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Research Program Report

for the

Radiological Research Laboratory (U)

College of Physicians and Surgeons

Columbia University

630 W. 168th St.

New York 32, N.Y.

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Submitted by

Dr. G. Failla, Director

January 22, 1947

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The experimental work that can be carried out to advantage in the Radiological Research Laboratory at the College of Physicians and Surgeons, Columbia University is explained in the "Introduction" of this Research Program Report and is divided into separate problems under "Research Problems".

This laboratory was set up some years ago for the express purpose of studying the biological effects of ionizing radiations and related problems. The suggested program, as well as the research carried out for the Manhattan District during the last three years, comes under this classification and does not necessitate a reorientation on our part. Practically all the laboratory facilities needed are already available. Funds allocated to us by the Atomic Energy Commission will enable us to do more work of the type we would normally do and will provide data needed in the practical applications of atomic energy.

Without outside support, of course, the choice of problems to be investigated in our laboratory would be somewhat different. In the proposed program we have taken into account the needs of the atomic energy project in general, and the most important ones (from this point of view) would have the highest priority.

After a certain special technique has been worked out, it is a relatively simple matter to collect data of general utility. It is much more economical, therefore, to collect

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three data in the laboratory in which the technique has been developed. We are prepared to do this when the occasion arises as indicated in the body of this report.

Research work of the type envisaged here involves the development of special apparatus. Unless the work of the staff is closely coordinated so that during the time that the apparatus is being built an individual can work on another problem, considerable loss of efficiency results. For this reason (and others inherent to the very nature of research) it is difficult to consider problems as separate items that can be followed according to a predetermined schedule.

The number of problems that we can undertake to study depends not only on the funds allocated to us, but on the scientific staff that we can maintain over a period of years. With the present high demand for scientific workers, it is impossible to hold good men on the uncertain basis of year to year grants. This problem, which is generally recognized, will no doubt be solved by the Atomic Energy Commission in the course of time. Pending this decision we suggest that the funds allocated to us for the fiscal year 1948 be the same as for 1947, that is $100,000.00. Inasmuch as I do not know what arrangement is being made with the University about overhead and similar charges, I cannot give at this time an itemized budget. However, salaries will account for more than half of the above mentioned sum. I shall be glad to submit an itemized budget at a later date.

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Introduction

Biophysical

In studying the biological effects of ionizing radiation of all types it is obviously important to establish equality of dose on a common basis. The roentgen is a unit of x-ray or gamma ray dose based on the ionization produced in air under certain conditions. It does not apply to other types of ionizing radiation.

In the ultimate analysis the energy absorbed by a cell or a tissue exposed to radiation must be responsible for the biological effect produced. Therefore, taking energy absorbed per gram of tissue as the common basis of dose should give the simplest correlation between dose and effect. We may call this the tissue dose. In the case of high voltage x-rays absorption in soft tissues and air takes place largely by the Compton process and the energy absorbed by one gram of tissue and one gram of air, under the conditions imposed by the definition of the roentgen, is nearly the same (that is, proportional to the electron density.) Since the chemical composition - and, therefore, the electron density - of living tissues varies to some extent (the extreme being the difference between soft tissues and bone) it is expedient to take the energy equivalent of one roentgen in terms of one gram of air, as the unit of tissue dose. This is approximately 85 ergs per gram, the uncertainty arising simply from the uncertainty in the average energy lost

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by an electron in producing an ion pair in air. We may now say that when, at a given point in a tissue, the energy absorbed is 85 ergs per gram of tissue, the tissue dose is one roentgen. The same unit of tissue dose may be used for all types of ionizing radiation. To distinguish it from the roentgen, which applies only to x and gamma rays, we may call it the "tissue roentgen".

It should be noted that in order to express the dose in tissue roentgens it is necessary to determine the energy absorbed per gram of tissue at the point of interest and under the conditions that obtain during the irradiation. In general these conditions are such as to make it difficult, if not impossible, to calculate with reasonable accuracy the tissue dose from physical data available at present. It is best, therefore, to make a direct measurement of the tissue dose.

Before the war we had developed a method and apparatus for the measurement of tissue dose applicable to any type of ionizing radiation and any set of conditions encountered in practice. This method is generally recognized now as the most suitable for the purpose. It embodies the use of an ionization chamber of special design, called an "extrapolation chamber" because in principle the final result is obtained by extrapolation. The practical application of this method to special cases is not always simple. The difficulties are largely in the construction of an extrapolation ionization chamber that truly represents

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the physical conditions existing in a tissue, insofar as the absorption of the radiation in question is concerned. The most satisfactory chamber is one in which the wall material contains all the chemical elements of a given tissue in the correct proportions. There are certain advantages in using air as the gas in which the ionization is measured and other advantages in using a gas mixture containing all the chemical elements of the wall material in the correct proportions.

In determining the energy absorbed per gram of wall material (and therefore per gram of tissue) from a measurement of the ionization produced in air, one must know the average energy lost by the "average" ionizing particle traversing the air in producing an ion pair and the relative stopping power of the wall material for such average ionizing particle, with respect to air. When the gas has the same composition as the wall material, it is necessary to know only the average energy lost by the average ionizing particle in producing an ion pair in the gas mixture. (This, of course, involves the reasonable assumption that the mass stopping power is the same for the solid wall and the gas medium of the same composition.)
The accuracy with which tissue doses may be determined by this method depends largely on the accuracy of the values chosen for these quantities. The greatest uncertainty arises in the case of heavy nuclei set in motion by fast neutron impacts or otherwise. We have succeeded in preparing a tissue equivalent material in which all the elements in a given tissue can be

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incorporated in the correct proportions. The material can be used as a wall lining in any gas tight ionization chamber. Suitable gas mixtures are not difficult to obtain. The question of stopping power and energy spent in producing an ion pair, especially in the case of neutrons, needs further investigation.

It should be noted at this point that until now it has been customary to measure fast neutron beams for biological purposes in terms of the ionization produced in a 100 r Victoreen chamber calibrated in roentgens. When this chamber reads 1 r it is said that the neutron beam dose is 1 "n". To estimate something approaching the tissue dose (as defined here) it has been assumed that 1 n is equivalent to 2.5 r. Our work has shown that there is no constant factor relating the n and the r for all conditions and particularly when the neutron energy spectrum is different. This means that the ionization chamber must be properly designed to meet the requirements of each particular case.

It is well known that equal tissue doses of gamma rays and fast neutrons do not, in general, produce the same biological effect. This is attributed to a marked difference in the average specific ion density along the path of the ionizing particles liberated in the tissue, in the two cases. It follows, therefore, that the measurement of the tissue dose per se even under the best conditions, does not permit one to predict what the biological effect will be. The additional required information is at least

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a fair estimate of the relative proportions of the total ionization produced by electrons, protons, and heavier recoil particles. Suitable methods to obtain this information will have to be developed before one can appraise the biological effectiveness of a beam of ionizing radiation of unknown composition or composed of widely different types of radiation.

Chemical

It is obvious that chemical changes must take place in irradiated tissues. Knowledge of these chemical changes would be valuable in understanding the biological effects of radiation. While a great deal of work has been done in this field, the results have been disappointing. For one thing it has been found that doses of radiation, which produce marked biological effects, cause extremely small changes in chemical systems irradiated in vitro. Chemical changes in tissues irradiated in vivo are also difficult to detect. For the moment it seems that the direct approach in linking chemical changes with biological effects is not very productive. Nevertheless exploratory work to discover new methods of attack should be encouraged.

4 We wish to point out now one case in which chemical experiments are certain to provide useful information. Practically no work has been done under conditions that permit the comparison of the chemical effectiveness of radiation of widely different specific ion density. This can be done in a variety of ways and in particular by using gamma rays and fast neutrons. By

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choosing the proper irradiation factors the "tissue" dose in the chemical system may be determined with sufficient accuracy. Furthermore, by using a medium similar to tissue, insofar as chemical elements are concerned, the physical factors could be made comparable to those obtaining in an irradiated tissue. For a given chemical system the results of such an experiment would be as follows: (1) Neutrons and gamma rays equally effective, or (2) neutrons more effective than gamma rays, or (3) neutrons less effective than gamma rays, on the basis of equal energy absorbed. If equally effective, one would then investigate whether the chemical reaction is independent of wavelength and of neutron energy. If so, it would be very useful in measuring tissue doses under conditions in which physical measurements are difficult. On the other hand result (2) or (3) would provide additional information relative to the influence of specific ion density on the biological effectiveness of radiation. Furthermore, by proper choice of the chemical system one can study simultaneously the important problem of direct and indirect action (through the intermediary of "activated" water molecules) with relation to specific ion density.

Biological

In spite of all the work that has been done to study the biological effects of ionizing radiation, practically nothing is known about the mechanism of the reactions. The "hit theory", which has been found useful in interpreting genetic effects,

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does not help in the case of changes brought about in a mass of irradiated tissue or in the whole body. Now the normal functions of a living cell require at least the passage through its membrane of food and waste products in opposite directions. Interference with this process by radiation may be brought about, of course, in many ways, directly or indirectly. Under ordinary conditions of irradiation, every part of the cell and its immediate surroundings receives energy. It is reasonable to suppose that what happens to the cell depends on the sum total of the changes occurring at every point in this region and probably elsewhere. In particular, changes in the properties of the membrane must contribute to the effect. By irradiating only the membrane of a cell and comparing the results with those obtained when the whole cell is irradiated, one could estimate the relative importance of membrane damage. This can be done, of course, only in special cases, but the results would be very valuable. A simple scheme is to irradiate the membrane of Arbacia eggs by rolling them in all directions over a suitable alpha ray plate.

It is well known that all types of ionizing radiation produce essentially the same biological effects, the difference, when there is one, being only in degree. However, there are some indications that under certain conditions alpha particles produce an effect that may differ in kind. This refers to the acceleration of bone repair by plutonium and the more rapid healing of skin

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lesions induced by radon ointment. These effects are not well established and more work should be done under carefully controlled conditions, on account of their practical and theoretical implications. As a source of alpha particles for such experiments polonium is preferable.

It has been shown that the biological effectiveness of fast neutrons is, in general, greater than that of gamma rays. For some biological effects it is less. The results of our experiments in which mice were exposed daily to fast neutrons indicate that eye injury (cataract) and sterility are produced more readily than in the case of x-rays (when the dose is so adjusted that the change in blood count, for instance, is the same). It is very important to know just what the numerical difference in dosage is in order that proper allowance may be made in the permissible daily dose for fast neutrons. In view of the fact that a few workers on the project have been accidentally exposed to fairly large doses of neutrons, it is also important to determine whether the same ratio of effectiveness obtains for acute exposures. Experiments designed to provide this information have already been started in our laboratory.

With moderate doses of ionizing radiation, biological injury becomes evident after the elapse of days or even weeks. It should be possible to alter the course of the reaction by intervention during this latent period. Thus far no effective way of accomplishing this result has been found. It is not

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likely that the problem will be solved (if ever) until we know much more about the action of radiation on living matter. However, the two fatal accidents that have occurred on the project and the possibility of others, justify almost any attempt in this direction. We wish to suggest the following experiment as, perhaps, something better than a "shot in the dark." Some years ago Dr. Temple Fay succeeded in keeping patients at a body temperature considerably below normal for rather long periods of time. It may be predicted with reasonable certainty that the latent period will be longer when the body is kept at subnormal temperature following irradiation. However, nobody knows whether the radiation injury would eventually be the same, less, or more. Some exploratory experiments with warm blooded animals should be carried out.

When radioactive isotopes are introduced into the body, accidentally or intentionally, the injury that may result depends largely on the concentration of the material in the different tissues. Knowing the concentration, the tissue dose can be determined with considerable accuracy. Many studies of the concentration of radioisotopes in different organs have been made and the work will be continued in many institutions. We wish to emphasize here a point that has not received the attention it deserves. In general it is not sufficient to know the <u>average</u> concentration of radioactive material in a tissue. One must know, also, the local concentration in particular structures of

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the tissue - if such exist. Other things being equal, the structure with the highest concentration will be damaged most severely. The matter of local concentration - or what may be better called irregular local concentration - assumes greater importance the less penetrating is the radiation emitted by the isotope. In the case of substances emitting very low energy beta rays or alpha rays it may even be necessary to determine the distribution within the cell itself. The only method permitting the study of concentrations on a microscopic scale is the radioautographic one. Recently this method has been materially improved in our laboratory by permanently superimposing the histological section of tissue on the emulsion of the photographic plate. Under the microscope one can see in the same preparation the tissue structure and the radiation effect on the emulsion, by focussing up and down slightly. The method will be applied to the study of local concentration in the case of biologically important isotopes. It is hoped that the method may be improved further to furnish quantitative data.

High Energy Radiations

Regional Nuclear Research Laboratories now being established are making plans for the installation of machines capable of producing ionizing radiation of several hundred million electron volts. The protection of personnel in such laboratories requires a fairly accurate knowledge of tissue doses produced by the radiation in body organs of relatively high radiosensitivity. For instance in the case of 100 Mev x-rays

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it may be expected that the tissue dose in bone marrow will be larger than in similar soft tissues, on account of the fairly long range electrons and positrons liberated in the surrounding bone. The increase should be determined experimentally and possibly correlated with the energy of the radiation to facilitate extrapolation to higher energy. Measurements for this purpose should be made with ionization chambers especially designed for the purpose and under proper conditions. In general a tissue equivalent wall material is necessary.

Protection Data for the Safe Handling of Radioactive Isotopes in Small Amounts

The widespread use of radioactive isotopes in biology, medicine and industry makes necessary the formulation of definite safety rules applicable to the special conditions obtaining in these cases. In the Plutonium Project much information on this subject has been obtained. However, the conditions encountered in the average laboratory where small amounts of certain isotopes are handled, are quite different. Very definite data based on actual measurements could be obtained with very little difficulty. Simple equipment for proper handling could then be designed on the basis of the data and the experience of the Plutonium Project. There is an urgent need for this work.

Training of Personnel

There is a considerable demand for persons familiar with the special problems and techniques of radioactive isotopes and ionizing radiation. Two general groups should be recognized

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and trained according to their particular requirements: (1) Professional and (2) Technical. Among the first group would be physicians, biologists, chemists, physicists etc.; in the second would be laboratory technicians with limited scientific background. Special courses of training should be instituted, but in all cases instruction on the health hazards peculiar to this work should be included. In addition to the training schools that may be set up in the large centers (such as Oak Ridge) there should be smaller laboratories distributed throughout the country, in which a small number of men could be trained.

Exchange of Information and Personnel

It is obvious that some laboratories will develop new techniques and obtain specialized information. For the sake of rapid progress, reports from the different laboratories should be circulated promptly. Also, provisions should be made for travel of personnel and a stay in another laboratory of sufficient duration to make the exchange of information or the learning of a special technique really effective. The same thing applies to the use of special facilities under advantageous circumstances.

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Research Problems

Our experience, personnel and laboratory facilities enable us to investigate to advantage the problems listed below. How many of these we can carry out simultaneously and what progress we make will depend on the funds allotted and on the assured duration of financial support. On a year to year basis we would not undertake to maintain a much larger staff than we have at present. The turnover would be too great and some of us would spend most of our time training new workers. Since the same question comes up in conjunction with all research activities, we would urge the Atomic Energy Commission to institute a plan whereby long term programs can be set up in different laboratories.

While all the problems listed below are important and come under the classification of radiological research, which is the field of chief interest to us, there are some that we would not undertake without a government contract. They are the ones that involve repetition of an experimental procedure in order to obtain more data. An example of this type of problem is the determination of tissue dose in the case of beta ray emitting isotopes uniformly distributed in tissue. Having developed the experimental method we would use it only to obtain dosage data in the case of the few isotopes used in our biological experiments. However, from that point on similar data for other isotopes can be obtained readily by technicians. It is more economical, therefore, to obtain the

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probably this can be done with rather simple apparatus to a degree satisfactory for practical purposes.

Study of stopping power and energy lost by heavy ionizing particles in producing an ion pair, insofar as these quantities influence the measurement of tissue dose. (Data relating to this problem are probably available on the Project).

B. Measurement of Tissue Dose Resulting from Radioactive Isotopes Distributed in the Tissue.

We have developed a very satisfactory method of measuring the tissue dose in the case of beta ray emitting isotopes uniformly distributed in a tissue. We have used only radiophosphorus so far. By the end of June 1947 we expect to have data on several isotopes of present therapeutic interest. Similar data should be obtained for all beta ray isotopes of practical interest. We are in a position to do this expeditiously.

It may be mentioned in this connection that under proper conditions the tissue dose is proportional to the product of disintegrations per second per gram of tissue and average energy of beta particle per disintegration. Therefore, knowing the isotope concentration in millicuries per gram, one can calculate the average energy per disintegration for any beta ray isotope from the simple measurement of the tissue dose. It would be useful to provide this information for inclusion in isotope tables - at least for all beta ray isotopes of reasonably

long half life. At present only the maximum energy of the beta particles is listed (and incidentally the accuracy is not always high).

The above presupposes that one can determine accurately the isotope concentration in terms of disintegrations per unit time. There is room for considerable improvement in this, but it is only a matter of time before the present experimental difficulties are ironed out. (Many others are working on this problem.)

In the human body radioactive isotopes are not necessarily distributed uniformly, and a high concentration may be limited to a small volume. In this case it is more difficult to determine the tissue dose but no less important. We should like to attack this problem and provide data for practical use. (One method will be discussed below.)

Obviously it is just as important to know the tissue dose when gamma ray emitting isotopes are introduced into the human body. The experimental procedure in this case is more involved, but we have definite plans of attack and we expect to undertake the work as soon as time permits.

C. Measurement of Specific Gamma Ray Emission.

In the case of isotopes emitting gamma rays it is of interest to know the specific emission in terms of roentgens per second per curie at 1 cm. from a point source. This constant is involved in all dosage and protection calculations.

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It is desirable to determine it at least for all isotopes of practical interest so that it may be included in the data given in isotope tables.

There are considerable practical difficulties in determining the amount of a gamma ray isotope in terms of disintegrations per unit time but the problem is being attacked by many laboratories and eventually it will be solved. It is not necessary to wait for its solution before the work on specific gamma ray emission is started. As a matter of fact, the latter will help solve the first problem.

The measurement of the gamma ray emission of an isotope in terms of the roentgen is not, in general, as simple as it might be supposed. There are many pitfalls. Through many years of experience in this field we have developed unique methods and apparatus for this work and we are in a position to carry it out most efficiently.

(The measurement of the specific gamma ray emission of an isotope is related to the measurement of tissue dose and the work on both problems would be planned to yield the maximum results with a minimum of effort.)

D. Study of the Quantitative Relationships in Chemical Effects Produced by Gamma Rays and Fast Neutrons.

This work was started recently. Apparatus and techniques are being developed for the measurement of changes of small magnitude. To save time we are making use of

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information gathered by Hugo Fricke in his careful work with soft x-rays.

The objective in mind has been explained in the "Introduction" where it has been pointed out, also, that the results are bound to be of considerable interest.

E. Further Study of Eye and Gonad Injury Produced by Fast Neutrons

From our previous work it appears that these two types of injury are differentially more marked with fast neutrons than with x-rays. Further study is very desirable for practical reasons.

The work has been started and will be extended to get reliable data on the x/n ratio under the irradiation conditions apt to be encountered in practice. With the same experimental Material (and if necessary some additional experimentation) an attempt will be made to account for this differential effect.

F. Study of the Biological Action of Ionizing Radiation

A promising method of attack in this difficult problem is to study the influence of radiation injury limited to the membrane of a cell. This can be done only in special cases, e.g. by irradiating the membranes of Arbacia eggs with alpha particles. In this limited form the experiment is quite simple.

Another method of attack we are planning to use involves the study of the passage through the cell membrane of compounds labeled with radioactive isotopes. Comparing such transfer in normal and irradiated cells should provide valuable information.

G. An Attempt to Reduce Ultimate Radiation Injury

Practically nothing can be done at present to prevent or materially reduce injury, once a person has received a large dose of ionizing radiation. In cases in which the over-exposure is such that a fatal outcome may be expected, almost any attempt to moderate the radiation reaction is justified. It is possible - although not very probable - that if, following the exposure, the patient's body is kept for some time at a temperature considerably lower than normal, the ultimate radiation injury might be less severe. It has been demonstrated by Temple Fay that the "cold treatment" per se is reasonably safe.

It is planned to perform first a few exploratory experiments with warm blooded animals to see whether the procedure is feasible.

H. Study of the Distribution of Radioactive Isotopes in Tissues and Cells.

The radioautographic technique, recently improved by Dr. Evans in our laboratory, will be used for this purpose.

It is hoped that the procedure can be made to yield quantitative data.

I. Protection Data for the Safe Handling of Radioactive Isotopes in Small Amounts

This involves the measurement of dosage rates at different distances from various sources under the conditions

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apt to be encountered in hospitals and biological laboratories.

Simple protective devices will be developed.

(Through experience we know a good deal about this problem already, but additional work is indicated.)

J. Training of Personnel

We are prepared to do our share in the training of personnel. The program should be correlated with that of other laboratories.

We will be glad to train new workers or members of other laboratories in special techniques peculiar to our laboratory.

K. Measurement of High Energy Radiations for Biological Dosage

We will be glad to make measurements on new generators of very high energy radiation to provide data for personnel protection. The methods and apparatus we have developed are particularly desirable for this purpose. It will be necessary, of course, to do this work wherever the source of radiation happens to be.

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