AECD-2976

TRAINING PROGRAM LECTURE NOTES

THE BIOLOGIC EFFECTS OF RADIATION

32609

S. T. Cantril

May 17, 1943

I. The Influence of the Nature of the Radiation on Biologic Effects.

1. Specific ionization.

The efficacy of radiation in producing biologic effects varies with the density of ionization produced by the incident radiation. The density of the ionization so produced along the tracks of the ionizing particle is termed the "specific ionization," and a separate report by Zirkle will appear dealing with this phase. In general, heavily ionizing particles (alpha particles and protons released by fast neutrons) produce greater injurious effects in mammals than more weakly ionizing ones (hard gamma rays). There are exceptions to this generalization in lower organisms depending upon the biologic criterion chosen for study.

The application of the specific ionization factor is best exemplified in the greater effectiveness of fast neutrons (as compared to 200 kv x-rays) per unit of exposure in producing, i.e. either lethal effects or blood damage in the rabbit. Here the ratio of neutron to x-ray effectiveness is approximately 6 - 7 (from work in progress by Zirkle and Jacobson). Studies of other effects in various organisms have been made, and the ratio is not always constant. For reasons of safety therefore we have diminished the allowable or tolerable exposure to fast neutrons by a factor of 10 as compared with that of gamma radiation.

2. The Effective Penetrability of the Radiation.

Whether or not external radiation will produce biologic effects, and also the nature of these effects, is dependent upon the ability of the radiation to reach the tissue in question. Although alpha particles are highly ionizing and destructive, their range of action (as from U or Ra) is small (approx. .1mm) when the radiation is external. On the other hand when the material which is alpha-radioactive is deposited within the body in a vulnerable organ (i.e. bone marrow) the limited range of the particle is no longer so great a factor, since the external shielding of the body (skin) is not a barrier. Similarly the low energy beta rays cannot penetrate the skin to an effective depth, but the same beta emitter deposited in the bone or thyroid gland may be most injurious. These are examples of internal radiation, and this will be discussed fully by Dr. Cole in a later section. The effectiveness of hard (high energy) gamma rays per unit density of ionization may not be as damaging as soft (low energy) x-rays, but the penetrability of the rays of higher energy, reaching more vulnerable regions in the body, may be a more deciding factor as a hazard than their lesser degree of specific ionization.

For different qualities of radiation with varying geometries, Parker has calculated that for equal surface dose there results from:

1K 282

	Relative total body ionization
Soft x-rays from large distance - - - - -	approx. 1.0
Gamma rays " " " - - - - - -	2.5
Gamma rays from point source at 100 cm. -	1.9
Gamma rays " " " " 10 cm - -	0.6

The above are examples of certain physical factors (wave length and geometry) which may alter the degree of ionization in the exposed individual, and thus vary the biological effectiveness of the radiation.

3. The Time Factor.

There are two components to the time factor in radiation exposure which need consideration. These are (1) the dosage-rate and (2) the total duration of exposure.

By the dosage-rate is meant the number of roentgens per unit of time. There is no experimental or clinical evidence at hand to indicate that the dosage-rate has any outstanding effect upon the biologic result achieved when all other factors remain constant.

The total duration of exposure to the radiation is an additional time factor apart from the dosage-rate. Its influence upon biologic effect is marked, and it must be reckoned with when radiation is used in the treatment of disease, or when one attempts to establish limits of tolerance for exposure to radiation under working conditions.

The "total duration" factor can best be illustrated when we speak of the "tolerance dose" -- by which we mean the amount of radiation to which a normal person can be exposed day in and day out without sustaining permanent damage. For gamma radiation the tolerance dose is given as 0.1 r in any one 24 hour period. The dosage-rate which may build up to the 0.1 r in the 24 hours is immaterial -- in other words, the 0.1 r can be received in a second, a minute, an hour, or over the 24 hours, but the total is not to exceed 0.1 r. The total duration of exposure here is the 24 hour period. To carry the illustration further -- suppose that an individual receives 0.1 r daily for 1000 days. He is exposed then to a total of 100 r in that period -- the duration of his exposure is 1000days. It makes a great difference to his welfare whether he receives the 100 r in a total duration of 1000 days or whether the duration for the same total exposure is 100 days. Thus for a constant total dosage (the dosage-rate being immaterial) the number of days required to reach the total dose (duration) is an important factor. The reasons for the influence of this factor are inherent in the reactive properties of most tissues, and this will be discussed in Part II which deals with the biologic factors which influence radiation effects.

2k 282

4. The Total Dose

The magnitude of the total dose has a bearing upon the biologic effectiveness. This factor is also closely linked with the reactive properties of the tissue in question, but it remains as the outstanding physical factor influencing biologic effects. The type of radiation, its penetrability, the geometry and duration of the exposure are the physical factors which determine the total ionization produced within the body or tissue in question. From the physical side the biologic effectiveness of the radiation is a function of the total ionization so produced.

II. The Influence of the Biologic Aspects on Radiation Effects.

1. Radiosensitivity

By radiosensitivity is meant the relative vulnerability to radiation of a tissue living in its normal physiologic milieu. It is a term derived from the therapeutic use of radiation in the the treatment of disease. We do not as yet understand why some tissues are more readily effected by radiation than others. Although we tend to think of each tissue as having an inherent radiosensitivity peculiar to that tissue, advances in the application of radiation to medical uses have come about largely by learning to adapt the technics of exposure to take advantage of the varying sensitivities of different tissues. Thus we have learned that a tissue which by one technic proves radioresistant, is by another technic less so. Although the term is therefore relative, we can properly think of different tissues as having varying degrees of vulnerability to a constant source of radiation.

Not only may we think of different tissues as having varying radiosensitivities, but different organisms react differently to the same ionizing dose of radiation. There are thus species differences for the production of the same effect. There may also be variations within strains of the same species. This is one of the obstacles in transposing to man the biologic effects of radiation found in the lower animals.

The problem is further complicated by various biologic events which can alter the radiosensitivity of a given tissue. Not all of these are known, and why, for those that are known, these alterations do result, is also a little understood problem. A few examples will serve to bring out certain of these factors.

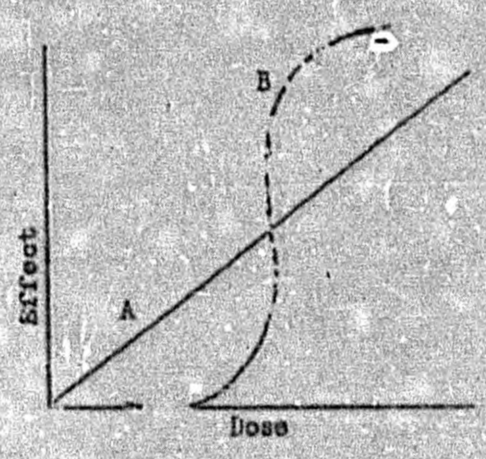
Contrary to the more accepted principles of pharmacologic action, the tissues which are less specialized in function tend to be the more vulnerable to radiation. The degree of specialization of a tissue is referred to as its differentiation -- and in general (though not axiomatic) the less differentiated cells are the more radiosensitive. The highly complex cells of the nervous system are apparently little affected by ionizing rays. At the other extreme the primitive cells of the reproductive or lymphatic system are extremely vulnerable.

3K 382

In general, the rate of growth of the cells within a tissue influences their vulnerability. More rapidly growing and active cells tend to be the more radiosensitive ones comprising a given tissue. In a developing rather than in a more quiescent phase cells in general are effected to a greater degree.

The composition of the medium, or the milieu of the cells comprising a tissue has an important bearing upon the radiosensitivity. This is in some way intimately associated with the complex physico-chemical alterations which must ensue within the cell when it is subjected to unnatural ionization. Whether the effect of the ionization is a direct one, taking place within the cell, or whether the effect is an indirect one resulting from alterations in the environment of the cell is still largely a matter of conjecture. As an example of the effect of the composition of the environment of the cell upon its radiosensitivity one may cite the diminished effect of radiation upon otherwise extremely radiosensitive tissues when they are subjected to a reduced oxygen supply during the time of exposure. Likewise there is experimental evidence to show that a change in the acid-base relationship, effecting the permeability of cell membranes, can for certain tissues increase their radiosensitivity. Physical factors such as heat, cold or previous radiation may alter either the growth rate or milieu of the cells, and thus produce a change in their vulnerability to ionization produced in them or in the medium in which they live.

It is pertinent to consider here what is meant by threshold as opposed to non-threshold biologic effects. If one were to plot a dose-effect graph for various tissues subjected to radiation, there would be general be two forms on the graph:



4K282

(A) Illustrates the character of the non-threshold effect. As the dose is increased there is a linear increase in the effect. There is not an initial threshold of dose which must be exceeded before an effect is obtained. To recognize a non-threshold effect, it must be one which is readily observed or measurable after exposure to minimal amounts of radiation. An example of a non-threshold effect is the influence of radiation upon the germ plasm of lower organisms.

(B) Illustrates the character of a threshold effect. As the dose is initially received the effect is not measurable until a certain threshold of dose is exceeded, when the effect then begins. Threshold effects are not linear but assume some form of S curve. The effects of radiation upon the skin and the blood forming organs are examples of threshold effects. Until the dose reaches or surpasses the threshold, the first signs of skin effect (erythema) or of effect upon the blood forming organs (as reflected in the circulating blood) are not seen.

The majority of radiation effects are thought to be of the threshold type. It may be that as more delicate indicators are found to measure effect, more of them will be seen to be of the non-threshold type.

The <u>reversibility</u> of radiation effects is of importance, particularly when one is concerned with occupational exposure. By reversibility is meant the return of a tissue to its previously normal state after radiation exposure is discontinued. The reversibility of any specific effect is dependent upon the reparative or regenerative properties of the tissue. Some tissues, such as skin, the blood forming elements, membranous linings of body cavities or glands, and peripheral nerves are endowed with a mechanism for repair and regeneration. Other tissues, such as muscle, brain, certain structures in the kidney or eye have no provision for regeneration. Repair in them is by the formation of a scar, which does not take over the function of the original tissue which it replaces. These effects are then said to be <u>irreversible</u>.

In order for an effect to be reversible it must not, however, exceed the limits of the normal capacity for regeneration. If this is exceeded, the effect is permanent and may lead to the complete destruction or exhaustion of the tissue. When the body economy cannot function in the absence of this tissue (i.e. blood) then death results.

Both the total dose of radiation and the total time over which it is given are factors on which the ability of the regenerative processes to function may depend. If the total dose is excessive, irrespective of the time over which it is administered, regeneration and repair may be impossible. Or if the total dose is one which will produce effects which are reversible if given over a time which does not exceed the rate of regeneration, the effect may become irreversible if the time is so shortened that insult exceeds repair.

5 K282

A tissue which has returned to apparent normal function following radiation damage may not, however, sustain repeated damage and will be unable to regenerate completely. Repeated radiation effect, initially followed by repair, will eventually exhaust the reserve for regeneration, and end in death of the tissue. It is for this reason that previously sustained radiation injury which has apparently undergone regeneration and return to normal function must be carefully observed and a repetition of the injury avoided. Skin which has been once damaged by radiation and then regenerates to carry on its function will not tolerate repeated injury with impunity. Bone marrow, which has remarkable powers of recovery from radiation injury, will eventually exhaust its recuperative reserve when subjected to doses of radiation which call too often or too strenuously upon it.

<u>Summary</u>

Before considering some biologic effects of radiation in more detail, let us summarize certain general principles which govern the effects.

The nature of the radiation influences the effects produced.

(1) Different types of radiation produce varying degrees of ion density along their tracks as the rays or particles pass through tissue.

(2) The ionization in a particular tissue is dependent upon the penetrability of the radiation to reach a certain location or depth within the body. This is both a function of the energy of the radiations and the geometry of the exposure.

(3) The total duration over which a dose is given bears upon the effect produced.

(4) The total dose received in a tissue has an important influence upon the effect -- the total ionization produced by the combination of the above factors determines the limits of the physical agent which can act upon the biologic medium.

The biologic aspects in themselves also influence the effect of the radiation.

(1) The radiosensitivity of a tissue or organism largely determines whether an effect will be produced.

(2) The radiosensitivity may in turn be altered by such factors as rate of growth, stage of activity or function and physical or chemical environment.

(3) Biologic effects may or may not be threshold effects.

(4) Certain biologic effects are reversible following radiation, and this is dependent upon the regenerative capacity of the tissue. The reparative processes may, however, be exhausted by either an excessive total dose or one which is given over a period of time which does not permit repair or regeneration to be accomplished.

(5) The repetition of radiation injury, following regeneration, will eventually lead to death of the tissue.

III. The Tolerance Dose in Relation to Occupational Radiation Hazard.

Dr. Wollan has previously discussed the potential exposure to the varying types of radiation, and has described methods for measuring the ionization produced by them in the body. A subsequent discussion will more specifically deal with the location and nature of the radiation hazards. With the foregoing brief review of certain factors which influence the biologic action of rays, it is of interest to consider now how certain of these factors must be taken into account when an attempt is made to establish tolerance dose levels.*

It was previously noted that the specific ionization factor must be considered, and that in dealing with fast neutrons, any level of tolerance set for gamma radiation should be reduced by a factor of 10 for slow neutrons.

The penetrability of the rays or the geometry of exposure may at times be more important in determining the degree of tissue ionization than the factor of specific ionization.

For X-rays, gamma rays and neutrons we are therefore concerned with effects upon the deeper structures of the body. For beta rays we are mainly concerned with injury to the skin, and here, as with gamma rays, penetrability is a function of energy. Beta rays of energy approximately 100 kev (corresponding to those of Xe) enter the skin to a depth of only about .1 mm. The long life fission products have beta rays with energies of approximately 1.5 Mev, which can penetrate well below the skin.

The factors of total dose and duration of exposure are most important in relation to tolerance levels. A single exposure to approximately 600 r of gamma radiation would produce so profound an injury to the blood forming organs that death would result in several weeks or months. On the basis of the tolerance exposure of 0.1 r per day it would require about 16 years daily exposure to have received 600 r.

---

* Our discussion here will apply only to external radiation. Dr. Cole will discuss tolerance in relation to internal radiation in a later section.

7K 282

The time element thus becomes important in relation to tolerance, and here again it is closely linked with the biologic factor of regeneration and repair.

A more detailed discussion of how the figure of 0.1 r per day was established is given in a separate report on tolerance dose. There was originally a combination of opinion and rather scant observation, loaded with a safety factor to give a tolerance dose. It seems that with added experience, however, the American level of 0.1 r per day, or the International level of 0.2 r per day for ex-rays and gamma rays, are not too heavily loaded with a safety factor to make them overcautious. The 0.1 r per day level is certainly not low by a factor of 10; 1 r per day would certainly lead to injury. A safety factor of 10 is therefore not too large when vital body processes are concerned.

The biologic effects upon which tolerance has usually been based in the past are those on the blood and reproduction organs. To this we would add skin as an index pertinent to our present work.

It is fortunate for our purposes that the circulating blood is a relatively early and available index of over-exposure to radiation. Certain aspects of this problem are not however commonly appreciated.

(1) The radiation affects the tissues which form blood. These are located in the bone marrow and lymphatic system scattered over the body. The alteration in the blood count thus reflects the injury to the blood forming tissues, not directly to the blood.

(2) The effect is rapid; an alteration in blood count may be observed within an hour after total body over-exposure. The rapidity and magnitude of the observable effect and the recuperation time depend upon the dose and regenerative powers of the blood forming tissues.

(3) Anemia is a late, not an early sign of over-exposure. When the production of red blood cells has been affected, the condition of the bone marrow is precarious.

(4) The white blood cells are the earliest index of over-exposure. The attached table indicates the nature of the alterations which may appear.

(5) We still are asked about the so-called "beneficial effects" of radiation on the blood when the dose is extremely small. Let us emphasize again that all unnecessary exposure should be avoided. The 0.1 r per day sets only the maximum allowable exposure; good sense will reduce this wherein possible.

(6) We have adopted a policy of not permitting a worker whose normal white blood count is less than 5000 to remain in a location wherein he will have possible radiation exposure. Men who show unusual sensitivity may have to be given work not involving radiation.

8K287

The Normal Circulating Blood Elements in the Adult (WINTROBE)

Type of Cell	Average Normal	Minimum	Maximum	Effect of Radiation on the Blood Producing Centers to Produce Changes in Circulating Blood
RED BLOOD CELLS	(million)			
Male	5.4	±0.8		Red blood cells decrease (anemia) is a late sign of overexposure.
Female	4.8	±0.6		Radiation induced anemia is extremely serious and often fatal.
HEMOGLOBIN content of red blood cells	(gm. per 100 cc.)			
Male	16	±2.0		
Female	14	±2.0		
WHITE BLOOD CELLS	(per c.mm) 7000	5000	10,000	White blood cell decrease (leukopenia), or alterations in the normal ratio of the two principal elements (neutrophils and lymphocytes) are the earliest objective signs of overexposure.
Segmented neutrophils	4000 (54-62%)	3000	5800	The effect may be: 1. Diminution of total white blood cells (leukopenia).
Juvenile neut.	300 (3-5%)	150	400	2. Inversion of normal neutrophil-lymphocyte ratio without leukopenia.
Lymphocytes	2100 (25-33%)	1500	3000	
Monocytes	375 (3-7%)	285	500	
Eosinophils	200 (1-3%)	50	250	
Basophils	25 (0-.75%)	15	50	

ZK 282

(7) We have no remedy as yet for permanently reviving a blood count which has been lowered by radiation. It is entirely up to the individual's blood forming organs to do this for him. Avoiding further radiation and observing the rules of healthful living will aid but not guarantee a recovery.

The elements of the reproductive organs which are experimentally effected by radiation are either (1) the progenitors of the sperm or ova and (2) the genes which make up the chromosomes and transmit hereditary factors.

Sterilization can be readily produced by radiation, but the dose necessary for this in man is approximately 600 - 800 r to the testes; in women (depending upon the age) a dose of 200 - 400 r to the ovaries will cause permanent sterilization. Gross negligence could produce over a period of years, alterations in the preproductive capacity of the individual. There is no evidence to indicate that exposure to our present tolerance level will do so.

The genetic effect of radiation is seen only in the lower organisms. Most of the information has been gained from work on the fruit fly. The effect most commonly produced is an increase in the normal rate of mutation.* Furthermore it has been found that this is a non-threshold effect and that the dose is cumulative. Thus the only possible way to avoid this effect (if it could be shown applicable to man) would be to stay completely away from all radiation. There is no evidence to indicate however that radiation mutations are produced in man.

The skin effect of radiation is important and very pertinent to our problem. One can neglect the skin effect of the alpha rays. The abundance of energetic beta rays in the various fission products, and the necessity to deal chemically with them, brings up a serious problem in exposure of the skin of hands. Uranium metal is likewise a rather potent source of energetic beta rays, an hour's handling contributing an exposure of .09 r/hr. of beta radiation penetrating through the skin.

Skin which is exposed in a relatively brief period to 500 - 800 r will develop an erythema, similar to that which follows exposure to the sun. We do not anticipate these large exposures as an occupational hazard unless there are no precautions whatsoever. We may not see reddening of the skin as the first sign of damage. Rather we fear the daily exposure of the hands to small amounts of radiation which if continued over a period of years may lead to irreversible changes. These late changes are dryness, cracking, brittleness or ridging of nails, loss of normal skin ridges and finally ulceration which may go on to cancer. The tolerable dose to the hands has never been established with any certainty. Radiologists who are cautious and protect their hands from soft x-rays by wearing lead leather gloves generally agree that they would occasionally expose their hands to 1 r per day when necessary. There are others, less conservative, [illegible]

---

* A mutation is an hereditarily transmissable abrupt alteration in the germ plasm.

10R 382

experience has shown that 1 r per day is a safe exposure for the skin of hands.

It is concluded

Be that as it may, we feel that when protection is possible to attain it should be used. We have held to the 0.1 r per day for the skin dose as well as for total body radiation by gamma rays; the neutron tolerance level is placed at .01 r per day. These tolerance levels may need later revision, but for the present they are felt to be adequate yet not overemphasizing safety at the expense of getting the job done.

has been held as a standard

END CB 1-24-51

11K 282

END