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I. Biological Effects of High Energy Radiation

Studies on biological effects of radiation have made use of the unique opportunities afforded here to examine the biological effect of high energy radiation. A new tool previously not available for biological study is afforded by the 190 mev deuteron and alpha beams produced by the 184" cyclotron, the 32 mev linear proton accelerator, and the 300 mev electron volt betatron. The utilization of protons, deuterons and alpha particles was made possible by the construction of a deflector system in the big cyclotron which brings these beams out into air as a parallel stream of rays. One of the unique properties of these beams is the fact that they penetrate several inches deep into animal tissue and that it is possible to achieve radiation of some internal organ without unduly affecting the skin of the animal or the intervening tissues.[1] Tissue volumes as small as 3/8 inches in diameter may be irradiated as deep as 5½ inches in the body with an ionization dose four or more times the dose to the skin. No other kinds of radiation are known which enable one to produce depth dose effects of this kind. The dose due to x-ray, for example, falls off rapidly as soon as radiation enters the body while with beta rays or high energy x-rays from the betatron, the inhanced dose effect is almost negligible when compared with the p, d, x particle beams. Diagram I gives the isodose lines for 190 mev deuterons.

[1]Wilson, R.R., Radiological Uses of Fast Protons, Radiology 47, 487, 1946

(See graph I). This isodose chart is similar to the topographical map of a mountain. One may distinctly see the position of the peak dose.

Many neoplasmas are encountered in radio therapy which regress and disappear after the application of radiation. However, treatment at present is most successful in tumors lying close to the surface of the skin, because in the past no satisfactory depth dose effects were achieved. The possible future therapeutic use of the deuteron or proton beams might remove this difficulty allowing the delivery of sufficient radiation to tumors whose localization is known. Among these are possibly some bone tumors, lung tumors, and brain tumors.

Intensive experimental work is being done with the deuteron beam to study the specific biological effects produced and the possible therapeutic applications. A group of mice have now been treated with this beam; all the mice had mammary carcinomas which lead to the death of all the animals. By the use of this beam, directed first through the body of the mouse before the beam was allowed to hit the tumor, a significant prolongation of life has been obtained in the entire group of mice and complete regressions and disappearance of tumors in 25% of the mice. This result is promising, but it is too early to tell whether or not eventual human application is indicated.

In addition to the above practical application, the high energy particle beams have many properties of interest in the study of the basic mechanism of the biological effects of radiation. Only a slight amount of work has been done on this so far, because the problems of instrumentation had to be solved first. Different portions of these high energy beams have different specific ionizations, i.e., some parts of the beam produce tracks that have more ionization per unit length than other parts. Placing biological specimens in the different ionization regions, a quantitative study of various biological effects becomes

possible, since they are dependent on the specific ion density.

In collaboration with the Oak Ridge National Laboratory, work has been done on chromosomal rearrangements in tradescantia pollen. The effects on the chromosome appear to be as much as 8 times as large in one portion of the beam as in some other portions.

Other aspects of this study concern the mechanism of action of radiations on water. Still other work is projected along the lines of producing mechanical changes in the fruit fly. The radiation sensitivity of bacteria is also being studied.

Finally, some work is being done on the effectiveness of the various ionizing portions of the beam on animal tissue and concerning the biological effects resulting when different regions of the animal body are irradiated.

Work has been completed which shows that the lethal biological effects of uranium fission are approximately 27 times more effective than B-ray ionization.

II. The role of trace elements in animal metabolism:

There are several trace elements known to play an essential role in the metabolism of mammals. Among these are iron, copper, cobalt, zinc, manganese and others. Most of these elements have suitable radioactive isotopes which have been and are going to be of much value in tracing the biochemical role of these elements in the animal body. We have undertaken a systematic study dealing with the turnover of essential trace elements with the determination of the distribution of these trace elements in the animal body and investigating the dynamic aspects of their turnover. That there is need for such technique is illustrated by many examples. The newly discovered vitamin, Vitamin B 12, contains some cobalt. An extremely small amount of this vitamin, of the order of 10 micrograms, constitutes

a whole therapeutic course. Also the known role of certain trace elements as co-enzymes is a considered factor in the establishment of these assay procedures to determine the concentration and distribution of these trace elements. Here one of the modern tools of nuclear physics, a chain reacting pile, offers another relatively new technique. This technique is called activation analysis, and it serves to determine the exact amount of minute quantities of certain elements. In this preparation the amount of cobalt distributed in the entire human body is only of the order of ½ micrograms. The technique of analysis is carried out as follows:

The biological material is first reduced to an ash of inorganic residue. This is then irradiated by means of slow neutrons in one of the piles. Many of the elements are present in extremely small quantities but if present they become radioactive in the high neutron flux. On later analysis the individual elements may be chemically separated; their radioactivity analyzed and assayed, and from the activity induced with the knowledge of the neutron flux, one is able to calculate the original amount of each element present. This technique for some elements appears to be the most sensitive technique of determination that has been used so far. (1,000 or more times the sensitivity of micro chemical methods).

Blood fractions, red cells, white cells, and plasma have been obtained from the blood of a number of people including normals, polycythemics, leukemics, and anemics. We irradiated the tissue ash from each of these groups and studied the trace elements present in the ash. A number of different radioactivities were found, and the induced radioactivity spectrum appears to be characteristic of the type of material used; i.e., red cells have a different induced radioactivity spectrum from white cells and from plasma.

Along with this work special attention has been focused on the biochemical activity of the nucleus of cells. This problem has many facets. However, we

are studying in particular those biochemical reactions in which metallic trace elements play an important role. Along with the microdetermination of the concentration of such elements, a systematic study is being carried on the turnover of these elements in nuclei of cells and in the cytoplasm of cells. Data obtained so far indicates that the element cobalt is consistently taken up in the nuclear material of cells of several tissues. It has a half time of turnover in nuclei of one day. It is rapidly excreted. The element zinc does not appear to do the same; it seems that very little of it appears in the nuclear fraction.

In animals which have tumors the uptake and distribution of the cobalt appears to deviate from the normal. These observations were done on mice and approximately twice as much cobalt was taken up in the nuclear fraction of liver cells of those mice that had actively growing mammary carcinoma tumors. The cobalt also appears in the nuclei of the tumor cells but at a somewhat later time. This study is being extended, and it is hoped that in the future all phases of the biochemical and biophysical activity of trace elements in animal tissue will be studied.

STUDIES ON SPECIFIC IRRADIATION

An old and obvious principle of cancer therapy is that of killing cancer tissue by subjecting it to the effects of high level specific irradiation. The diffuse nature of many neoplastic growths makes the metabolic or molecular solution to the problem of specific irradiation an attractive approach. Ideally a substance should be found which, when administered in a practicable manner, would become localized entirely in cancer tissue and not in normal tissues. If such a substance were synthesized incorporating suitable radioactive isotopes, selective irradiation of the tumor tissue would result and the irradiated tissue would involute if sufficient irradiation were applied. Such materials may

eventually be found through studies of biochemical processes. A number of organic compounds (tyrosine, dopa, phenylanaline) have been tried, which from our knowledge of tissue metabolism might have localized in certain neoplastic tissues, but these showed insufficient specific concentrations in the cancers studied. Another particularly promising substance is ready to be tested, stilbamidine synthesized with radioactive carbon. Stilbamidine is known to localize in multiple myeloma cells[1] but the degree of localization is not known. Unfortunately, the cancer known as multiple myeloma is unique to man and does not have a counterpart in experimental animal tissues so that we must wait to test this material until it is considered safe to use radioactive carbon in man. If this particular compound should localize a hundred times or more in myeloma tissue than in normal tissue, radioactive stilbamidine would then be an ideal agent for treating patients suffering from multiple myeloma. Other materials are being developed in this laboratory which localize in some of the body organisms and tissues, particularly the radioactive colloids of chromic phosphate, zirconium citrate, and strontium lactate. None of these colloids have the property of concentrating in neoplastic tissues, but when they are given intravenously they can be made to concentrate specifically either in the liver or the spleen or the bone marrow. These sites are involved in the cancerous blood dyscrasias, leukemia and polycythemia, and therapeutic radiation of leukemia and polycythemia patients is being carried out now at this laboratory using these colloids. The results of specific bone marrow irradiation or specific liver irradiation are at least as good as other irradiation methods for treating these diseases by irradiation. The advantage of the colloids is that the irradiation dosage to other body tissues is greatly reduced. Methods of infiltrating the lymphatic tissues with

[1] Snapper, I., Influence of Stilbamidine on Multiple Myeloma, J. Mt. Sinai Hospital 13, 1919, 1946

radioactive materials have been developed in this laboratory and recently a method of promise has been developed which consists of introducing the radioactive colloid into a lymphatic vessel. Such infusion of the colloidal materials in the case of certain of the yttrium colloids leads to a uniform and widespread infilteration of the lymphatic network of nodes above this site of infusion. The experimental results to date are sufficiently good so that experimental therapy in cancer patients will be tried immediately. Among the patients that will be tried first will be lymphosarcomas and mammary carcinomas because of the considerable lymphatic involvement in the spread of these cancer tissues.

Experimental animals of several types are being studied with regard to the biochemical problems of specific organism irradiation. Most of these studies involve specific irradiation of either the liver or of the bone marrow. Some of these problems concern the depression of nucleic acid formation. It is now certain that some depression of nucleic acid formation can be induced remotely from the site of irradiation. This supports the concept of a chemical substance being formed on irradiation of tissue which provokes further biochemical response to irradiation. Immunity studies have been made on animals who received high levels of specific irradiation of liver and spleen. No change in antibody formation was noted using four different antigenic substances in spite of the fact that whole body irradiation of 200 to 400 r greatly depresses this mechanism and that these animals received at least 10,000 r as specific irradiation to the liver and the spleen.

RADIOACTIVE CARBON STUDIES

Fifteen simple organic carbon preparations have been studied as to the rate of conversion of labeling carbon to carbon dioxide. This includes compounds in which one or another position of carbon is labeled with radioactive carbon.

There is practically a different rate of utilization and amount of utilization of each carbon compound and each carbon position within these carbon compounds. It is expected that this information may eventually lead to determination of certain limiting reaction rates in the path of carbon metabolism related to certain phases of intermediate metabolism. However, from the empirical approach certain significant differences are being noted between certain of the patterns of utilization of some of these carbon compounds in the normal as compared to the neoplastic animal and in the liver irradiated as compared to the normal animal. The two compounds showing effects of this sort to date are methyl labeled pyruvic acid, carboxyl labeled propionic acid and beta labeled alanine. The functional mechanism of this effect is not understood but since it is sizeable it is not as likely that it is strictly the result of the metabolism of the carbon within the tumor of the cancerous animals as it is that this is a reflection of change in the total metabolism of the cancerous animal. The laboratory is being developed for diverse work on carbon compound metabolism. The conversion compounds which are a part of the pathway of metabolism of any particular carbon atom can be separated and identified by apparati which are now installed in the laboratory, and this will increase the scope of the carbon biochemistry which will be done.

LARGE MOLECULES

The medical and biological program of the laboratory also includes a study of some large molecules of biological importance. Part of this program is the study of the physical chemistry of the colloids used for selective irradiation purposes. There are, however, some obvious protein molecules whose quantitative study is important in the program of irradiated tissues. Among

these are the plasma proteins, the albumins and lipoproteins. Physical chemical methods have now been devised for the analysis of these constituents and sub-constituents in the plasma of both man and experimental animals. There are already noted major changes in the lipoprotein fractionation following lethal and near lethal irradiation dosages to experimental animals. This program will be continued particularly with regard to liver irradiation.

CIRCULATORY STUDIES

A number of methods for measuring regional circulation in body tissues have been devised at this laboratory. These methods include assessment of tissue, perfusion rates of muscle, spleen, bone marrow, liver, thyroid and brain. The work is not primarily supported by the Atomic Energy Commission, but there are variations of this work which are important in the general study of irradiation effects upon tissues and metabolism of normal and neoplastic tissues.

GRAPH I.

ISODOSE CURVES FOR 190 MEV DEUTERONS