

REPORT ON MEETING OF REVIEW COMMITTEE

FOR

BIOLOGICAL AND MEDICAL RESEARCH DIVISIONArgonne National Laboratory
June 7-8, 1965

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ANL Policy Advisory
Board 1965

At the December, 1964 meeting members expressed a desire to learn more about the operation, mission and programs at the Laboratory before detailed discussion of policy matters be undertaken. For this purpose, a meeting was held June 7-8, 1965. All members were present:

Drs. Titus C. Evans (ex officio), Jacob Furth, Peter C. Nowell, W. J. Schull, Robert L. Sinsheimer, Lauriston S. Taylor and P. W. Wilson.

The presentations by both administrative and scientific staff of their programs were highly informative; the Committee commends all those responsible for preparing these presentations. Specific comments on some of the matters presented will be made in the next two sections.

ADMINISTRATIVE PROGRAMS AND FACILITIES1. Central States Universities Program. (D. Grahn)

The Committee looks with favor upon expressions of greater cooperation between Universities and the Division of Biology and Medical Research of Argonne. Such cooperation in the past has taken the form of university faculty members working for Argonne for one or more summers or for a full year. Some thesis work has been carried out at Argonne and the student's faculty advisor has made regular visits to supervise the over-all thesis program. It is hoped that the AMU post-doctoral fellowship program can soon be extended to the biological sciences.

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Many students from colleges have worked and trained at Argonne.

Argonne has electron microscopes, radiation sources and other equipment that some universities do not have.

It seems to the Committee that this program, the AMU program, etc., are within the limits compatible with the original objectives of the National Laboratories to further atomic energy knowledge and applications. The continued development of these cooperative programs (which the Committee considers to be desirable) seems likely, within the not-very-distant future, to force a reconsideration of the role of the Argonne Laboratory, to be viewed as a regional scientific center providing extraordinary facilities and research opportunities for workers in many areas of science, throughout the Midwest. In the view of the Committee it would be wise to anticipate this development.

It is well to point out, however, that the availability of the Division for cooperation and service to universities will be limited by time, space, and personnel, and these are committed to programs of need to the AEC and to our country as a whole. As the National Laboratories have been established to further atomic energy knowledge and applications, it would seem proper that activities of a general nature should be provided only to the extent that they help or at least do not hinder in the attainment of this primary goal. Our immediate concern is that the proposed program of cooperation not detract from the already crowded facilities for radiation research.

2. Monoenergetic Neutron Facility (D. Grahn, W. K. Sinclair)

The proposal for the monoenergetic neutron generator was debated at some length within the Committee; several contributed written statements for this report. Since unanimity was not reached, the Chairman

decided to include all of these. The majority apparently concluded that the proposal is meritorious. In support of this view the following statements were made:

"Many of the difficulties that have confronted the investigators of relative biological effectiveness of fast neutrons have had to do with the heterogeneity of the presently available neutron beams. The proposed machine will apparently provide a homogeneous neutron beam and will simplify the dosimetry and the understanding of the biologic effects. It should contribute greatly to determining relationships between RBE and LET, to the establishment of more precise quality factors for radiation protection guides, and it should aid in determining the possible usefulness of fast neutrons in tumor therapy.

"A location adjacent to present facilities would be desirable for convenience and economy reasons but this has to be balanced by the need to reduce the exposure hazard. The present plans for protection appear to be progressing satisfactorily.

"However, as this is a prototype of a sort, it may well be worthwhile to enlist the help of the Division of Radiological Physics and to consider the effectiveness of shielding at present fast neutron facilities to insure satisfactory shielding without undue expense, penalty of access or restriction of use.

"Leaving out of consideration problems of cost and space the mono-energetic neutron program would appear to have a special value in determining the RBE for neutrons and in the relationships between RBE and LET. A great deal of theorization based on few concrete facts, now have the RBE question thoroughly confused. The new installation should help to provide some positive answers to some of the questions. What is

required is a critical evaluation of the RBE values at given energy bands which are as narrow as possible and as free as possible from X-ray 'contamination'."

What might be regarded as the minority report subscribed to by at least two members follows:

"The monoenergetic neutron generator will certainly permit the relative biological effectiveness of fast neutrons of various energies to be determined with much greater precision than has hitherto been possible. The enthusiasm of workers in this field for such a unique instrument is therefore quite understandable and such a project seems a desirable one for the Argonne Laboratory to undertake. However, it should be pointed out that the proposed facility is not likely to lead to unusual or unexpected developments in knowledge or technology. The presently accepted values for RBE of fast neutrons are not likely to be in error by factors greater than two or three.

"The Committee would therefore be disappointed to see this project given a priority such that it would interfere with badly needed improvements relevant to the whole program of the Biology Division, such as a significant increase in laboratory space and development of a program in the molecular biology area."

3. JANUS. (G. A. Sacher)

The plans, presented by Dr. Sacher, for investigation of both acute and long-term effects of fast neutrons at varying doses and dose rates in relatively large numbers of mice, and for comparing these data with the results of similar gamma-ray exposures, should provide much-needed, detailed documentation of neutron toxicology. The additional hope, to

compare neutron effects on tissues of the whole animal with neutron effects on cell cultures derived from the same tissues, is an attractive idea, but the Committee wonders if culture techniques for many types of parenchymal cells are, as yet, sufficiently advanced to permit such comparisons to be made.

Since long-term experiments with experimental animals require many years for completion and are very expensive, it is suggested that these experiments should be designed following joint consultation with a group of specialists with special reference to the parameters to be investigated, strain species of animals used, observations to be made systematically and the like.

4. Regional Laboratory Animal Center

The plans for a "Regional Laboratory Animal Center" are well discussed and explained in a detailed application for "Research in Laboratory Animal Medicine" now being requested from NIH in an amount of \$220,950 (for the first year); most of the amount is allocated to salaries. The nucleus of the team would be the 3 DVM scientists and an MS now at Argonne, to be supported by 3 additional graduate workers. This program embraces all aspects of diseases commonly encountered in laboratories such as Argonne (mice, rats, hamsters and dogs), including genetics, nutrition, bacteriology, virology, parasitology, etc.

The "Principal Investigator" (i.e. in charge of the operation of the facility) would be Dr. Flynn. Dr. Flynn is an energetic research-oriented veterinarian, well chosen to supervise the animal colony and study problems pertinent to animal care and disease. He does apparently well in his present administrative job and writing, and deserves support

for what he and his staff can do research-wise. Whether ANL now possesses the capabilities to build a center, or even to do more than a fraction of the ambitious program mentioned, requires further consideration. So diverse are the disciplines enumerated that no one department of a large organization can carry out this entire research program, in our opinion.

The proposal for a "Regional Laboratory Animal Center" is motivated by several recommendations to Congress and the President by learned societies pointing to the necessity of conducting the outlined studies on small laboratory animals. Although in favor of the NIH request which would permit enlarging the present research program, many of the members of the Committee believe that ANL is not ready at present to create a major research center with a diagnostic laboratory, special breeding facilities, training of geneticists and animal behaviorists, etc. This would call for construction of new facilities, attraction of additional competent scientists, and a budget estimated to reach about \$2,000,000 per annum by the 5th year.

It seems that plans for such a Center should be postponed until after the organization of the AMU is completed so that participation of talents of scientists from midwestern universities will be available.

5. Sister Laboratory Program (M. R. Zelle)

The "sister laboratory" program in Korea and in Taiwan did not seem to the Committee to be a particularly hopeful or valuable activity for the Division at this time. While recognizing the potential utility of such contacts, the current program seems to promise little return for the invested time and effort of the Director and others. At best, it should be evaluated as a service function, not as a research program.

SCIENTIFIC RESEARCH PROGRAMS

1. Environmental Radiation Studies (P. F. Gustafson)

The Committee was very favorably impressed with the program of Dr. Gustafson. Started at a time when fallout measurements were in their infancies, this study has been continued in an imaginative way and is developing sound techniques and analytical procedures. One never knows when it will be called upon in the event of a resumption of atmospheric testing or a large nuclear accident; then it becomes an essential program. It is largely basic although from time to time it responds to programmatic needs. Early predictions were based on little or no facts, but it was believed that a small steady long-range program such as this would obtain answers to some of the early uncertainties.

The group also appears to be highly motivated in the sense of cooperating with others. For example, the free balloon program was worked out in collaboration with the Weather Bureau (Machta). Gustafson would like to extend this program to measurements of radon and radium daughters in the atmosphere. In relationship to other programs this would appear to be worth while. There is close cooperation between his group and various parts of the Division of Radiological Physics.

We are particularly interested to learn that by means of bremsstrahlung measurements they can determine body burdens of Sr^{90} as low as $.01_{\mu}\text{c}$. This has been done on animals and could be extended to man. It should be explored in connection with other studies of Sr^{90} in man. Their findings on the cesium turn-over in bone also looks interesting.

2. Genetics (D. Grahn and Kubitschek)

The genetic activities of the Division range from studies of genetic variation in radiation sensitivity in the mouse, to induced mutation rates for sex-linked recessive lethals, to mutations in continuous cultures of bacteria, and to a computer analysis of chromosomes. A program of this diversity is justifiable, since clearly all of these studies are logically within the mission of the laboratory, and do not appear to represent unnecessary replication of work at other institutions. Whether all facets of this program are being explored with verve and imagination is moot, and particularly is this so with respect to the computer analysis of chromosomes. It would seem that an early appraisal of the accomplishments of this phase of work, its relationship to similar efforts elsewhere, and its ultimate potential are highly desirable. If it is to be continued, acquisition of a well-trained cytogeneticist appears essential.

Since many of the genetic activities of the Division have been and are directed toward a greater understanding of radiation fitness in the mouse, a closer look at this program seems warranted. The studies immediately relevant to an understanding of mammalian radiation genetics include a concern with genetic variation in radiation sensitivity as reflected in variation in the LD₅₀, the estimation of induced mutation rates for sex-linked recessive lethals, and an appraisal of the distribution properties of the sex ratio in mice. To the Committee's knowledge each of these activities is unique. The first of these studies was initiated a decade or so ago by Dr. Grahn and has been pursued with vigor and imagination since. Some of this program has been amply documented

in the literature. Briefly stated, radiation sensitivity suggests the action of multiple loci operating additively or nearly so. Work to be done in this area concerns the mechanisms whereby these genetic effects are mediated. Of greater current interest is the work regarding sex-linked lethals in the mouse because of the apparent alteration in the sex ratio in man as a function of parental exposure to ionizing radiation. Many difficulties have been encountered, partially because few sex-linked visible mutations are known in the mouse, and most of these depress viability. The technique which has been proposed, largely by Grahn, appears adequate. This study is worthy of support not only because of its direct bearing upon an important area of study in the evaluation of radiation genetics in man, but for its potential contribution to experimental methodology as it applies to the house mouse. The third study, namely, the distribution properties of the sex ratio in the mouse, may be viewed as fundamental to an interpretation of the effects of induced mutations of a sex-linked recessive lethal. To summarize, the program in mammalian genetics, though small in comparison to that at Oak Ridge, is sound, has been productive, and involves little overlap with work at other institutions.

3. Plant Radiobiology (S. A. Gordon)

Dr. S. A. Gordon reviewed the radiobiology program, paying particular attention to the following:

- a) A system found in animal tissue producing a substance with auxin activity. This system is inducible, has a circadian rhythm, and shows interesting variations among different organs.

- b) An exceptionally radiation-sensitive system in plants which converts indole-acetic acid to auxin.
- c) An analysis of the inhibitory effect of leaf irradiation upon root formation in cuttings. The inhibition and correlated disturbances in RNA metabolism could be reversed by application of auxin. This system appears to offer a promising route into the investigation of the mechanism of auxin action.
- d) A direct effect of relatively low doses of far-red light to produce chromosomal aberrations when directed upon animal cell cultures in an appropriate stage of DNA synthesis.

It appeared to the Committee that these extremely interesting observations in plant physiology and radiation biology might be most successfully and fruitfully explored by collaborative application of some of the sophisticated biochemical knowledge available in the Division.

4. Toxicity and Metabolism of Radionuclides (W. P. Norris)

Apparently there is something still to be desired in the area of physical dosimetry in connection with animal irradiation experiments. Arrangements might be made with the Division of Radiological Physics to make temporary assignments, from time to time, of one of their staff members to the Division of Biological and Medical Research to work out physical dosimetry techniques. Assistance now available toward fulfilling this need on a casual basis does not seem to be adequate. A natural outgrowth of such a shortcoming would be to establish a Physical Dosimetry Program in the Division of Biological and Medical Research.

This would appear to be an unwise duplication of capabilities, since the two Divisions are so close together.

POLICY

The Committee wishes to comment on personnel employment and tenure policies, and on its own function with regard to matters concerned with the operation of the Division.

1. Personnel. It seems that the problem of tenure appointments complicates the Division's administration. For example, there appears to be a clear need for a competent biometrician to assist investigators with experimental design. But the Director is not optimistic that this appointment can be made at this time because of personnel complications that would arise. It is suggested that a major effort be made to revise the present system and at the same time not make ANL appointments too unattractive. The Director should have the authority to weed out ineffective personnel with adequate notice and should use this authority. An active program of supervision and review of all the younger appointments to the Laboratory should be made after a specified number of years as to whether the individual will be released or retained. For example, one might consider making senior staff appointments on a term basis of say 3, 4, or 5 years, after which positive action for permanent appointments would be considered. A stated period of employment for new personnel, with positive action by the Director required for subsequent retention, would make the separation of unsatisfactory younger individuals minimally painful.

Operation of the Review Committee. Members of the Committee believe it is now time to look at its own operation and clarify its function. Should it be primarily to help the Director with regard to specific problems such as the personnel (as above) and specific research items? Or should we, as a review committee to the University of Chicago, be concerned not with details but with over-all policies, programs and planning? For example, before a major new project is initiated - such as the proposed animal disease laboratory - should the opinion of this Committee be sought? Members of the Committee believe that they can be most useful before decisions of important policy matters are made rather than after. We believe that it is desirable to meet with the appropriate administrative officials at the University of Chicago to explore these questions.

The next meeting of the Committee will be held at the Argonne National Laboratory on May 9-10, 1966, if arrangements can be made.

Titus C. Evans
Jacob Furth
Peter C. Nowell
W. J. Schull
Robert L. Sinsheimer
Lauriston S. Taylor
P. W. Wilson, Chairman

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