403038

UNIVERSITY OF CALIFORNIA

ATOMIC ENERGY PROJECT
POST OFFICE BOX 31
BEVERLY HILLS, CALIFORNIA

September 7, 1948

Dr. Lauren Donaldson
School of Fisheries
University of Washington
Seattle 5, Washington

Dear Dr. Donaldson:

Transmitted herewith for your files is a copy of Dr. Stafford L. Warren's opening remarks at the courses recently offered by the Extension Division, University of California at Los Angeles. In addition, there is a copy of each of the press releases submitted by the Public Information Branch, University of California at Los Angeles, to the members of the press in attendance.

Sincerely yours,

Robert J. Buettner
Prin. Admin. Asst.

RJB:m
encls.

BEST COPY AVAILABLE

Opening Speech by Stafford L. Warren, M.D.

...The Course in The Application of Nuclear Physics to the Biological and Medical Sciences convened on August 2, 1948 at 9:30 A.M. in the Chemistry Building, University of California at Los Angeles, Westwood, California...

DR. S. J. WEINBERG: Members of this class, it my pleasure to welcome you and introduce the general chairman for the course. It is not very often that the University has had the pleasure of playing host to a group as specialized and select as this one, coming as you do from the Vetrans Administration, the Armed Forces, the universities, the State and civic groups, Public Health Departments, and also the ranks of radiologists. We hope to repeat the course or a modification of it every second year.

There is one piece of information you don't have. The last lecture will be given by a recent Nobel prize winner, Dr. Carl Anderson of the California Institute of Technology who will discuss cosmic rays and the application of these rays in the matter of this course.

Equally distinguished in the field of biophysics is the General Chairman of this course, Dr. Stafford L. Warren, Dean pf the Medical School, University of California, Los Angeles , of whom most of you have heard. He is also a professor of biophysics of this institution. Dr. Warren.

DR. STAFFORD L. WARREN: It gives me great pleasure to welcome you here for many reasons, not the least of which is the fact that this is in a way the first course given by the faculty of the non-existant medical school, plus a lot of imported talent. This important talent is the little brass" of this course, and the medical school talent is the working group. There are a lot of reasons for this course that you probably all know individually since there is a wide variety of representation here as Dr. Weinberg pointed out. There are two fundamental reasons for this course being giventhis summer. One ofcourse is the desire of the University of California to take its place with other universities in extending the knowledge, information and usefulness of radioactive isotopes techniques throughout the country, and it is hoped that a goodly number of you will return to your institutions and act there as a small focus to spread the information and the techniques which you learn here. The second one is the ever present worry about the future conflict in which contamination by radioactive materials will be a major problem for all technical and professional men.

As physicians and technical men, groups such as this will have to be the backbone of any defensive or protective organizations that are set up. It is not unlikely that Dr. Bryan will discuss the contamination aspects of the laboratory problem very extensively when you come to deal with the active radioactive materials later on in the course

I would like to make a few remarks about the application of nuclear physics to medicine and biology, particularly emphasizing the dynamic aspects of biological phenomena. Perhaps I am sensitized to this a bit because recently I have been arguing with the physicists a great deal. The physicist, chemist and engineer, when they are dealing with experimental programs, think in terms of a very small percentage of error, because they can deal in general with rather fixed conditions and situations--- and by making two or three measurements and then using a lot of mathematics they can come out with an answer which has a chance at least of being quite precise. In biological problems you are dealing with a dynamic system which is continually changing. Of course the physicist is also, to a certain extent, but not just in this same way. In dealing with biological problems you have to bring a little different point of view to bear upon the experimental observations or the factual observations. In this same regard we have the greatest misconceptions today in both the national and international picture where medical and biological laymen attempt to apply static and precise explanations to phenomena occurring in large areas of contamination. You cannot just say you are going to have so many microcuries or curies of contaminating material spread in such and such an area uniformly. There is no such thing as uniformity on a large scale, nor is there uniformity in the distribution of these materials in the animal, and in the plant, or in the stream, or on the ground, or in the air. I have discussed this a little because you will be dealing with some animals and some plant materials, and you may be struck with the fact that your information is not comparable to that of your neighbor because you are using two different animals. That is why so much of the distribution data is plotted on the basis of percentage. The body is very much like an engine going at a moderate rate of speed, and you have to pick off your sampling while the engine is working because the biological processes are working and you can't stop them. If you stop them you get an abnormal result. The problem is always to obtain your data without your method of sampling causing distortions. Of course by experiment you do change the situation from time to time in order to bring out certain deviations which give you a clue or might give you a clue to what the normal physiology is. Now, this concept of the non-static position of biological materials is a little bit new to biologists in general, although many will not admit that it has crept upon them from the period of the first use of isotopes. Those of you who know much about the field know that before the war, a good deal of work was being done with isotopes, and a great deal of confusion resulted.

This was due to the fact that previous work with ordinary conventional laboratory procedures had built up evidence of which was interpreted upon static conditions. Points of reference were few and based on long time intervals. With the advent of radioactive isotope multiple samples could be done with great ease and considerable accuracy. Wide-spread comparison of organ contents could be inside. As a good illustration let's take sodium balance in the body. For a long time there was considerable mystery as to what happened to the sodium chloride. You can make measurements of sodium chloride in the plasma of the human or of the dog or other animals and you find that it fluctuates from moment to moment, from hour to hour, and from day to day. It took a long time to realize that there were tides in the blood and in the interstitial tissue and in the storehouses of the body which reflected the status of the fluid balance in the body and the needs. Under great demand such as excessive sweating the sodium chloride could be pulled out of the storehouses and the radio-sodium located in one of the hither to overlooked store-houses, namely the bone. The bone carries about twenty per cent of the salt resident in the body. That changed the concept of the availability of the bone to store things that were utilized from time to time. The bone was ordinarily thought of as a fixed structure mainly designed for weight bearing. It was known to fix certain poisonous metals but they were there to stay. The bone is a great sponge for some substances. It is a calcium appetite mineral with a wide molecular lattice work. In that lattice work can be stored easily--stored and removed--substances which are used in the day to day activity of the body. If you don't have this dynamic concept of change then the findings which you will obtain in the use of isotope techniques will be entirely unexplainable or confusing. How many samples--how many points--do you need to fix a relationship. That is a very difficult problem and can only be settled by a proper statistical approach. You might need as many as 100 points, or you might need only five or ten. There has been a great deal of useful work done up to now with isotopes in which trends have been indicated from experiments carried out with three to four analyses; at a point on time interval.

After the injection or the introduction of the isotope into the biological matter. It is obvious that a good deal of that earlier work will have to be done over, but it was satisfactory at the time since it did show a trend. This was a necessary device to get information quickly during the war. It cut down the number of animals that were used tc give a particular point, saving both time and materials.

Somebody will have to do the hard routine unexciting work of going over a great deal of that earlier data and doing it on a large enough scale to fix more of these poi than we are able to fix now. In some cases it is not important to completely establish concentration. In fact, it is unrealistic to try todo so because the concentrations do not mean much of themselves, it is only their relationship to other concentrations in t biological material, (The body, for instance--) that is important.

When dealing with your Geiger counter equipment it will be pointed out there a a lot of errors, there is difficulty with the geometry of the set-up, there are difficu with the ashing techniques. There are lots of losses. All of those defects you want t take in your stride, but become familiar with the technique--its purposes and the princ that govern it in general.

I would like to have you leave this course withe the feeling that there is a l to be learned yet, and there certainly is. You may get the impression in these three weeks that everything is known, and that is distinctly not the case. We are at a front that has hardly been touched, or hardly been explored. Our equipment is greatly impro over what we had before the war, but it still leaves a lot to be desired. Any of you who have an inventive frame of mind should certainly give yourselves the opportunity o inventing improvements. They are badly needed. The equipment is too expensive for wi spread use, and medical schools and biology departments that use this equipment ordina are not budgeted to operate on this level. Personnel is very expensive too, partly be the market is not saturated yet. I can't promise you all better jobs than you have no but I am quite sure you will be much more efficient, after you have had this training course, in your own job at home. It is not unlikely that a few of you will be stimulated by this course so that you will really read a lot and you will improve your experimental procedure. Some of you will be able to set up programs using these techniques and will train new men and women in this field. There is a great lack of trained personnel both in the Atomic Energy Commission's program and in the universities' programs as a whole, and in industry, and crew people are badly needed. I wish you lots of luck during this three weeks. We have a good group to talk to you.

K.B.
a.W.

Release AUG 1 1948

Mastery and "know-how" in handling the tools and techniques of the atomic age will be the aim of a three-weeks course in the application of nuclear physics to the biological and medical sciences, to be given August 2-20 at the University of California at Los Angeles.

Set up to provide much-needed training for personnel interested in atomic research, the course is presented to the University Extension in co-operation with the University of California Medical Schools in Los Angeles and San Francisco.

Under the leadership of Dr. Stafford L. Warren, dean of the U.C.L.A. School of Medicine, general chairman, and Dr. Fred A. Bryan, associate clinical professor of medicine, director of the course, a staff of 21 noted experts from the Radiation Laboratories in Berkeley and Los Angeles and from radiation centers in other parts of the United States will serve as instructors in various fields of atomic physics and medicine.

"To our knowledge, this is one of the most comprehensive training programs of its kind yet offered anywhere," said Dr. S. J. Weinberg, associate clinical professor of medicine at U.C.L.A. and head of postgraduate medical instruction in the southern area.

Application for admission have come from all over the nation, said Dr. Weinberg Universities, medical schools, research and public health organizations, the Army, and such agencies as the Veterans Administration and the Office of Civil Defense are sending men to participate in the course. One application has been received from the Curie Institute of Paris, France's national institute for atomic studies

"Science today is faced with an acute shortage of personnel adequately trained for radiation research," said Dr. Bryan, course director.

"The University of California, in setting up this curriculum, is attempting to meet the tremendous need for skilled workers. People trained in this course will be able to assist in establishing diversified research programs all over the country.

"Established radiation centers like Oak Ridge have had time to assemble trained personnel. A great many medical and industrial laboratories, however, have a tough problem recruiting research workers with a sufficient background in radiation.

DYSTER

"Through the combined past experience and acquired knowledge of the leaders in the field who will teach our classes, we will be able to offer basic principles all together—laboratory techniques as well as measures protecting the health and safety of scientific workers and the general public alike. Enrollees in the three-weeks course may perhaps save themselves in acquiring such skills."

Lectures and laboratory studies constitute the curriculum which will be given at U.C.L.A. Enrollees will be trained in the use of radiation detectors, including the well-known Geiger counters and other such devices, and in the use of radioactive isotopes, with emphasis in the personal safety factor in the laboratory handling of "hot" materials. Problems of decontamination and disposal of active atomic waste products will also be discussed.

All morning lectures will be held in Room 234 of the Chemistry Building on the U.C.L.A. campus. Afternoon sessions will be held in the Physics Building.

###

DKB
a.W.

Release
AUG 2 1948

INTRODUCTION TO ATOMIC AND NUCLEAR STRUCTURE

Benedict Cassen Ph.D., Atomic Energy Project
University of California at Los Angeles

There has been a natural tendency on the part of the medical and biological research profession to regard the subject of atomic and nuclear physics as a secondary tool to aid them in their problems. In a certain sense, the medical and biological specialists are right in so doing, but it is unfortunate that at least until recently, few of them realized that the maximum use of this tool requires a knowledge and training as vast as, or vaster than, that required for the field of medicine and biology. ?

On the other hand, there are very few trained physicists interested in applying their knowledge to medical and biological problems. They regard these subjects as too complex and see many simpler problems requiring solution.

In these introductory lectures, we will attempt to impart to the medical and biological groups some of the highlights in the fields of physics which have suddenly made these groups more conscious of their importance. These fields are popularly referred to as those of "atomic energy."

The choice of this term is somewhat unfortunate, as the word "atom" has too many meanings. To the ancient philosophers, an "atom" meant the smallest possible unit of a material substance and literally meant something which can not be cut. Much later the term "molecule" was used for the smallest unit of a material substance which cannot be subdivided without radically losing its original properties. In many cases, in inorganic physics as well as in biology, this definition of a molecule is hard to justify but it is still useful if applied with care. In most cases a molecule can be subdivided into smaller units which are now called atoms and which are the fundamental units of chemistry.

There are now 96 different species of atoms known. Several of these have been discovered very recently. Substances made up of only one type of atom are called elements and these include many well known materials.

As the result of ingenious experimentation and clever theorizing, it has been incontrovertibly demonstrated that atoms consist of a very small electrically positive nuclei surrounded by a definite pattern of electrically negative charge composed of electrons. For many years it was thought that the nuclei consisted of protons (hydrogen nuclei) and electrons, but with the discovery of neutrons in 1932 it has been conclusively proved that the atomic nucleus is composed of protons and neutrons. The fact that the nuclei seem to eject electrons in the so-called process of beta decay has been tentatively explained by a process involving concepts not at all easy to describe to the uninitiated. This explanation requires a massless, or almost massless, particle which has been called a "neutrino". Very recently the apparent ejection of "mesons" (heavy electrons) has been observed. This brings us to the fringe of the deep unknown, at which point we might appropriately ask: have we finally indivisibility or will the process continue? Aesthetically there seem to be too many "fundamental" particles.

Until the early part of the last war the measurable properties of atomic nuclei, except for their mass and positive charge, were very small and difficult to ascertain. At tremendous expense, relatively small amounts of naturally radioactive substances such as radium could be concentrated and atomic species of different nuclear masses (isotopes) could be separated.

This situation was radically changed by the discovery that certain nuclei could absorb neutrons and break up into other nuclei and neutrons. It was quickly shown that more than one neutron could be obtained from the "fission" started by one neutron. This opened up the tremendous possibility of the "chain reaction" which has become a reality in nuclear "piles" and nuclear atomic bombs. Nuclear physics suddenly emerged from the study of small effects to a big industry with many applications to medicine and biology some of which are described by my colleagues in this series of lectures.

In my following lecture details of the processes of emission of alpha, beta and gamma rays will be described. A description of the principle of operation of radiation detecting and measuring devices will also be given.

K.B.
O.W.

Release
AUG 6 1948

HEALTH PROTECTION AND SAFETY IN THE

HANDLING OF RADIOACTIVE MATERIALS

Louis B. Silverman, Health-Physicist,
Atomic Energy Project, U.C.L.A.

ABSTRACT

The development of the Atomic Bomb has resulted in the making available of relatively large quantities of radioactive isotopes. The use of these isotopes is rapidly becoming widespread and they have become one of the most valuable tools to modern reseachers, especially in the fields of medicine and biological sciences.

Due to the nature of these radioactive materials definite health protection and safety measures must be taken to prevent the longtime high radioactive contamination of work areas or the public domain.

During the last war, on the now famous Manhatten Project, a newly specialized branch of radiology was developed and designated as Health-Physics. This branch of Raidology has now assumed the status of an independant field of science. It is concerned with the health protection and safety of persons working with radioactive materials and with the determination levels of radiation that can be tolerated.

The main objective of Health Physics is to reduce to a minimum radiation caused injury to the individual and to the race.

Currently with more and more chain reacting piles and cyclotrons being put into operation, and their radioactive products and byproducts going into greater and greater and more diverse uses daily, the need for Health-Physics is proportionately increasing.

The two main requirements of all persons working with radioactive materials are:

(1) That no one shall be exposed to penetrating radiation above the tolerance level. The tolerance level has been based upon the accumulated data and experience of radiologists and medical men.

At present, tolerance has been set at 0.1 rem(reentgen equivalent man) per 24 hour period. This level of irradiation according to available

changed to 0.3 r/week or 0.05 r/24 hr. period Sept/3/1948 information can be tolerated by the average individual during a large fraction of his lifetime without any injurious effects.

The most effective protecting from these penetrating radiations is distance from the source. However, in cases where the distance becomes greater than the handling techniques allow, then massive shielding and remote control of handling devices are used.

(2) The other main requirement is that radioactive contamination must be controlled so that there is no unwanted migration of radioactivity into places where it may harm persons (i.e. by accidental or unknown ingestion, inhalation, or irradiation) or where it may harm experimental work or products.

Since radioactivity is always associated with matter, the prevention of contamination becomes a problem of material control. However, this problem differs from the normal problems of material control in that the amounts of material may range downward to small fractions of a micro-microgram (a fraction of a million millionths of a gram).

The control of these submicroscopic and invisible quantities of materials becomes similar to the problems of bacteriology and toxicology combined. However, unlike infectious or poisonous materials, radioactive contamination must be contained because it cannot be killed or neutralized. The reduction of any radioactive contamination depends upon the half-life of the material, its decay products or its complete removal.

The problem of disposal of radioactive waste materials seems, at the outset, to the individual working with relatively small amounts of these materials as a minor factor compared to his immediate general research problems. Nevertheless, when the sum total of all the radioisotopes used in the entire country is considered, the amount becomes large and the indiscriminate disposal over the years may result in serious contamination of water sheds. The disposal probelm has been recognized for its potentialities. Specific rules governing this phase are included in all health and safety regulations on the handling of radioactive materials.

The success of the Health-Physics program in connection with the recent handling of huge amounts of radioactive materials can be measured in the no radiation-injury record of the Manhatten Project and in the successful results and conclusions of the various research problems on that project.

There is one aspect of Health-Physics that is not pleasent to think about and that concerns the problems which would arise in case of an atomic bombing in any future war. The health-physicist would be the logical person to regulate the health protection of the rescue teams, the surveying of contaminatied areas or equipment and the monitoring of the rehabilitation program. He would also assist and cooperate with the medical services in checking the radioactive contamination of victims and the survivors.

The future applications and success of this new field of science are yet to be fully realized. We have started a new era with the development of the Atom Bomb. The dangers of radioactivity are cummulative and the effects may be far reaching. However, if the use of these radioactive isotopes does involve the most hazardous potentials, they still can be used safely in all fields of endeavor for the benefit of the entire race. It therefore becomes the moral obligation of each individual or organization working with radioactive materials to fulfill all the regulations and reccommendations of the health-physicist for their own immediate health protection and for the general good of all mankind.

L.B. Silverman 7-28-48

K.B.
a.W.

Release
AUG 10 1948

BIOLOGICAL EFFECTS OF RADIATION

Andrew H. Dowdy, M.D.
Professor of Radiology
School of Medicine
University of California at Los Angeles

(Abstract of lecture before University Extension course at U.C.L.A. in "The Application of Nuclear Physics to the Biological and Medical Sciences

The different types of radiation of both practical and theoretical consideration will be discussed, with a brief description of the origin, physical characteristics and ionizing properties of each.

Specific ionization refers to the relative number of ions produced per unit length of tract when radiation interreacts with matter. Biologica reaction subsequent to exposure to radiation is a result of ionization. Biological damage may or may not parallel the degree of ionization, and the factors which influence the degree of ionization, as well as what is meant by the relative term "radiation sensitivity" will be described.

All living tissue can be injured by radiation of sufficient intensity and total dosage. (Indeed, inert substances such as glass and diamonds can be altered by radiation.) Injury may be manifested as a result of either acute or chronic radiation, and of local or total body exposure.

Damage to tissue probably occurs in two ways: (1.) direct action of radiation *per se* on the functioning cell or organ, and (2.) indirect effect of radiation upon the cell or organ by bringing about changes in its environment.

Direct action effects are:

(1) damage done to cell membranes by causing changes in the permeability of the membrane.

(2) a breakdown of protein into small molecules, causing changes within cytoplasm which may alter the osmotic pressure of cells.

(3) mitotic mechanism damage, which may be brought about by suppression of complete interruption of cell division; by the breaking of chromosomes; or by definite injury to the genes.

Indirect radiation action brings about changes in the activity of cells by virtue of changes in cell environment, such as enzymatic inhibition and interference with circulation.

Biological effects of acute total body radiation and of chronic total body radiation, with respect to the difference in the mechanism of these two kinds of radiation, will be reviewed briefly in the lecture.

K.B.
A.W.

Release
... 1 1 1948

THERAPEUTIC APPLICATION OF RADIATION

Andrew H. Dowdy, M. D.
Professor of Radiology
School of Medicine
University of California at Los Angeles

(Abstract of lecture before University Extension course at U.C.L.A. in "The Application of Nuclear Physics to the Biological and Medical Sciences".)

The selection of radiation for therapeutic use depends upon:

(1) the availability of material (radiation)

(2) the experience and expertness of the individual administering the radiation

(3) the type and character of the disease to be treated.

In general, the biological results from different kinds of radiation are the same if certain differences in physical characteristics are taken into consideration. (To illustrate: one would hardly use a shotgun to shoot a fly off a wall when a fly swatter would do. By the same token, since radio-iodine effectively demonstrates a selectivity for thyroid, there is no need to treat cancer of the thyroid by total body radiation. It should be stated, however, that radio-active iodine is applicable as a therapeutic agent in only a relatively small percentage of thyroid cancers.)

While it is not generally recognized, particularly among the laity, radiation therapy is used for other than malignancies. The radiation treatment of lymphoid hyperplasia in the posterior nasopharynx, a condition which may cause much of the deafness among children, is a case in point. The overgrowth of lymphoid tissues which blocks the opening of the eustachian tube and impairs hearing can be destroyed by localized treatment with minute quantities of beta radiation. In approximately 80% of the cases so treated, one treatment proved effective.

It is the opinion of this lecturer that radiation itself is not the answer to the cancer problem, nor will the greatest advantage of radioisotopes be derived from their present therapeutic application as such, important though this application is. Rather does it seem that the greatest advantage of radio-isotopes will come from their use as a research tool in pushing back the frontiers of science. Their particular application in biology is in furthering the study of cell physiology.

As concerns radiation, it is the amount of radiation absorbed by ionization which produces biological reactions. Radiation energy is absorbed in the tissues by the process of ionization. The exact steps in the physico-chemical changes resulting from these ionizations are not known.

Problems yet to be solved in the use of controlled nuclear energy are:

(1) development of a practical clinical method for detecting biological changes resulting from exposure to minute amounts of radiation.

(2) selective alteration of tissue sensitivity to various types of radiation.

(3) protection of tissue against the deleterious effects of radiation.

(4) finding a therapeutic measure to ameliorate damage and hasten recovery once damage has ensued from radiation.

K.B.
G.W.

Release
AUG 12 1948

TECHNIQUES AND STUDIES IN THE USE OF IODINE 131

Dr. Robert Fink, Research Biochemist, Birmingham V.A. Hospital and Associate Clinical Professor of Physiological Chemistry, School of Medicine, University of California at Los Angeles

(Abstract of a lecture delivered in a University Extension Course at U.C.L.A. on "The Application of Nuclear Physics to the Biological and Medical Sciences.")

The metabolism of iodine has been the subject of a large amount of research during the two decades since the thyroid gland was shown to concentrate iodine to a very marked degree as compared with other tissues. This research received a tremendous impetus when radioactive iodine became available for biological studies about 10 years ago and made it possible to study the rate of iodine assimilation by the thyroid under normal conditions. In spite of the intensive work on the problem, however, a great deal remains to be learned about how the thyroid captures iodine from the blood stream and converts it into the thyroid hormone which controls the body's metabolic rate.

Some recently developed chromatographic techniques show promise of being the tools required for the job of filling in much of the missing information about this process and perhaps many others as well. For example, radioisotopic tracer techniques have been used in conjunction with filter paper chromatography, a procedure in which a tiny droplet of body fluid or tissue extract placed on a sheet of filter paper is split into its individual chemical components by a liquid which creeps down the paper and carries the chemical substances present in the original droplet along at different rates. Spraying the paper with a suitable color reagent then given a chromatogram showing colored spots corresponding to the position taken by the chemical substances present in the droplet in relatively high concentration. If radioactive substances are present, however, preparing a radioautograph of the chromatogram by placing the paper against photographic film in a dark room will show the positions of the radioactive compounds even though the actual amounts present would have to be increased a thousand or even a millionfold in order to be seen or weighed or studied by ordinary chemical techniques.

By conventional chemical studies, even with radioiodine, the iodine containing substances of the thyroid have been separated into only three fractions:

1. Inorganic iodide (such as that in iodized table salt).

2. A fraction having solubility characteristics similar to those of diiodotyrosine (the result of adding two iodine atoms to a molecule to tyrosine, an amino acid found in most proteins).

3. A fraction with solubility like that of thyroxine, the substance believed to be either the thyroid hormone itself or an essential part of that hormone. (Thyroxide is made up of a diiodotyrosine molecule combined with iodine-containing portion of another diiodotyrosine molecule, and thus contains four iodine atoms).

When the thyroids of rats injected with radioiodine were studied by "chromautograms", i.e. radioautographs of chromatograms, as described above, radioactive spots were found at the positions taken by pure inorganic iodide, diiodotyrosine and thyroxine, but in addition there were a whole series of unexpected radioactive compounds. The most intensely radioactive of these unexpected spots has been tentatively identified as monoiodotyrosine since it coincides exactly in position and shape with the colored spot obtained when a relatively large amount (i.e. a few millionths of a gram) of monoiodotyrosine is added to the original droplet of thyroid extract. Some of the others are in approximately the positions which one might expect to be occupied by compounds similar to thyroxine but containing one, two or three iodine atoms. It would appear then, that a relatively simple new technique has opened the way to a most detailed study of the steps by which the thyroid hormone is synthesized.

The same technique has been used in a preliminary fashion for a study of the steps in the formation of sugar from radioactive carbon dioxide in plants (photosynthesis), and a similar procedure has been used by Dr. Borsook at Cal. Tech. in studying the metabolic breakdown of the amino acid lysine. The latter study also demonstrated the presence in the animal body of an amino acid which had escaped detection by conventional chemical techniques.

A closely allied procedure which appears to show promise employs radioactive reagents, rather than color reagents, for detecting the presence of non-radioactive compounds in the filter paper chromatogram. Development of such a procedure, by making possible the detection or even the accurate determination of substances present in fantastically low concentrations in urine, blood or other fluids, might well lead to valuable applications in clinical diagnosis.

K.B.
a.N.

release

AUG 12 1948
AUG 13 1948

First use of an original technique which has opened the way to a minutely detailed analysis of the steps by which the thyroid gland manufactures the secretion which controls the rate of body function was described today by Dr. Robert Fink, research biochemist, Birmingham V.A. Hospital and associate clinical professor of physiological chemistry in the U.C.L.A. School of Medicine.

Dr. Fink, member of a husband and wife research team, discussed the new work in a talk given in a University Extension course at U.C.L.A. on "The Application of Nuclear Physics to the Biological and Medical Sciences." He summarized results of research performed in collaboration with his wife, Dr. Kathryn F. Fink, assistant clinical professor of biophysics in the U.C.L.A. School of Medicine.

Two recently developed medical research tools were combined by the Finks to produce the remarkably simple and sensitive new method for studying thyroid activity.

Radioactive isotope tracer techniques were used in conjunction with what Dr. Fink called "filter paper chromatography," a sort of blot test devised in 1944 by a British researcher for the purpose of detecting different chemical components of a substance by means of their different degrees of solubility.

In this procedure, said Dr. Fink, a tiny drop of body fluid or tissue extract is placed on a sheet of filter paper or special blotting paper. A liquid is applied to the filter paper in such a manner that it "creeps down" the paper like spilled ink wetting a blotter. The creeping liquid meets the original droplet of test material and carries the chemical substances present in it along at different rates, depending on the solubility of each particular component.

The paper then is sprayed with a suitable color reagent, which gives a "chromatogram" showing colored spots corresponding to the positions taken by the chemical substances present in relatively high concentrations in the original droplet.

If radioactive substances are present, however, said Dr. Fink, a radioautogra of the colored filter paper is also prepared. A radioautograph could be called a "self-picture," and is made by placing the filter paper against a photographic film in a dark room. Radioactive substances on the filter paper will expose the film by film exposed by light. The black spots on the film, said Dr. Fink, exactly matched the colored spots on the filter paper.

The infinitesimally small amounts of material which can be detected by this method would have to be increased by a thousand or even a million in order to be seen or weighed or studied by ordinary chemical techniques, said Dr. Fink.

Conventional chemical studies, including radioiodine, have been successful in separating the iodine containizing substances of the thyroid into only three fractions, he said.

When the thyroids of rats injected with radioiodine were studied by the new technique utilizing radioautographs of chromatograms, radioactive spots were found as expected at the positions taken on the filter paper by three known fractions, but in addition there were a whole series of unexpected radioactive spots indicating unknown compounds.

The most intensively radioactive of these, according to Dr. Fink, had been tentatively identified as monoidotyrosine, a substance which never has been isolated from thyroid. It coincides exactly in position and shape with the colored spot obtained when a relatively large amount of monoiodotyrosine is added to the original droplet of thyroid extract.

The same technique has been used by the Finks in preliminary studies of the steps in photosynthesis, the formation of sugar from carbon dioxide on plants, a process essential to the food supply of the entire world.

A similar procedure has also been employed by other reachers in studying the breakdown in the body of the amino acid lysine, one of the essential building blocks of protiens.

Summarizing the uses of the new technique, Dr. Fink said:

(1) unknown or unexpected compounds can be detected,

(2) the position on the paper gives a clue to what these compounds might be

(3) The technique permits a matching of unknown with known compounds

(4) if the compounds fail to match, the filter paper is of great assistance in giving an assay procedure evolving steps in purification of the

A closely allied procedure employs radioactive reagents rather than color reagents for detecting the presence of non-radioactive compounds in the filter paper chromatogram, said Dr. Fink.

It shows a promise of making possible the detection and perhaps even the accurate determ/ination of loterally sources of substances present in a speck of tissue so minute as to be practically invisible even under a microscope. ?

Such/a procedure might well lead to valuable applications in the clinical diagnosis of many diseases, said Dr. Fink.

####

AUG 13 [redacted]

THE GENETIC EFFECTS OF RADIATION

Albert W. Bellamy, Ph.D., Professor of Zoology and Divisional Dean of

Life Sciences, University of California at Los Angeles

(Abstract of a lecture given at U.C.L.A. in a course on "The Application of Nuclear Physics to the Biological and Medical Sciences.)

About the only point at which the three fields of genetics, medicine and radiation meet is in the matter of mutation. Mutation rates in Laboratory plants and animals are easily altered by exposing chromosomes or their germ cells to suitable doses of radiation, usually X-rays. Increases of several thousand percent are usual.

The significance of increased mutation rates in man were highlighted by the exposure of a considerable number of human beings to gamma radiation following the atomic bomb explosions at Hiroshima and Nagasaki. Various dire predictions have been made that mutations induced by radiation released by the bomb detonations would alter the genetic structure of the Japanese population. Whether or not this is a sound conclusion can be judged to some extent after the essential data have been examined.

The essential problems before us in this discussion are: (1) to review briefly the mechanism of inheritance; (2) the general nature of the mutation process; and 3) the manner in which radiation can alter the genetic structure of a population.

From the standpoint of mechanism we have, for the most part, three things to consider:

(1) The nature of the gene and its mode of action.

(2) The relationship of genes to chromosomes and the orderly patterns they form in the chromosome.

(3) The behavior of homologous chromosomes in the process of sperm and egg formation and the existence of chromosomes of at least two general types: the sex chromosomes or heterosomes and the other chromosomes or autosomes.

The gene is better known for what it does than for what it is. It is thought that the gene consists chiefly of nucleic acid, possibly as small a quantity as one molecule or less.

2...Effects of Radiation (Dr. Bellamy)

In physical size the gene approaches the dimensions of the viruses. The resemblance has prompted several workers to refer to certain viruses as "naked genes". The diameter of a gene is almost certainly not less than two or more than 10 millimicr or about 1/2,500,000ths of an inch.

Like the viruses, it has the interesting property of self-duplication. Each time a chromosome divides in the process of cell division, not only is each gene re-duplicated in a very precise manner, but also the genes retain their characteristic order and arrangement in the chromosomes.

There are processes, however, by which the order of genes in the chromosomes may vary or can be altered experimentally in several precise and predictable ways. These processes are: crossing over; inversion; translocation and the like. These processes can be accelerated by exposure to radiation.

It will be useful to remember that the majority of gene mutations are recessi This means that both parents must contribute the same gene in order that the dependent characteristic may develop in the offspring. Just why the majority of gene changes result in recessive characters is an oddity of nature for which there is no good explanation.

We should remember also that most mutations, recessive or otherwise, result in characters that either do not help the individual or more usually, and in varying degrees, render it less able to survive than its normal relatives. Medical men will have no difficulty in understanding that any change in a system as delicately balanced as that in a living organism is likely to be for the worse rather than the better.

Mutations occur normally at some characteristically low rate, and from causes as yet unknown. Cosmic radiation has been suspected, but there is no good evidence to indicate that this is so. Laboratory organisms bred in regions where comic radiation is high in quantity do not show a mutation rate significantly different from that in control organisms bred in regions of low amounts of cosmic radiation.

3...Effects of Radiation (Dr. Bellamy)

Calculations show that mutation rate within temperature ranges in which organisms live and thrive, increases (in Drosophila) about two to five times for each 10 degree rise in temperature.

One of the most puzzling properties of the gene, at least to the theoretical physicist, is the stability of the gene--a property of great practical as well as theoretical importance.

Since the diameter of the gene is almost certainly between two and 10 millimicron this means that a gene involves in the order of a million or so atoms.

In terms of statistical mechanics this small number of atoms should exhibit a ver irregular behavior. However, as such things go in biology, the gene represents one of the most stable configurations known.

That even mathematical physicists regard the gene as an interesting object and concept illustrates the fact that the boundaries between the several sciences are becomin ill-defined and diffuse. That there should be reciprocal contributions between medicine and genetics is not surprising. But that genetics should arise to the point where it see to tarnish a little the bright sanctity of an important concept in theoretical physics is little startling. (Namely, by presenting the puzzle of explaining how so small an amount of material could be so stable.)

The second part of this lecture will be devoted to mutations, about which enoug information has been accumulated so that we can classify variations into several categor

(1) Modifications--variations in the expression of a character due to function process in the organism or response to the environment. Every character of the organism gene determined or not, responds developmentally to function and to environment.

(2) Gene recombinations--which account for the multitude of relatively small characteristics by means of which we distinguish members of the same species or of the same family from each other.

(3) Mutations---processes by which germinal material changes in such a way that a new character--or one not previously known--appears suddenly and is inherited without further change. Or at any rate, without further change until a new mutation occurs affecting the same locus or trait.

The cause or causes of mutation have long been a puzzle. Investigations are far from complete and many questions are as yet unanswered. In the discussion of possible causes of mutation, it should be clear that by causes of mutation we refer always to chan in mutation rate. Just as the investigator using a Geiger-Muller counter estimates radioactivity in terms of counts above background, so the geneticist measures mutation ra as a multiple of the base or natural rate.

Radiant energy: Twenty-one years ago Muller demonstrated clearly that mutation rate can be increased by exposing Drosophila banana fly to X-rays. Ultra-violet light wa also found to be effective.

Since 1927, mutation rate changes following exposure to X-rays, gamma radiation and in a few instances to particle radiation (mainly beta) have been studied in a considerable number of organisms ranging through the viruses, bacteria, plants and animals. Increases up to several thousand percent are not unusual. This is one place, however, w expressing results in percentage may be a little misleading. With a base rate of ~~10-6~~ 10^{-6} a increase of 100% in rate would mean two mutations in a million; 3000%, 30 in a million. The trick for the geneticist, is to find those few in a million.

There can be no reasonable doubt that at least one of the causes of mutation is ionization (from radiation) and change in energy levels resulting in a chemical change : the genes.

Other forms of radiant energy---Ultra-violet light and very high frequency rad waves: Experimentation with ultra-violet light is complicated by reason of its small penetrating power. Small but significant increases in mutation rates of Drosophila and corn have been demonstrated.

Very high frequency electromagnetic fields have not been well investigated. Significant changes in the lethal mutation rate and other changes have been demonstrate in Drosophila, however.

####

A.W.

Release

[redacted]

Abstract of Talk to be Given by
John S. Lawrence on August 13, 1948

THE EFFECTS OF RADIATION ON HEMOPOIESIS

John S. Lawrence, M.D.
Professor of Medicine, School of Medicine, U.C.L.A.

A consideration of the effects of radiation on the blood-forming tissues brings one into a controversial field. Varying modes of application, varying physical properties in different types of radiation, and varying effects in different animal species studied have resulted in confusion. The extent, location, and type of injury on blood-forming tissues dependant upon these and other complicating factors. Fortunately, these changes are often quantative rather than qualitative. The remarks today summarize our present experiences with the effect on blood-forming tissues. The data reported deal chiefly with studies employing X-rays and gamma rays. Special effects peculiar to certain other types of radiation such as alpha, beta and internal radiation will be mentioned where such exist.

In this discussion, we shall consider the effects of radiation when administered in the following ways:

1. Single dose to the whole body as a whole
2. Repeated small doses to the body as a whole
3. Single or repeated doses to <u>one</u> area
4. Internal radiation

Single Doses of Roentgen Radiation to the Body as a Whole

By way of introduction, much confusion will be avoided in considering radiation effects on the blood-forming tissues if the following facts are recognized:

1. The adult cells in the circulating blood are very resistant to damage by radiation. It is the young, parent cell types in bone marrow and lymphoid tissues which are the precursors of the circulating cells which are so sensitive to radiation injury.

2. After a single dose of radiation to the body as a whole therefore, the changes in the circulating blood at any one time after exposure, depend to a large extent upon the length of life or rate or turnover of circulating cells. We can look on the circulating cells as populations composed of species each with its own average life span. If the birth rate is reduced to zero or near zero by radiation and the adults remain relatively unaffected, depopulation of the circulating blood cells will be proportional to the life span of each species of cell. Thus, marked reduction in the population of short-lived cells will become apparent before marked reduction of the long-lived cells.

There is reason to believe that the average life span of the white blood cells is a matter of a few hours, that of the blood platelets is a matter of a few days, and that of the red blood cell a matter of more than 100 days. After a single dose of radiation, the theoretically anticipated order of disappearance of circulating cells would be first the white cells, second the platelets, and third the red blood cells. Indeed, the red blood cell population might be expected to become reduced so slowly after certain dosages of radiation that regeneration (active production of cells) might occur before the reduction in numbers had attained a magnitude readily detectable by current laboratory methods. The fundamental damage to parent red cell types in such a case could be said to be masked because of the longetivity of the circulating red blood cell.

3. The blood picture, after any one dose of radiation, is affected by the radiosensitivity of the various parent cells. A given dose might profoundly damage one cell type and only slightly damage another.

4. The ability of tissues to regenerate is one of great importance. Repair of damage will be more readily effected by tissues with marked capacities for regeneration.

Most worthwhile observations on effect of single doses of radiation have been made in animals. Detailed data on the effects of varying dosage of radiation on rats will be presented in the body of the lecture. The exact amount of radiation required to produce a given effect on a given cell varies with different species, but the following observations seem reasonably well established.

1. The lymphocyte-(a type of white blood cell) producing tissues are the most sensitive to radiation damage, The tissue producing platelets, red blood cells, and granulocytes (the latter is another type of white blood cell) are less sensitive and have a sensitivity roughly comparable one to the other. Here is some evidence that the red blood cell-forming tissues may be intermediate in sensitivity between the lymphocyte and other blood cells--more sensitive than the latter, less so than the former.

2. As was expected on the basis of knowledge of the life span of

the different types of circulating blood cells, actual experimental observation confirmed that:

- (a) The short-lived white blood cells disappeared or were reduced first, the lymphocytes in less than 24 hours, the granulocytes within 72 hours.
- (b) The blood platelets (intermediate life span) were reduced next—first reductions in rats at about five days.
- (c) The red blood cells (long-lived) were the last to show reductions.

3. In the rat, regeneration was evident by the fifteenth to eighteenth day in most cell types except for the granulocytes was still incomplete by the twenty-fifth day after exposure. In other species, regeneration may be slower. The lymphocytes were still more greatly reduced after twenty five days than were the other cell types.

4. In animals receiving large doses of radiation, a sharp drop in numbers of red blood cells occurs around the seventh day after radiation. This is thought to be due to bleeding, nutritional, factors, and possibly to other little-understood factors and not entirely to simple destruction to parent cells. This sudden anemia does not occur with lower radiation dosages.

5. In certain species (and perhaps all species), severe radiation damage is accompanied by the release of an anticoagulant heparin-like substance into the circulation. The blood clots slowly which, together with the reduction in blood platelets, results in an abnormal tendency to bleed. bleed

Repeated Small Doses to the Body as a Whole

The experimental findings are difficult to summarize but very important since it is chronic radiation repeatedly received in small doses which is the commonest form of radiation exposure in man. It is clear, however, that within limits the effect of chronic radiation is cumulative and that the total dosage received by an organism is of great importance regardless of how small the individual exposures. Secondly, chronic radiation definitely increases the incidence of leukemia in animals. Thirdly, after apparent recovery from chronic radiation, injury to the blood-forming tissues and several abnormalities may develop even after radiation has been discontinued.

Radiation to a Local Area of the Body

It has been the subject of much controversy whether or not local radiation may, in some direct way, damage hemopoietic tissue outside the field of radiation. Local radiation, of course, damages any blood forming tissue in the direct field. At the present, all attempts to demonstrate any "indirect effect" peculiar to radiation on the blood forming tissues had failed. However, the reduction in white blood cells sometimes found in man after treatment to local areas thought to contain but relatively little blood-forming tissue remains poorly understood. The question requires further critical study.

Internal Radiation

This involves chiefly the use of radioisotopes and differs from other types of radiaiton chiefly in that relatively non-penetrating radiations such as alpha and beta rays can be introduced into the body where they may radiate tissues they could not reach by external application. This opens the possibility of giving radiation to special cells and tissues without apparently affecting others. Radioactive iodine and radioactive phosphorous are examples of substances thus employed. In general, the effect of radioactive phosphorus in the blood-forming organs corresponds closely to the effects attainable by external radiation.

The Effect of Neutrons

The effects on the blood-forming tissues are essentially similar to those of X-rays. Using fast neutrons, the biologic damage resulting from 1n (amount of neutron radiaiton producing same amount of ionization as 1r X-radiation in an ionization chamber) is about eight times as great as that resulting from 1r.

Effects of Radiation on Man

The purpose of all the animal work reviewed is to get a better idea of the effect of radiation on man. Acute exposures to single doses of whole body radiation may occur in man, as an accidient, or after detonation of an atomic bom.b. They are otherise seldom encountered. In individuals studied in Japan who were exposed to radiation at the time of the detonation of the bomb, the abnormalities in the blood were found similar to those experimentally in animals. The first abnormality noted was reduction in the number of white blood cells, the second was reduction in blood platelets, and the third was reduction in red blood cells.

However, most human exposures are more likely to be of the nature of small amounts received repeatedly. The animal work suggests that the cumulative dose is highly important, that leukemia may occur more frequently in individuals exposed to chronic radiation than in the population as a whole, and the relaps may occur after apparent recovery from radiation damage. From a practical point of view, any departure from the normal findings, whether an increase or a decrease or a quanitative change in any of the blood cell types should be viewed with suspicion in individuals who have been exposed to chronic radiation. In practice, a reduction in white blood cells, particularly granulocytes, is the commonest evidence of damage in man. What additional effects of chronic radiation will be found cannot be said.

a.W.

AUG 13 1948

METHODS AND TECHNIQUES IN THE USE OF IONIZING RADIATION IN GENETIC STUDIES

Albert W. Bellamy, Professor of Zoology and
Divisional Dean of Life Sciences,
University of California at Los Angeles

ABSTRACT

In general, the geneticist is interested in effects of radiation on the germ cells and the techniques are modified accordingly. Techniques differ also with the type of radiation used.

Wherever possible only the germ cells are exposed. This can be done in the case of plant pollens. Sperm can be irradiated in cases where artificial insemination is feasible. Or, by suitable shielding in some instances, the testes alone may be irradiated. If total body radiation must be used, the dosage will be less than if only germ cells are exposed, since a dead or injured organism is quite uninteresting genetically.

Ionizing Radiations

Neutron radiation. Total body radiation. Exposures at high and low [illegible] the simplest way of getting some difference in dosage. Sufficient [illegible] and very expensive [illegible] chamber.

Gamma radiation: The techniques are about the same as X-rays, having due regard to the greater penetrating power of this high energy radiation and the source from which it is obtained. In some instances, economy of time and effort will be obtained by using a radium needle, a radioactive isotope of suitable characteristics and geometry and the like, located at the center of a ring of cultures. tr

X-rays. Techniques are as given above. Here as elsewhere, experience with specific material is necessary in order to determine dosages, having in mind the characteristic of the radiation available and the filtering, etc., needed in certain instances to yield interpretable data.

Beta rays. [illegible] electrons. Since beta radiation produces [illegible] to

handle and to calibrate dosage, there is no particular advantage in taking the extra pains to [illegible] sources for ionizing radiation.

In the field what is coming to be known as health physics, however, it is important to discover the extent to which ingested beta emitters may be significant mutagenic agents, as well as damaging in other ways, e.g., to the blood forming tissues. However much one may hope that we, or any people, may never have to contend with contamination of large land areas by radioactive materials, sound planning is not based upon wishful thinking. We need not know the extent to which all of the biologically significant radioactive isotopes are stored and perhaps concentrated by a sizable factor in what tissues. Otherwise we have no way of knowing what physical concentration of a radioactive contaminant in the soil and elsewhere may present a biological hazard--or the magnitude of the hazard.

We know enough about many of the beta emitters to estimate types of [illegible] to be expected following ingestion. We do not know which of them has a [illegible] in relation to half-life such as to present a genetic hazard— a [illegible] which, in the extreme case, might be equally as disastrous as immediate physical damage, but which might not appear for many, even thousands of generations in the future.

Alpha rays. High speed helium atoms. Effects similar to beta rays but with lower penetrating power. Probably not of genetic significance unless, under experimental conditions, the alpha emitter can be applied within a millimeter or less of the germ cells. It is not known whether or not any of the alpha emitters would tend to concentrate in any of the tissues of the gonad.

Non-ionizing radiation: Ultra-violet; infra red; very high frequency radiation. We turn now to the speculative part of this discussion.

A rough approximation of effects on the genetic structure of a human population exposed to gamma radiation such as would accompany the denotation of an atomic bomb at a height comparable with those used in Japan. The approximation will be [illegible], indeed, [illegible] are no [illegible] available which will permit anything approaching an accurate estimate. There are too many gaps in essential information.

Mutation rates are not known for man and are not likely to be known for [illegible] to come. Haldane (19[illegible]2), however, estimated the mutation frequency of two human genes; for hemophilia and epiloia (a syndrome characterized by mental deficiency, tumorous, [illegible] face, and epileptic attacks) as 10^{-5} for each. Even though this figure may be reasonably accurate for these two genes, it is not known whether they represent a relatively high, average, or low rate in comparison with others. In Drosophila (fruit fly) comparison of nine sex-linked recessive characteristics shows that the locus having the lowest rate differs from the highest by a factor of [illegible]. This means that for all we know the average mutation rate in man might differ from 10^{-5} [illegible] orders of magnitude.

In attempting to arrive at a more or less generalized approximation, we will assume a typical American city as having a population density of 10,000 people per square mile, and that it is exposed to radiation from a source some distance from the city.

Let us assume further that 40%, or 4,000 persons per square mile will be between the ages of 1[illegible] and 39, and that the proportion of males and females is 50-50. We will neglect non-reproductive matings and assume simply an average value of three offspring [illegible] or 6,000 offspring per square mile.

Our estimate is based on Drosophila data. The total yield of sex-linked lethals in this species of about 3 per 1000 Roentgen units of total body radiation.

If we assume the same rate for man and correct for dosage—man cannot take 1000 r and live—we arrive at .006 as the yield at the assumed dosage in man. We can write this as 6 sex-linked lethals per 1000 X-chromosomes, or 1 sex-linked lethal in 167 X-chromosomes.

Having assumed an average progeny of 3 per mating we have for the 2000 females between ages of 15 and 29; [illegible] per square mile. We assume equal numbers of males and females.

The 1000 mothers should have among them 2000 divided by 167 or 12 X-chromosomes carrying a sex-linked lethal. Half of their sons will receive this mutated chromosome and will die.

Lethal characters are of course very different to detect. And even this relatively large number would go undetected in a human population. Technically trained persons will see from these figures that the sex ratio would shift in favor of females by about one part in a thousand. There would be about five males less per thousand population.

Visible recessive characters (eye color, feeble mindedness, hemophelia, etc.) occur less frequently that the lethals by a factor of abrut 13. Our estimate of increases in these visibles is based, however, on Haldane's estimate of one in 100,000 for the natural mutation rate in man. We assume further that exposure to radiation will increase this rate about 30 times. This gives us a mutation rate of about 3 in 10,000 after radiation.

The genetic equilibrium operates in such a way that the probability of any one now living seeing a mutation that may have been induced during the atomic bomb explosions in Japan is almost nil.

What can happen many generations later, however, is a very different story. Even though the calculations of Haldane, Fisher and Wright indicate that it may take some hundreds of thousands of generations for a mute gene to become established in a population, eventually of some of these genes will show up.

If enough of them are disabling in their action, their social and economic significances can become very large indeed.

A.W.

release

AUG 14 1948

Nature operates in such a way that the probability of any one now living seeing hereditary changes which may have been induced during the atomic bomb explosions in Japan is almost nil.

So said Dr. Albert W. Bellamy, professor of zoology and divisional dean of life sciences in the University of California at Los Angeles, during a talk given at U.C.L.A. today (Friday, August 13) in a course on the Application of Nuclear Physics to the Biological and Medical Sciendes.

Various dire predictions that mutations induced by radiation released by the bomb detonations would alter the genetic structure of the Japanese population must be considered in the light of the essential data, said Dr. Bellamy.

No monsters have been observed as a result of the explosions and it is highly improbable that any ever will be. The majority of gene mutations are recessive in character, which means that both parents must contribute the same gene in order that the recessive characteristic may develop in the offspring. The changes are transmitted as (1) lethal characters which are fatal to the offspring and very difficult to detect, and (2) as visible recessive characters, which involve eye color, feeble mindedness, hemophelia, etc., and occur about 13 times less frequently than the lethals.

Therefore, the slow dissemination of a population by the transmission of lethal characters would be more likely to occur than any sudden and widespread outcropping of monstrosities.

Although genetic changes which may have been brought about by atomic bomb radiation have not yet been observed and would not be in any case for some time to come, what might happen many generations later could be a very different story, said Dr. Bellamy.

While little data permitting of sound interpretation exists concerning the genetic effects of radiation upon man, it is well known that the mutation rates in laboratory plants and animals are easily altered by exposing chromosomes (microscopic cell units which carry hereditary material) or germ cells suitable doses of radiation, usually X-rays. Increases of several thousand per cent are usual.

Speculating on a rough approximation of effects on the genetic structure of a human population exposed to gamma radiation (high energy, heavily penetrating rays) such as would accompany the detonation of an atomic bomb at a height comparable with those used in Japan, Dr. Bellamy emphasized that the approximation would be "very rough indeed, since no available information permits anything like an accurate estimate."

Mutation rates are not known for man, he said, and are not likely to be known for some time to come. Haldane, a British scientist, has however, estimated the mutation frequency of human genes as one in 100,000.

Continuing his imaginary set of circumstances, Dr. Bellamy assumed a typical American city as having a population density of 10,000 per square mile, and that it was exposed to radiation from a source some distance in the air.

He assumed further that 40 per cent, or 4,000 persons per square mile were between the ages of 15 and 39; and that the proportion of males and females was 50-50. He neglected non-productive matings and assumed an average of three offspring per pair, or 6,000 offspring per square mile.

Dr. Bellamy based one estimate on the known mutation rates for Drosophila, the banana fly, whose total yield of lethal changes is about three percent per 1000 Roentgen units of total body radiation.

He corrected this dosage for man--humans cannot take 1000 Roentgen units of radiaiton and live--and correlatedqthe result with calculations based on Haldane's estimate for one in 100,000 for the natural mutation rate in man.

The 2000 mothers (half of the 4,000 persons per square mile) would have among them 12 male-determining chromosomes carryihg a sex linked lethal, said Dr. Bellamy. Half of the sons from these 12 mothers would receive this mutated chromosome and would die. There would be about five males less per thousand population.

Increases in visible recessives, based on Haldane's estimate of one in 100,000 would be increased about 30 times after radiation. This gives a mutation rate of about three in 10,000 after radiation, Dr. Bellamy said.

take some hundreds or thousands of generations for a mutant gene to become established in a population, eventually some of these genes will show up.

If enough of them are disabling in their action, said Dr. Bellamy, their social and economic significance can become very large indeed. But this will not be in our lifetime nor that of our grandsons

####

a.n.

PHARMACOLOGICAL APPLICATIONS OF RADIO ISOTOPES

Thomas J. Haley, Ph.D.
Chief of the Pharmacology-Toxicology Division
Atomic Energy Project
University of California at Los Angeles

This discussion will concern itself primarily with pharmacology and toxicology seeking to point out practical applications or radio-isotopes to problems in these fields. Not all the isotopes are useful in such studies because of not only the length of time involved in the study itself but also the short half-life of the required element and the difficulties encountered in organic synthesis.

From a pharmacological and toxicological viewpoint much is known concerning amphetamine (B-phenylisophopyl amine) and its N-methyl derivative. Both compounds have been shown to be potent stimulants of the motor cortex causing increased activity in both man and animals. In man this activity may have a duration of from six to eight hours depending upon the individual. However, the excretion of either compound is not completed even 48 hours after the final dose. This is of particular interest in as much as it has been shown that derivatives of B-phenylisopropyl amine are inhibitors of amine oxidase, one of the body detoxication mechanisms. Further, phenol oxidase has no effect upon the metabolism of these drugs because there is no phenolic hydroxyl group in the molecule. The only enzyme system thus far shown to attack these drugs is the ascorbic-dehydroascorbic acid system. Asorbic acid itself has also been found to attack amphetamine causing deamination. In the course of further studies on amphetamine excretion it was found that the drug is quantitatively excreted by dogs poisoned with either carbon-tetrachloride or hydrazine. This might indicate that the liver is the organ for detoxication of this type of amine. Upon the basis of these considerations it is possible to design an experiment which should lead to an elucidation of both the detoxication mechanism involved and the rate at which excretion takes place. Utilizing either or both Tritium (H^3) and C^{14}, as in the biosynthesis of epinephrine from radio phenylalanine, the amphetamine and desoxyephedrine molecules can be tagged on the aliphatic side chain and the unine of the animal collected. Extraction of the urine according to the usual methods would give both free and combined amine. Conversion of these extracts to either $B_2C^{14}O_3$ (barium carbonate with C^{14}) or T OH (Tritium hydroxide) would enable the investigator to obtain more accurate data on the fate and excretion of these B-phenylisopropyl amine derivatives. Isolation of the degradation products would entail much greater effort, but both tagging isotopes are sufficiently long-lived to enable such an investigation to be carried to a successful conclusion (H^3 12 yr. B^- 0.015 and c^{14} 5100 yr. B^- 0.15). At the time of the development of maximum motor activity mice which had been injected with either drug could be sacrificed and the brains and/or other organs removed. These organs could be prepared and sectioned and the sections used to make autoradiographs. This would aid in localizing the exact area in the tissue in which the drug was contained and in the case of the brain slices aid in determining the exact site of action of these drugs.

Another element which has been studied is arsenic. Studies concerned with the fate of inorganic arsenic in the body have been carried out by many investigators. Both normal and pathological animals have been used. Recently cacodylic acid containing radio arsenic has become available. This organic arsenical in general behaves like the inorganic arsenic compounds, but its excretion rate is much slower. It would be of great clinical value to study the excretion rate and sites of storage in the body of sodium and iron cacodylates because of the large amounts of these compounds used in this country. If they behave as inorganic arsenic compounds it would be expected that they would concentrate in globin and acid-acetone soluble heme fractions of the blood proteins. Further, it would be expected that skeletal muscle would contain the greatest amount and that excretion would take place via the kidneys. It should be pointed out that the particular animal used in this type of experiment determines where the greatest concentration of arsenic will be found. Rats have a high blood level concentrated in the erythocytes while in general all other animals show low blood levels, but high levels in the epididymis and liver. Another factor which must be considered is the mode of administration because the oral route results in the excretion of cacodyl oxide, a garlic odored gas, in expired air, thus inducing an additional health hazard not seen with hypodermic administration. Radio arsenic (As^{74} 16 d B^- 1.3 B^+ 0.9 0.58) could also be applied to the study of the metabolic fate of the organic arsenicals used in treatment of protozoan infections provided that the experiment was of short duration. One compound which would be easily studied is Carbarsone (p-carbamidophenylarsonic acid) because it has proved especially effective in the cure of intestinal trichohonas infections in rats. Such a study might shed light on the mechanism of action of this potent amoebicide.

A toxicological study of the formation of ethereal sulfate would be of great practical importance because this body detoxication mechanism is the one employed in the detoxication of phenols. The problem entails much work because injected sulfate (Na_2SO_4) is readily cleared by the kidney and ingested sulfate cannot pass the intestinal membranes to any extent. In fact the latter property is one of the reasons for the use of sulfates as cathartics. Radio sulfur (S^{35}) could be administered as methionine or one of the other sulfur-containing amino acids. A phenol could then be given and the excretion of total and ethereal sulfate in the body could be definitely proven.

QW.

METABOLISM OF IODINE 131

Richard J. Winzler, Ph.D.
Associate Professor of Biochemistry
School of Medicine
University of Southern California

Dr. Winzler, Associate Professor of Biochemistry at USC, will discuss recent work on the iodine metabolism and the thyroid gland using radioactive iodine. The name of the course is "Application of Nuclear Physics" to the biochemist and medical sciences at the University of California. He will discuss notable advances in the knowledge of thyroid physiology and iodine metabolism which have been made in recent years, using this radioactive isotope which is produced at the Atomic Energy Commission Laboratory at Oak Ridge, Tennessee.

Radioactive iodine has been found to concentrate very rapidly in the thyroid gland of patients suffering from an overactive thyroid gland. The rapid uptake of small or "tracer" amounts of radioactive iodine can readily by used as a means of diagnosis of hyperthyroidism by placing a geiger counter tube over the patient's neck. Hyperthyroid patients may then be given larger therapeutic amounts of radioactive iodine, the destructive radiation then selectively destroying the overactive thyroid tissues in which it accumulates. Radioactive iodine is also widely used by experimentalists to study fundamental problems in biology and medicine involving the destitution and metabolism of iodine in the animal body.

Dr. Winsler will discuss his own work in collaboration with Dr. Paul Starr and its relation to the work of other researchers. He has been especially interested in making organic compounds containing radioactive iodine and is using these compounds in the study of their fate in the animal body. His studies have also been concerned with the influence of physiological state upon the accumulations of radioactive iodine in the thyroid gland and its incorporation into the thyroid hormone.

###

a.W.

AUG 1 9 1948

1

Review of the Use of Tracers in the Study of Amino Acids

Dr. David Howton, AEC ATOMIC ENERGY PROJECT,

U.C.L.A.

In the old search for understanding of the mysteries of living organisms, the study of amino acids and the proteins which are synthesized from them is of primary importance for this reason: whereas the carbohydrates and fats serve chiefly as sources of energy (released in their oxidation by the organism), the proteins are intimately involved in the intricate processes responsible for the integrity of the organism as a unit. In support of this view it should be sufficient to point out that the enzymes essential for the complex syntheses and degradations which compromise life are all largely protein in nature; and this is to say nothing of their important role in immunological specificity, the blood-clotting mechanism, and the structural units of the organism.

The importance of proteins has been recognized by biologists for a long time, but the extreme complexity of their fine structure (which is germain to their many complex functions) has made the study of them very difficult. Hence it was with no small degree of excitement that students of the metabolosm of amino acids and proteins greeted the rather sudden availability of appreciable quantities of isotopic forms of all the elemental substances important to living systems. As will become apparent in the course of the talk, isotopes are extremely powerful tools in the study of metabolic processes. Not only can isotopes help solve problems which are very difficult without them, but it is apparent that many problems may now be solved which were previously impossible of solution, without elemental substances of unnatural isotopic composition and means for determining this difference.

That biologists (using the term in its broadest aspects) were awaiting just such a tool is attested by the exceedingly rapid growth of the number of applications of nuclear physics to the biological and medical sciences. Despite its really great youth, the field has grown to a size difficult to encompass in three weeks of courses; and in one hour I cannot hope to cover completely the many instances already in the published literature on the metabolism of the amino acids.

I can only hope to acquaint you with some of the things which have been done and are being done and the techniques used in doing them.

Some of the things I shall say about the techniques of tracer studies in amino acid metabolism have very probably been covered, at least to some extent, in previous lectures in this course, but considering the host of material which you are given to absorb, some repetition can certainly not be amiss.

So the following remarks apply to isotope metabolism studies in general:

The basic assumption in such studies is that the organism cannot distinguish appreciably between isotopes; this is essentially true for all but the isotopes of hydrogen, whose atomic weights are 100 or 200 per cent different from the common isotope; the quite appreciable physiological effects of "heavy water" have been much publicized; these effects are very probably due to the inhibition of certain enzyme systems, recently shown in some cases. That living systems do not distinguish appreciably between isotopes differing in atomic weight by only a few per cent is indicated by the fact that isotope concentration is not markedly different in the atmosphere, certain of whose constituents have been processed and reprocessed by plant and animals for a long time, from those same constituents from other sources presumably not subject to such processes.

With radioactive isotopes, particularly those emitting particles of high energy, one may expect some anamolous results; these can be minimized by using low concentration, and it is fortunate that such concentrations can be detected and determined with considerable accuracy.

Tagged materials ingested by the organism will naturally be subject to considerable dilution and the isolation of the metabolites of these materials may not be quantitative by any means; in setting up the experiment, careful consideration must be given to the dilution factor, isolation efficiency, half-life and emmission energy of tag (if radioactive), and isotopic potency of the ingested material whose fate in the organism is to be studied.

Careful consideration must also be given to the lability of the tracer atom in the organic chemical structure it is to help in tracing through the organism. Will the tag stay with the structure whose metabolic fate is of interest, or will it be exchanged with other materials and be lost in the great pool of metabolites? Such exchanges are often interesting in themselves but in other instances may well determine the success or failure of the experiment.

As experiments dealing with simple, readily-available tagged materials (such as carbon dioxide and the minerals) become exhausted or lead to more complex questions, the student of the metabolism of tagged materials must come to rely more and more on the ingenuity of the synthetic organic chemist. He must not only be able to place the tagging atom in a desired and unequivocally-known position in the compound, but he must also arrive at this endproduct with the least possible loss of precious isotope concentrate. He must devise a synthesis with a minimum of operations, with maximum yields at each step, and one which will involve the tagged starting material as close as possible to the end of the synthesis.

In the study of certain metabolic processes one must face the problem of the precursor of interest being destroyed before reaching the site of conversion; others, such as proteins or phosphorylated compounds, may require hydrolysis, (thus possibly destroying an integrity essential to the experiment) by the organism before entering the metabolism cell; such problems can be studied using simpler organisms, where the precursor can be applied directly to the cell, but here uncertainties exist in the legitimacy of such results when translated to more complex organisms. Extreme lability of a precursor is sometimes counteracted by the "flooding" technique, in which unusually large amounts of precursor are fed to the organism; although this technique may give results unobtainable otherwise, it is wasteful of tagged materials and may lead to abnormal results.

Another attack is on the complexity of the organism by employing slices or homogenates of a specific tissue; such studies may give very valuable information, but it is difficult to justify a quantitative translation of the results to the situation in the intact animal; here too, a negative result is in doubt because of the abnormal conditions of the experiment.

In some metabolic processes, certain compounds may be essential intermediates and yet never exist at any one time in any but very minute quantities, excessive amounts of such intermediates being metabolized by other paths. Problems posed by a situation of this kind can be met by using known precursors of greater stability with respect to transformations of no interest in the particular experiment.

These foregoing points will be illustrated by examples from the literature (work of Schoenheimer, Rittenberg, Du Vignead, Borsook, and others).

The remainder of the hour will be devoted to a presentation and discussion of other published work and of work being done by groups at the California Institute of Technology, illustrating the extreme utility of isotopes in the study of the metabolism of amino acids.

David R. Howton.

AUG 20 [illegible]

THE RADIOISOTOPE PROGRAM OF THE UNITED STATES VETERANS ADMINISTRATION

George M. Lyon, M.D.
Special Assistant for Atomic Medicine and Chief Radioisotope Section,
U.S. Veterans Administration, Washington, D.C.
(Abstract of lecture presented during University Extension course on "The Application of Nuclear Physics to the Biological and Medical Sciences" at U.C.L.A., Friday, Aug. 20)

Just one year ago the U.S. Veterans Administration initiated a radioisotope program within certain of its hospitals.

The purpose of this program was to bring to the veteran patient the benefits of the peace time application of atomic medicine.

To this end a Central Advisory Committee on Radioisotopes was appointed to make recommendations as to policies with respect to such a program. Last September the Central Advisory Committee recommended that a radioisotope program be initiated in a limited number of hospitals of the Veterans Administration. They recommended further that it be a program characterized by conservatism, sound medical practice and devotion to the best interest of the individual patient.

In order to carry out this program a Radioisotope Section was established within the Research and Education Service of the Department of Medicine and Surgery of the Veterans Administration. The duty of this Section has been to assist in the organization and the supervision of the radioisotope units within such hospitals as are authorized by the Chief Medical Director to engage in work with radioisotopes.

Radioisotope Units have been established at eight of the hospitals of the Veterans Administration. These are Framingham, Mass.; Bronx, New York; Cleveland, Ohio; Chicago, Illinois; Minneapolis, Minnesota; Van Nuys, California; Los Angeles, California and Dallas, Texas. It is expected that three more units will be established during the current fiscal year.

Units have been established only in hospitals having close cooperation with associated medical schools in which there have already been going and active programs in the radioisotope field.

It would not have been possible to initiate such a program had it not been for the good working relationship which exists between the associated medical schools and the staffs of the hospitals of the Veterans Administration. In each instance, before the Chief Medical Director has authorized the establishment of a Radioisotope Unit in a hospital of the Veterans Administration, the Deans' Committee of that hospital has appointed a Radioisotope Committee to represent the Deans Committee in drawing up plans and making specific recommendations relative to the setting up of such a unit. Once the unit is established the Radioisotope Committee bears the same supervisory relationship to the unit that the Deans' Committee bears to the hospital in matters relating to the medical care and treatment of veteran patients. The active interest and cooperation of the Deans' Committees and their skilled representatives has made it possible to develop within the hospitals where such units are established radioisotope programs which are in quality and in effectiveness, the equal of those programs conducted within the best teaching medical centers of this country. Representatives of the universities who are engaged in similar work in those universities, serve as consultants or as part time personnel in the Radioisotope Units of the Veterans Administration.

Work within the Radioisotope Units is divided into three general phases - treatment of patients with radioisotopes, the employment of radioisotopes in diagnostic procedures and the employment of radioisotopes in medical research.

As yet the radioisotopes have a limited application in the treatment of patients. Here conservatism and sound medical judgment are meticulously observed in all of the hospitals. This must be the case until the exact position of these new tools can be more exactly known.

The radioisotopes offer almost unlimited opportunity for the development of new diagnostic procedures and the improvement of older diagnostic procedures. Each month finds new and important applications in this field. From these the individual patient will gain much benefit and many medical problems will be more quickly and accurately solved.

It is in the field of medical research where the benefits which may be achieved either directly or indirectly, that hopes can confidently be held high. While the benefits to be so gained may, on the surface, not be so obvious, they are none the less real. Already our knowledge of the metabolism of the thyroid gland and its abnormalities has been greatly increased, and diagnostic procedures have been improved. Already important studies on the volume of the blood, on the behavior of red blood cells and on the patency of peripheral blood vessels are making possible more accurate medical diagnosis. Who can foretell the benefits to be obtained from radioisotope studies in phosphorus, potassium and calcium metabolism? Or what may be learned with relation to the behavior of zinc insulin within the body? Or what may be learned about bacteria and viruses in the body or in regard to the immuno-chemistry of the human body? Or the behavior of hormones, drugs et cetera tagged with radioisotopes? Or to what extent the complicated problems of metabolism may be solved? It is not an overstatement to say that progress can be expected to be rapid and on a wide front as greater use is made in medical and biological research when this new tool is applied in attempts to solve such problems. Each of the units I have described is set up to engage in some phase of this important work. In each there is a capable sciantific and technical staff, well equipped with the required training and background and provided with the modern equipment and facilities needed to do this work, to do it wisely and with safety to all concerned.

Although this program within the Veterans Administration has been in effect only one year, it has already been instrumental in drawing to the medical staffs of the Veterans Administration en hospitals some of the very best medical men in this country. It has already played a significant role in assuring to the veteran patient many of the medical advantages of an atomic era.

###