelial Function in Rabbits". I am left with the impression that there is no particular correlation between erythropoiesis and the distribution of scannable reticuloendothelial-containing marrow.

The compound DFP, labelled with phosphorus 32 may not have much of a future as a red cell label.

In summary, the experimental radioisotope program which was described to us is an interesting one and it may produce needed information about new agents for renal and bone scanning in particular and colloid tracers in general. There are more exciting research programs going on in other institutions, but I think that this one should continue in its present directions with the possible exception of the laminographic scanning program, and the continued investigation of DFP as a red cell label."

Dr. Richard King contributed the following comments on the medical isotope program:

"The work in the medical radioisotope program at the ORAU is lagging behind

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work done in many private institution. With the development of the new radio-pharmaceuticals and the rapid acceptance of generators to produce short half-life isotopes, it would not seem necessary to devote a great effort at ORAU Medical Division in this field. It is well known that much of the pioneer work in the clinical application of radioisotopes, and in the development of clinical instrumentation, was done at Oak Ridge. The fruits of this work are now being seen in many institutions in this country where with the use of generators, radiation pharmacists and biochemists are now developing many of our newer materials.

Unless the ORAU wants to enlarge its program of the training of physicians in clinical nuclear medicine, I think much of their effort could be well spent in fields other than the medical radioisotope program. It is true that Dr. Hayes is doing some interesting work with short half-life isotopes and this, of course, should be continued and broadened. I feel that the Medical Division, because of its inheritance, is placing an undue emphasis on the clinical aspects of nuclear medicine."

Concerning Part III, Lipid Metabolism, Dr. Donald B. Zilversmit had the following comments:

"The lipid group is under the direction of Dr. Fred L. Snyder. Dr. Snyder was trained with W.E. Cornatzer at the Univ. of North Dakota and obtained his Ph.D. in 1958. He has been a research scientist at the ORAU Medical Division since that time. At the Medical Division he has published some 40 papers, including several review articles. His papers deal in part with lipid methodology, with the metabolism of lipids in irradiated cells, with the lipid composition of tumor versus normal cells, and with the biochemistry of glycerol ethers, Dr. Snyder has made substantial contributions in developing sensitive thin layer chromatographic and gas liquid chromatographic procedures. He has made good use of the instrumentation facilities available in Oak Ridge and has developed a number of automated procedures.

Apart from his research activities at Oak Ridge, Dr. Snyder is also teaching and collaborating with investigators at other universities.

The visitors were impressed with Dr. Snyder's work and hope that in the future quality will not suffer because of over-expansion. Dr. Snyder's co-worker, Dr.

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Randall D. Wood, is a lipid biochemist who obtained his Ph.D. at Texas A & M University in 1964. Due to personal circumstances, he was not available for an interview at this meeting.

In summary, the Committee recognizes that Dr. Snyder's program has great potential, not only for the development of chemical lipid technology, but also as a center for collaboration with clinical investigators at the Division. It is perhaps somewhat disappointing that this collaboration is at the moment only minimal. Dr. Goswitz is carrying on some studies on the lipids of lymphocytes and patients with chronic lymphocytic leukemia, but it appeared, on the surface at least, that this was not so much a collaborative study as an independent venture of Dr. Goswitz after learning some methodology in Dr. Snyder's laboratory. A closer collaboration between Dr. Snyder and the clinical staff on diagnostic procedures based on ether lipids in tumor tissue might be desirable."

Following these formal presentations the Committee visited various laboratories for discussion with individual staff members. Again it was pointed out that the time allotted for these visits was inadequate.

On the morning of Tuesday, January 23, 1968 the fourth and fifth portions of the program were presented in the Medical Division Conference Room. In regard to Part IV, Theoretical and Experimental Studies on Metabolism, while the Committee was favorably impressed by Dr. Lushbaugh's obvious capabilities, there was a definite lack of enthusiasm for some aspects of this program. These criticisms were voiced by Dr. King:

"The study of the carcinoma of thyroid with combined surgery and radio-iodine therapy, for instance, has been evaluated and reevaluated many times in many places. The consuming interest of Dr. Lushbaugh and his group in studying chromium 51 labelled red cells to me is not really understandable. I do feel that Lushbaugh and his group should continue the studies in metabolism and compartmental space studies by whole body counting, neutron activation analysis, and any other way they see fit, but I do not understand the concentration on chromium 51 labelled red cells. I think the presentation of Dr. Bergner from Sweden was lacking in every respect. I wonder why he is there and what his position is."

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Dr. King concurred with Dr. Langham in urging support for the whold body counting system program, neutron activation analysis techniques for compartmental space and trace element metabolism studies.

The final formal presentation in immunologic studies was moderated by Dr. Gengozian. This was one of the most impressive features of the Medical Division Program and Dr. R. E. Billingham contributed the following comment:

"Dr. Gengozian's group deserves great credit for pioneering for the use of the marmoset as a convenient primate for immunological and radiobiological investigations. They have established the feasibility of domesticating and breeding these interesting animals in sufficient numbers for experimental use and have already made important contributions to our knowledge of their basic biology. An exciting, well-conceived program is well underway to elucidate the natural fraternal twin hematopoietic chimerism and the associated tolerance of skin homografts. This project merits a high degree of priority with regard to space and support with both personnel and money.

Although there are serious medical, medico-legal and moral problems and risks involved in the preliminary trial clinical immunotherapeutic program in which it is proposed to treat patients suffering from leukemia and other malignant diseases with thoracic duct lymphocytes from specifically sensitized donors, careful, critical evaluation of this approach is desirable.

The fundamental studies on radiation immunology in mice are good and promise to shed important light on the etiology of graft-versus-host reactions, and on the primary immune response.

Expansion of this ably and energetically directed research group would certainly be in the best interests of ORAU."

Following the formal presentations at 1:30 p.m., the Committee met with Drs. Pollard, Andrews and Kinsely. General aspects of the program were discussed especially the relationship of ORAU with the Medical Division and the possible role of the Medical Division in community hospital activities. In this regard, the relationship of the Medical Division to the Heart, Cancer, Stroke program was also briefly mentioned.

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The executive session of the Committee in which the general problems were discussed and topics assigned to various members of the Committee concluded the visit to the Medical Division.

In addition to the above specific statements on the formal presentations, the Committee contributed the following general comments on activities of the Medical Division.

General Comments

Facilities: The Committee was greatly impressed by the excellent laboratories and especially with some of the unique installations such as the whole body radiation facility and the marmoset colony.

Staff: At the level of the principal investigators the staff was considered to be highly competent. In some areas it was felt that the addition of a second experienced individual would strengthen and stabilize the department. Furthermore it would provide necessary help in training of graduate students and post doctorate fellows. Relationship between the administration, chief of departments, physicians and basic scientists seemed excellent. However, Dr. Zilversmit made the following observation:

"The Medical Division as now constituted seem to contain two rather polarized groups; the clinical investigators concerned with long-term radiation effects, chemotherapy and diagnosis, and the basic science group concerned with immunology, lipid chemistry and isotope kinetics. It would appear that these groups function, with certain exceptions, as independent units and that the Medical Division might be able to make a more unique contribution to the whole collaborative efforts between these two groups."

A very important and vital aspect of the Medical Division activities is the relationship to ORAU. This seemed too loosely and poorly defined and the Committee is of the opinion that a much closer and more active relationship should be created. In this regard communication should be greatly improved, visits of Medical Division scientists to associated medical schools be increased

and the feasibility of an active exchange program between the medical school faculties and staff of the Medical Division should be investigated. Some members of the Committee were also of the opinion that the associated medical schools should make a larger financial contribution to ORAU.

Training Program: Much of the reputation of the Medical Division is based on the justly famous training programs. While Dr. Langham felt that teaching and training objectives should be oriented toward research experience and capability, Dr. King felt strongly that training in basic isotope handling should continue and he made the following comments:

"ORAU obtained its reputation by and large from the training courses it has developed and by the number of graduates of these courses. The Medical Division now states that they really have no consuming interest in training on a routine basis for housestaff of various specialties, or for physicians wishing to enter clinical nuclear medicine. Perhaps their mission has changed, but to me this can be one of the most fruitful efforts on their part if they again would make an effort toward developing training programs. There are many institutions where residents in radiology, as well as other specialties do not have facilities and staff to receive basic indoctrination in nuclear medicine. If the ORAU is to continue to be supported by federal funds, in my opinion it should partially justify such support by making training facilities available to those in this part of the country who desire such facilities. I realize as Dr. Andrews stated that he really does not have a large enough patient load, and a varied enough type of nuclear medical practice to support such a training program. If they want to continue the medical radioisotope program at the important level which they place it, they could step up their routine nuclear medical practice and use such patients for a training program."

Objectives: The Committee was of the opinion that the research program should continue with its primary objectives, i.e. the study of biologic effects of radiation and the use of isotopes especially in patients with cancer, malignant blood diseases, and allied disorders. The program base should not be broadened

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nor over-diversified but efforts should be concentrated in a few fruitful areas.

Obviously in a first brief visit, no Committee regardless of the competency of its membership, can make a complete and accurate analysis of a large and varied research program. It is hoped that this report will provide some measure of constructive criticism and aid in the development of a strong and well oriented research program for the Medical Division of ORAU.

Rupert E. Billingham

Frederick J. Bonte

Richard E. King

Wright H. Langham

Donald B. Zilversmit

William C. Moloney, Chairman

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	DATE			
TO (Name and unit) <i>File memo</i>	INITIALS	REMARKS <i>to John Totten. Since we have a copy we will get another - he will only send us a copy of the letter of transmittal</i>		
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