Biologic Significance of the Tolerance Dose in X-Ray and Radium Protection

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One-tenth to two-tenths roentgen per day has become generally accepted as the daily intensity of X-rays or gamma rays a human being can safely withstand. The acceptance of this value has a most interesting, though somewhat peculiar background, and the standard has been made to apply to only part of the injuries produced in humans. The purpose of this report, therefore, is to review carefully the history of the present safety standard, to list the important types of injury now recognized, and in particular to show how the present concepts of protection cannot be applied to a certain class of injuries.

The paper by Cowie and Scheele (5) indicates clearly that questions on protection are continually arising among practicing radiologists and radiation workers for which accepted answers are not available. The lack of answers is owing in part, it seems, to insufficient basic information and in part to failure to consider information now at hand.

HISTORY OF THE TOLERANCE DOSE

Serious irradiation injury has been suffered in humans since the very advent of X-rays. As early as July 1896, only a few months after the discovery of X-rays by Roentgen (November 1895), a severe case of X-ray dermatitis was described by Marcuse (6). Injuries of a lesser nature (soreness of the eyelids and depilatory effects) were reported even before this.

\(^1\) Recommendations of the International X-ray and Radium Protection Commission, 1934 (1), 1937 (2), and the reports of the U. S. Advisory Committee on X-ray and Radium Protection, 1931 (3), 1936 (4).

(7, 8). The great enthusiasm which accompanied the observation of bones and internal organs by fluoroscopic means caused many persons to subject their bodies to prolonged exposure to the new radiations. Owing presumably to the low penetrating power of the radiations then available, most of the injuries were confined to the skin—especially of the hands. In 1902 the first X-ray-induced carcinoma was reported by Frieben (9). This occurred in a physician some months after the first appearance of an X-ray dermatitis. As a result of injury sustained already by X-ray workers, the number of X-ray tumors increased rapidly during the next few years despite the fact that numerous warning articles were published; and by 1911 Hesse (10) was able to collect 94 cases, 50 of which occurred in radiologists. In 1904 Milchiner and Mosse (11) reported degeneration of white blood cells (of the rabbit) both of the lymphoid and myeloid series, and in 1905 Heineke (12, 13) demonstrated the remarkable sensitivity of lymphoid organs of animals to X-rays.

Injury to the reproductive organs resulting in sterility was noted in rabbits and guinea pigs as early as 1903 by Albers-Schönberg (14) and in 1904 by Bergonie and Tribondeau (15). This, in fact, is the work which led to the generalization on radiosensitivity of cells that is now called the law of Bergonie and Tribondeau. Permanent and temporary sterility in humans has been much discussed since those early experiments, and a considerable literature has accumulated on the
subject—mostly in later years, as one may observe by referring to the monograph by Colwell and Russ (16) (1934). Bone necrosis following severe X-ray dermatitis of the hand was noted in 1899 by Walsh (17). Experiments on animals in 1903 by Perthes (18) demonstrated inhibitory effects on bone growth, and extensive osteogenic sarcoma resulting from gamma radiation in watch-dial painters was described by Martland (19) in 1931. Diseases of the lung including tumors have been an industrial hazard among miners in certain localities (Bohemia and Saxony) for centuries, but it was not until 1926 that radon in the atmosphere was suspected as being one of the causative agents producing the tumors (16, 20, 21).

Postconception irradiation injury to offspring resulting in monsters and deformities must also be mentioned as one of the ill effects caused by radiation, particularly in the case of therapeutic doses (Zappert (22) in 1925; Hickey and Hall (23) in 1927; Murphy (24, 25) in 1929; and Abels (26)). Thus, while other deleterious effects have been noted, such as injury to vascular endothelium, glandular disfunction, radiation nephritis, meningomyelitis, and the like, enough have been mentioned to indicate that a considerable variety of injuries were recognized early in irradiation history.

It is of interest also that as early as 1902 attention was given to the question of how much radiation a radium or X-ray worker might withstand. At that time the suggestion was made by Rollins (27) that "if a photographic plate is not fogged in seven minutes, the radiation is not of harmful intensity." Although it was known within a few months after the discovery of X-rays that this radiation is more effectively stopped by lead than most other materials and as early as 1903 that scattered radiation existed (Taylor (7)), there is no record of further work on protection for a period of 13 years despite the fact that cases of injury continued to accumulate. This was due largely, it seems, to the fact that those who had the privilege of working with X-rays and radium were so much impressed with the new opportunities for research and advancement of human welfare that they refused to give attention to matters of personal injury.

What is believed to be the first organized step toward protection from roentgen rays was taken in 1915 following the reading of a paper on protective devices before the British Roentgen Society (Russ (28)). At that time a resolution was passed providing that the council of this society should meet and take steps toward securing safety for X-ray operators. Because of the war activity which existed then, this plan failed to bring forth important advancements. As a result of the war demands, caution gave way to action, and protection measures were again forgotten. The taking of increased risks at this time probably was a factor which contributed to an unfortunate development in 1919–21, both in this country and in Europe when a number of prominent radiation workers died of apparent irradiation injury, particularly aplastic anemia. Unfavorable publicity developed, and definite action resulted.

While some steps toward protection were taken in France immediately after the war, the first roentgen-ray protection committee was formed by the American Roentgen Ray Society in September 1920. Following the publication of certain terse comments in the London Times in March 1921, concerning the sad plight of X-ray workers, the British X-ray and Radium Protection Committee was formed. The British committee (29) presented its first recommendations in July 1921, and the American committee (30) made some suggestions for protection in September 1922. The two sets of recommendations
were much the same in substance, protection being dealt with chiefly from the standpoint of absorptive screening and remoteness (meaning significant distance). Taylor (7) gives a vivid account of the early history of X-ray and radium protection, in his chapter in *The Science of Radiology*. Later general developments are described by Leddy (8) (1940), Kaye (31) (1940), and Taylor (32) (1941).

From the standpoint of safety, it is interesting that the early committees (1920–21) recognized merely “visible injuries to the superficial tissues, derangements of internal organs and changes in the blood” as the injurious effects to be guarded against (29). While “derangements of internal organs” is indefinite, it is known that damage to the reproductive organs was an effect about which there was considerable concern.

The next important development was an attempt to ascertain some estimate of the limit to which an individual could be exposed to radiation without sustaining noticeable injury—in other words, to find the “tolerance dose.” The procedure followed by a number of investigators was to formulate some kind of quantitative evaluation of the amount of radiation (usually X-rays) reaching persons who had worked with the agent for a number of years and remained in good health. The results obtained are shown in table 1. Up to and including 1928, the tolerance doses were expressed in terms of the erythema dose but this can readily be changed to roentgens by multiplying by 600, the number of roentgens of 200-kv. X-rays required to produce a mild erythema. It should be mentioned also that the results were based on a very small number of individuals in each case, from two to “a very limited number” (33), thus causing the findings to have limited reliability.

**Table 1.** — The tolerance intensities recommended by different authors

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Erythema per month</th>
<th>r/day</th>
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<tbody>
<tr>
<td>Mutscheller (33)</td>
<td>1925</td>
<td>0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>Sievert (34)</td>
<td>1925</td>
<td>0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>Glocker and Kaupp (35)</td>
<td>1925</td>
<td>0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>Solomon (36)</td>
<td>1925</td>
<td>0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>Dutch Board of Health</td>
<td>1927</td>
<td>0.002</td>
<td>0.04</td>
</tr>
<tr>
<td>Barclay and Cox (37)</td>
<td>1928</td>
<td>0.0084</td>
<td>0.168</td>
</tr>
<tr>
<td>Bouwers and Van der Yunk (38)</td>
<td>1930</td>
<td>0.01</td>
<td>.2</td>
</tr>
<tr>
<td>Failla (40)</td>
<td>1932</td>
<td>.01</td>
<td>.02</td>
</tr>
</tbody>
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Kaye (41) in 1928 referred to the works of Mutscheller, Sievert, Solomon, Dutch Board of Health, and Barclay and Cox and adopted 0.12 r/day (1/1000 erythema dose in 5 days) as an intermediate value. In 1928 the question of protection from X-rays and gamma rays came before the Second International Congress of Radiology for consideration and action. In view of the fact that the recommendations in use in England were adopted by the Congress almost in toto, it is clear that Kaye’s tabulation on tolerance dose must have influenced the steps that were taken. It should be noted, nevertheless, that the recommendations (42) adopted by the International X-ray and Radium Protection Commission, which were set up in 1928, contained no reference to tolerance dose, merely stating, as had been done previously in 1921, that the known effects to be guarded against are: “(a) Injuries to the superficial tissues, (b) derangements of the internal organs and changes in the blood.” Likewise, the Commission’s report (43) made in 1931 contains no statement in regard to the tolerance dose, although in the two subsequent reports (1934 (1) and 1937 (2)), this dose is tacitly stated as being 0.2 r/day.

As an outgrowth of the International Commission there was formed in the United States an Advisory Committee on X-ray and Radium Protection (Taylor (44)) to deal with particular problems in this
country and draw up recommendations. This committee published its first proposals (3) in 1931 in which the tolerance dose was set forth as 0.2 r/day, thus being in general agreement with Kaye's estimated figure given in 1928. In a later report in 1936 which is the last (4), the tolerance dose is stated as 0.1 r/day, no explanation being given for the change. In a recent publication (1941) on the subject of radiation protection, Taylor (32), who is chairman of the American committee, referred to the safety value as being 0.02 r/day, a still smaller figure, but one which is in agreement with that recommended by Failla (40) in 1931. Surely the variations cited indicate an uncertainty in regard to the tolerance value and a trend toward reducing it to provide greater safety.

It is noteworthy that by far the greater amount of writing on radiation protection has been done by physicists. This is fortunate because protection for the most part is provided by cutting down the amount of radiation reaching operators, a type of work on which physicists are most able to advise. It seems so obvious today that remoteness (because the inverse-square-law principle applies) is one of the most important factors in protection and that lead is one of the most effective absorbers; yet at one stage these things were not known. According to Kaye (31), some persons very early in the history of X-ray and radium proposed that X-rays could best be stopped by red silk or a thin layer of rubber sheeting. It is clear, however, as physicists themselves have pointed out the protection problem is by no means entirely a physical one. Kaye (1935 (49) and 1940 (31) said:

There are, of course, a number of uncertain variables which do not lie within the province of physics, but are wholly biological, such as (1) the effect of local as against general exposure to radiation, (2) the amount of previous exposure, (3) the duration and frequency of individual exposures, (4) the intervening degree of recovery (this latter being first suggested in 1940), (5) general idiosyncrasy, and (6) selective sensitivity of particular parts of the body.

The unsettled character of the subject is further stressed by Taylor (32) in 1941, when he says:

Obviously, the determination of this tolerance dose is difficult and at best uncertain. The biological factor differs too greatly among individuals to permit the use of a sharply defined tolerance. To be well beyond the danger limit one must apply a generous factor of safety to the result of any physical measurements.

Statements of this type, made by such eminent persons in the field, emphasize strongly the need for attention to be given to the biological side of protection. Whereas answers to the questions raised by Kaye and those raised currently by radiologists are not known for all of the types of injury now recognized, there is, nevertheless, a considerable body of biological information that can be brought to bear upon the general problem of protection, some of which will be discussed.

**TYPES OF INJURY**

As stated above, the early protection workers recognized only the following as irradiation changes to be guarded against: (1) Injuries to the superficial tissues; and (2) derangements of the internal organs and changes in the blood. This same wording has been used in all four of the prepared recommendations presented by the International X-Ray and Radium Protection Commission with the exception of the last (1937) where (2) was

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2 Mutscheller (33), Glocker (33), Sievert (34), Solomon (36), Bouwers (39), Barclay (38), Kaye (41), Failla (40), Taylor (7), Braestrup (45), Eoans (46), Stenstrom (47), Quimby (48), Read and Mottram (21). So far as we know there are but few exceptions (Read and Mottram (21), Liddy (8)).
modified to read as follows: "Changes in the blood and derangements of the internal organs, particularly the generative organs." It seems strange that protection, as defined, has been made to pertain only to certain of the recognized injuries without certain explanations or inferences being made. Taylor (32) 1941 says:

By the "tolerance dose" is meant the amount of X-ray energy that a person can receive continuously or at repeated intervals without suffering any damage to the blood or reproductive organs.

In this case the type of exposure has been more specifically described, but, so far as the type of injury is concerned, the description is incomplete. It seems natural that physicists have avoided making commitments on biologic matters, but it seems strange that radiologists have not shown greater concern for the types of injury to be guarded against.

From the foregoing citations and from later experiences, the following may be listed as among the more important known types of injury:

1. X-ray dermatitis
2. Tumor induction
3. Sterility
4. Leukopenia
5. Leukemia
6. Anemia
7. Bone necrosis
8. Glandular disfunction
9. Fetal injury

More recently still another type of injury has been discussed—the genetic. Muller (50) in 1927 found that mutations can be produced with X-rays in the offspring of the fruit fly, Drosophila melanogaster. His experiment was a simple one. Adult males were exposed to radiation and then allowed to inseminate normal virgin females. Offspring obtained from this mating were examined for abnormalities which were present in a considerable portion of individuals, depending on the amount of radiation administered. The same result was obtained when ova were irradiated instead of sperm. The changes produced were of the most diverse characters, eye color, shape of wings, number of bristles, etc. Since such modifications became fixed in the germ plasm and were passed from parent to offspring through succeeding generations, they are properly termed "mutations"—in this case, X-ray-induced mutations. Such mutations have been produced in a wide variety of organisms, both plant and animal, by numerous investigators. Accordingly, we may accept as well-established the fact that X-rays produce inheritable changes in the germ plasm. Radiation-induced inheritable changes in the form of mutations may be termed "radiogenetic."

Whether X-rays produce radiogenetic changes in humans is as yet uncertain. However, in view of the fact that no other process is more universally established among different species of living forms than that of chromosomal inheritance, there appears to be no good reason for believing that such changes are not produced in humans the same as in Drosophila. Miscarriages and abnormal children have occurred among the offspring of radiologists and radiation workers; but only very limited attempts have been made to determine whether the proportion is higher than among persons not associated with radiation. Hickey and Hall (23) circulated a questionnaire for the Committee on Sex of the National Research Council requesting information as to the degree of injury produced in the offspring of radiation workers and reported their findings in 1927. Among other things, these authors stated that of the 377 radiologists investigated (usually only the father in each family coming in contact with radiation), 138,
or 36.6 percent, of the couples were sterile; that of the 262 children born to these couples before radiation employment, 2.6 percent showed some form of abnormality; whereas of the 412 born after this employment, 4.0 percent showed abnormalities; and that of the childbearing couples the average number of children per family was 2.2 as against 3.0 for physicians and surgeons living in comparable circumstances.

Murphy (51-54) in a series of papers in 1928 and 1930 reported the results of a study of several hundred cases of preconception and postconception irradiation. While Murphy found that approximately 10 percent of the preconception irradiated offspring were abnormal, the abnormalities appeared to him to result almost entirely from modifications produced in the mother by the radiation. Naujoks (55) in 1929 made a study of 91 X-ray workers and found the percentage of sterility high (24.2), the percentage of abortions about normal, and the percentage of developmental defectives rather high (4.0). These reports, preliminary as they may be, show without question that preconception irradiation injury is being produced in the offspring of humans. Whether this includes some of genetic type, however, is not clear, but judging from the results obtained with animals, including mammals (mice; cf. Snell (56) 1939, and Hertwig (57) 1939), the abnormalities may include some of this type, perhaps a considerable proportion.

Since genetic injury involves important implications and since the mechanism of genetic injury appears to be basically different from that of part, if not all, of the types of injury mentioned, the next section will be devoted to a more complete description of the mechanism of induction of genetic changes as understood at this time. As it happens, radiogenetic injury as seen in lower forms is the only one for which really definite answers can be given to the questions raised by Kaye.

THE NATURE OF RADIOGENETIC CHANGES

Hereditary components of germ cells, or for that matter any somatic cells, are known to be located as specific chemical entities in linear arrangement along the chromosomes resembling knots on a string (fig. 1). For the most part, each chemical entity, or gene, is of specific type and is required in normal ontogeny (life of the individual). Thus, not only is the presence of these entities essential, but so also is a specific linear arrangement. The genes are self-perpetuating through succeeding cell generations, and each acts at the proper place and at the proper time.
during the life of the individual to exert its influence on the course of biologic activity. Hence, it is quite understandable that an external agent which would act to modify the specific organization of the chromosome would cause changes in the nature of the biologic behavior. This, in fact, is just what X-rays do to chromosomes. By some means or other (which need not concern us here) the radiation acts on chromosomes to produce the following effects (fig. 2):

(1) Gene mutation, in which the gene itself is permanently and irreversibly changed.

(2) Chromosome aberration:
   (a) Deletion, in which a part of a chromosome is struck loose and becomes lost through subsequent cell division.
   (b) Translocation, in which a chromosome part is struck loose and becomes attached to a chromosome at a new position.
   (c) Inversion, in which a section of a chromosome is struck loose and becomes reversed end for end.

For the most part, these effects have been observed in the fruit fly, Drosophila. One not closely associated with the field of radiogenetics might ask why an organism so far down the evolutionary scale is used when our main interest centers in man. The answer, however, is not far to seek. First of all, these forms can be maintained in large numbers in the laboratory with relative ease. They have comparatively short generations (about 2 weeks), thus making it possible to accumulate results rapidly. They have a great variety of characteristics such as eye color, shape of wings, number of bristles, etc., which can be followed genetically. A very important characteristic is that their chromosomes are unique in certain respects (small number, blank sex chromosome) which permit breeding analyses that otherwise would not be possible. Perhaps most important of all is that fact that Drosophila have giant size salivary chromosomes, permitting a correlation of chromosomal losses and deficiencies with breeding results. All of the forms of chromosome aberration mentioned have been witnessed cytologically in salivary-gland cells and correlated with visible external characteristics in many cases. It has, in fact, been possible to observe an external characteristic, such as a notched wing, and predict a deficiency that will be found at a particular location on a particular chromosome, and vice versa. It is thus apparent that a great deal is known about Drosophila genetics, giving one the assurance that findings with radiation are backed up with a broad background of information. For a description of this whole phenomenon

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<td>DELETION</td>
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<td><img src="https://academic.oup.com/jnci/article-abstract/1/6/789/953118" alt="Diagram of chromosome aberrations" /></td>
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FIGURE 2.—A chart illustrating different kinds of chromosome aberration. The letters in each case represent genes located along chromosome fibers, and the dotted lines show where breaks have been produced in the fibers by radiation. In the case of deletion, chromosome parts including genes are lost; in the case of translocation, chromosome parts together with genes are relocated along the chromosome body; in the case of inversion, a chromosome part with genes becomes reversed end to end.
of genetics, the reader is referred to the recent textbook by Sinnott and Dunn (58). Suffice it to say here that the mechanism of inheritance and the induction of mutations appears to take place in man very much the same as in Drosophila. Hence, the findings in Drosophila may be used as a guide in the study of the conditions in man and may even serve as a basis for certain temporary measures of protection.

The visible characteristics induced by radiation through modification of the chromosomes vary over the widest range. In Drosophila, they may pertain to eye color, shape of wings, number of bristles, etc., as previously mentioned, but in particular to abnormalities in development resulting in death. Since genes in some way exert a great influence over the nature of development and later life, it is obvious that some of those having to do with early development are of vital importance and organisms deprived of their influence are doomed to die. Such genes are called vital, and the mutations resulting from their destruction are called lethal.

Since the changes induced in a cell by radiation are produced purely at random and lead to disorganization, it is to be expected that while disorganization is for the most part deleterious, it is likewise to be presumed that occasionally a change will be produced which is beneficial to ontogeny. In nature, through the process of natural selection and survival of the fittest, only those changes are retained which do not lead to racial destruction. In forms other than Drosophila, including man, the biologic changes produced by X-rays would likewise be expected to be completely of a random nature and predominantly detrimental.

Mutations are known also to occur spontaneously among cells, that is, without the aid of any known external forces. Although it is usually held that spontaneous mutation is a rare event, this opinion has rested more on the stability of species and on the low frequency with which mutants are found in nature than on data from deliberate attempts to measure the exact frequency of mutation. Muller (59) has devised special techniques for measuring mutation rate in Drosophila and has estimated that under ordinary laboratory conditions a particular mutated gene of the lethal variety may be expected in D. melanogaster in 0.1 to 1 percent of individuals, that is, in the chromosomes of their cells. Visible sublethal changes have been observed about one-tenth as often as the lethal variety (60). For purposes of illustration let us remember the value of 1 percent for the normal lethal mutation rate and 0.1 percent as the normal sublethal rate, leaving the matter of variability and the condition in humans to be discussed later.

Muller (59) in 1933, judging from a large amount of data obtained by himself and by others as well, estimated that the normal mutation rate is practically doubled in Drosophila melanogaster by a dose of 30 to 40 r applied to the germ cells lying in the gonads, an amount of radiation which is about equivalent to the doses delivered in some of the longer fluoroscopic examinations, or, as indicated by Cowie and Scheele (5), the amount that will reach the gonads of a good many operators at the present time in a few days to a few weeks of routine work.

Thus, judging by Muller’s estimates, one might expect the probability of lethal mutation to be changed from 1 in 100 to 2 in 100 by a dose of, say 35 r, and that the chances of a visible mutation being produced would be changed from 1 in 1,000 to 2 in 1,000. From the standpoint of protection this at first might seem to show little cause for alarm, since if the
tolerance standard of 0.1 r/day is being maintained, more than a year's exposure would be required to make the chances of abnormality in offspring greater than 2 percent. Thus, with chances so much in their favor (assuming that the same conditions hold in humans), most radiation workers desiring children would be willing to take the risks involved. There are, however, certain characteristics of the genetic effect which make its dangers greater, especially when considered from a long range point of view (60). These, however, can best be presented after describing still other characteristics of the genetic effect and contrasting them with the characteristics of other effects.

THRESHOLD VS. NON-THRESHOLD REACTIONS

Curves may be drawn to show how the number of organisms affected in a particular way by radiation varies with the amount of radiation administered. For purposes of illustration let us consider two effects, one the induction of gene mutation and the other inactivation (killing) of tumor fragments. When a dose-effect curve is prepared for gene mutations, it is found to have the characteristics of curve A, figure 3 (composite results obtained by a number of investigations, which are generally consistent, are shown together by Schultz (61) (1936)). On the other hand, if one gives varying amounts of exposure to different samples of tumor fragments and observes these for "takes" when transplanted into animals, the number inactivated by the different doses will be found to vary as indicated by curve B, figure 3. Such curves have been presented by Sugiura (62) (1937).

These curves have one outstanding difference. Curve B has a distinct toe or threshold character, whereas curve A has none. In the case of tumor fragments, it is clear that a considerable increment of dosage must be administered before any fragments are inactivated. In the case of gene mutations, on the other hand, this is different, the number of germ cells in which mutations are produced being directly proportional to the amount of radiation given. This means that as soon as exposure begins, mutations begin to be produced among the individual cells and that the mutations are produced by single random events. This is in marked contrast with tumor-fragment inactivation in which the effect is brought about only after a building up of irradiation events (the nature of which is of no interest here). The induction of mutation, therefore, involves a probability reaction, whereas the killing of tumor fragments involves one of accumulation. Said in another way, the former involves a single-event type of action whereas the latter involves a multiple-event type. Single-event action also may conveniently be termed "hit" or "target" action.

The reason why the first reaction can be said to be of single-event type and the second of multiple character is simple and for purposes of illustration let us consider an analogy. Suppose that an army is
coming over a hill and one is shooting into it at random with poison-tipped arrows. In this case, whenever a hit is registered, a soldier is killed because the injury is deadly. Killing, here, is purely a random matter. Suppose, on the other hand, several hits would be required as a rule to incapacitate a man, then some time would necessarily elapse between the beginning of shooting and the time when an appreciable number of soldiers had accumulated enough injury to be knocked out. This property of accumulation distinguishes clearly the second type of action from the first. In the second case, a soldier may escape with injury, but in the first, he either escapes with no injury or he does not escape at all.

In case of the radiologic considerations, it is clear that the proof of a single-hit killing action rests on the question of whether the curve has a threshold character, a point which is difficult to establish by experimental means. However, if the reaction is of non-threshold type certain other characteristics are automatically indicated, some of which can be investigated experimentally. Since the process of mutation induction with X-rays appears to be of single-event type, it is important to indicate the other characteristics which it should have. First, however, it should be stated that mutational changes, by definition, are irreversible (i.e., except in the case of inverse mutation) since the change becomes fixed in the cell and remains so permanently. The following would, therefore, be expected: (1) That the duration of the exposure would not affect the result—in other words, that a particular dose of X-rays given in a few seconds or in a few days to a population of individuals would produce the same proportion of mutations in each case; (2) that the effects of different treatments would be entirely additive; (3) that the effect would be directly on the chromosome; and (4) that the temperature of the specimens during treatment and the rate of metabolism would have no influence on the results obtained. These things, in fact, have all been well substantiated, particularly in *Drosophila* (cf. the following for reviews: Timofeeff-Ressovsky (60) 1937; Muller (59) 1933; Goodspeed and Uber (63) 1939).

Reference to mutation in this section has been limited strictly to the gene-mutation type, in order to make precise statements about the quantitative aspects of the reaction. However, with certain considerations the target hypothesis applies equally well in the case of chromosome aberrations and in this case we have the advantage of visible proof of what is happening. Sax (64), in a recent paper, studied X-ray-induced chromosome aberrations in *Tradescantia* and presented dose-effect curves for the changes involving single chromosome breaks in one case and double chromosome breaks in another. The first were of the characteristic non-threshold type, whereas the others were of the threshold, which is precisely what would be expected on the basis of the target hypothesis.

Thus, on the basis of the foregoing considerations, it is possible to give answers to the questions raised by Kaye as far as X-ray-induced mutations are concerned: (1) The changes result from local rather than general exposure; (2) the results of previous exposures are additive with subsequent ones; (3) duration and frequency of exposures do not influence the reaction; (4) recovery does not occur; (5) general idiosyncrasy is important (to be discussed further); and (6) the question of the selective sensitivity of different parts of the body does not apply here.

It has been shown, in fact, in *Drosophila* that they are additive in succeeding generations.
Dose-effect curves are not available for the other types of injury listed so that it is not possible to classify them as to single- or multiple-event types of reactions. However, since X-ray dermatitis, sterility (as distinguished from radiogenetic injury), lymphopenia, leukopenia, anemia, bone necrosis, glandular dysfunction, and fetal injury fail to appear if the dosage is kept small, these reactions appear to be of the multiple-event type. While the induction of tumors or leukemia by X-rays may also be of this type, a satisfactory answer cannot be had until we know more about tumor etiology (e.g., whether X-ray tumors are of single- or multiple-cell origin).

Thus, while certain aspects of some of the reactions are not adequately understood, it appears plain, nevertheless, that we have two distinct types of reactions with which to deal in protection—types, in fact, which require very different considerations.

CONCEPTS OF PROTECTION

At the present stage in the history of protection, it is clear that the idea of tolerance dose automatically implies threshold-type reactions—that is, that there must exist, so far as the injurious effects are concerned, doses below which no effect is produced. But, as already mentioned, there exists at least one type of injury—and an important one—to which the tolerance-dose idea simply cannot be applied in the same sense. In the case of radiogenetic injury it is now apparent that for any given increment of dosage, no matter how large or how small, there exist certain chances of mutation and that these chances vary directly with the dose. Hence, instead of tolerance dose, it would seem more appropriate to speak of tolerance injury. Such an expression would imply, and correctly so, that any value that might be associated with the term would be entirely arbitrary. In such a case we would set the amount of genetic injury we are willing to tolerate and regulate accordingly the amount of radiation that will reach the gonads before childbearing.

After the dual character of the protection problem has thus been recognized, the question arises, very naturally, as to what safety value 0.1 r/day has in the case of the threshold-type reactions and the injury value it may have in the case of the non-threshold type. The published information in regard to the first is, so far as we know, all given in the table showing recommended tolerance intensities. As mentioned, these findings are based on the most limited investigations, but in view of the fact that the tolerance standard of 0.1 to 0.2 r/day has been used by a number of institutions and generally satisfactory results have been obtained, it is obviously better established than is indicated by the findings in the table so far as the more conspicuous injuries are concerned. Since only recently have we begun to be aware of the fact that radiation may be a factor in inducing leukemia, that a very long interval may occur between exposure and the appearance of radiation-induced tumor, and that such tumors may be induced without the previous appearance of precancerous lesions, these experiences furnish no adequate proof that 0.1 to 0.2 r/day is safe for all threshold reactions. Cowie and Scheele (5) and Uhlmann (65), however, indicate that irradiation injury is by no means uncommon. One gains the impression, nevertheless, from the report by Cowie and Scheele that the present skin injuries are resulting more from failure to maintain the standard rather than from an incorrect standard.

As to the safety value of 0.1 r/day in
the case of genetic injury in humans, there is no information; no curve is available as in the case of *Drosophila*, showing how the number of mutations produced varies with the dose of radiation reaching the germ cells. However, should it become advisable, as Muller has suggested, to relate the rate of induced mutations to that of the spontaneous type, it would be necessary to know something of the spontaneous rate and how constant it may be. Fortunately, there is some information on this point for lower forms.

**THE CONSTANCY OF SPONTANEOUS MUTATION**

Muller (66) and Timofeeff-Ressovsky (60) show, in their work on *Drosophila*, that the rate of any given kind of mutation is quite constant. For a particular lethal type, Muller has shown that it occurs (spontaneously) in about 1 out of every 1,000 germ cells. It has been found, however, that the spontaneous rate is not the same for different types of mutations. The specific organization along the body of the chromosome seems to cause the stability at various points to differ, thus causing certain types of mutations to occur more frequently than others. In addition, there are the so-called mutable genes, such as those that have to do with size, color variety, etc., which undergo changes more frequently.

From the foregoing, it would seem that while the different kinds of mutations are known to occur at different rates, one should be able to relate the rate of induced mutations of a given type to the rate of spontaneous mutations of the same type with a fair degree of reliability.

To illustrate just how such a relation might be used, let us assume that the development of feeblemindedness was known to occur spontaneously in 1 out of every 1,000 offspring, and that the normal rate was doubled by exposure to 35 r (as Muller has found for a particular effect in *Drosophila*); then if the tolerance intensity of 0.1 r/day is being maintained, the incidence of mental weakness would be increased from 1 in 1,000 to 2 in 1,000 with about 1 year of exposure. Among other things, this illustration goes to show how much information is needed, since so very little is known of mutations in humans. Lest one should gain the impression, however, that mutations are of rare occurrence, attention should be called to the fact that when all possible mutations are taken into account in *Drosophila*, lethal, sublethal, large, and small, as high as 75 percent of the chromosomes have been reported to have mutant genes (Dobzhansky and Queal (67) 1938).

**GENERAL CONSIDERATIONS**

From what has just been said, it appears that spontaneous mutation may be of more frequent occurrence than is usually suspected, and the question arises very naturally as to what extent spontaneous mutation contributes to the course of evolution. Without entering into a discussion of the subject, it seems safe to say at this stage of our knowledge that spontaneous mutation contributes some, if not a great deal, to the process of evolution. Thus, since radiation enhances the mutation rate, since the germ cells of children give rise by direct cell lineage to the germ cells that become functional in later life, and since the exposure (in adults and youth alike) is becoming constantly greater through radiography, therapy, industry, and merchandising (fitting of shoes, etc.), it seems clear that because of the use of radiation, evolution is being moved forward at an ever-increasing rate—a situation which indeed may have far-reaching social implications.
As it becomes apparent that a significant amount of mutation occurs spontaneously among cells and that radiation adds to this effect, the question arises as to whether prospects for the future use of radiation really furnish cause for alarm. If we accept the normal rate of mutation or the normal rate of evolution without concern, why then should we not be equally unconcerned if the tempo is merely stepped up one, two, or even several fold? In nature the process of natural selection through survival of the fittest is constantly in effect, thus retaining only those changes which aid in racial survival. Hence, may we not say that the same forces will be in effect if the tempo of evolution is stepped up and that the end result will be very much the same as at present? While an adequate answer is not available on this point, the outlook is against such an assumption, three reasons for which may be given: (1) Increasing the tempo of evolution would cause a greater proportion of the less fit in any given generation or at any time. This is true because time aids in a more rigorous selection of the fittest. Surely there would be universal agreement that this is undesirable. Whether the increase in less fit will be enough to cause concern depends entirely on how much the tempo is increased. (2) It appears that whereas normal mutation tends more to be associated with less stable chromosome areas where less consequential variation occurs, X-ray-induced mutation appears to be more widespread in character and more devastating, thus causing a greater proportion of harmful and lethal mutations. Lethal changes, of course, would have little or no effect on racial well-being, but they would be a matter of much concern in the first generations. By this it is meant that X-rays produce a greater proportion of changes in germ cells that cause abnormalities in development and result in abortion or infant mortality. (3) With the tendency for detrimental hereditary changes to be genetic recessives, the more rapid production of these in the general population would have the effect of replacing strong characters with weaker ones, thus leading toward racial weakness.

There is a strong tendency at this time, especially by those who are faced with the need for using X-rays to aid patients and so to save lives, to say that, since there is almost no evidence that genetic abnormalities are induced in humans, the good that they are doing far outweighs the possible damage done to future offspring. This challenge cannot be met at this time, but the indications cited above (especially by Zappert (22), and by Hickey and Hall (23)), limited as they may be, furnish ample evidence that the germ plasm of man is not excluded from the possibility of irradiation injury. The opponents of radiogenetic change may point to apparently normal sons and daughters of radiologists who have received a great deal of radiation before these children were conceived, or to menstruating daughters whose mothers received considerable pelvic preconception irradiation. These are important examples and they carry weight, but they do not prove that the unfortunate cases derived their abnormalities from sources other than radiation. It is likewise possible to point out cases of serious abnormalities in offspring of persons who received preconception irradiation, but since we are unable as yet to distinguish preconception irradiation injury from the spontaneously occurring abnormalities, such cases cannot be said with certainty to be due to the influence of irradiation. It is thus apparent that much more information is needed, particularly of the type obtained by Hickey and Hall.

While these considerations are specu-
ative and do little more than stimulate our imagination, they, nevertheless, suggest that radiation, as it will be used in the future, will in all probability exert an appreciable influence on the course of evolution. Until we know more about the nature of the process and of the desirability of the influence it will have, we are faced with the problem of what to do in the meantime. Should we curtail the exposure to radiation before the childbearing period or should we disregard the indications and trust that no unfortunate circumstances will develop? Until more information is available, surely it is preferable to take the attitude that exposure of the germ line should be avoided as much as possible. As Muller (59) said:

We must remember that the thread of germ plasm which now exists must suffice to furnish the seeds of the human race even for the most remote future. We are the present custodians of this all important material and it is up to us to guard it carefully and not contaminate it for the sake of any ephemeral benefits to our own generation.

From the discussion given, it is clear that no significant indication can be made of the injury value of 0.1 r/day in the case of radiogenetic changes in humans. However, since it may have a derogatory effect, the extent of which is as yet unseen, and since the exposure of personnel is usually much lower than 0.1 r/day if the recommended physical standards of protection are followed (5), surely it is advisable to keep the exposure of germ cells well below the present standard of safety and to avoid exposure completely before childbearing.

PROTECTION ATTAINMENTS AND NEEDS

By way of retrospect some of the apparent protection accomplishments and some of the apparent needs for the future are listed here:

(1) A tolerance dose (usually 0.1 to 0.2 r/day) has been recommended by various protection committees. Judging more from unpublished results than from published, it would seem that so far as certain types of injury are concerned (skin damage, blood changes, general sterility), this standard provides fairly adequate protection, when general body exposure is concerned. So far as other injuries are concerned (induction of tumors, including leukemia), our experience is as yet too limited even to allow surmises. We know little of the rate of accumulation of irradiation effect in these cases, or indeed whether such is necessary, nor do we know actually whether X-ray dermatitis is a necessary forerunner of X-ray tumors.

(2) In regard to local exposure it has been emphasized by Cowie and Scheele (5) and by Quimby (48) that severe injury may be produced on the hands (particularly in the case of gamma rays) while the exposure of the body is within the limits of the safety standard. Thus, it does not seem advisable to presume, as some have done, that “since the tolerance standard contains a generous factor of safety, we need not distinguish between local and general effects.” Instead, it would seem safer and more consistent to have the standard apply locally the same as generally.

(3) Heretofore, the safety standard has been made to apply almost exclusively to changes in the superficial tissues and derangements of the internal organs including changes in the blood. In view of that which has been said, it is desirable to have the safety standard defined more specifically. It is suggested, therefore, that the tolerance dose for threshold-type reactions should be related to the most sensitive injury effect known, and then that it be assumed that all other types of injury are automatically cared for. It is suggested
further that the tolerance dose in the case of whole body exposure be defined with respect to lymphopenia for two reasons: (1) Lymphocytes appear to be the most sensitive cells in the body; and (2) because a lymphocyte record provides a fairly satisfactory quantitative measure of the degree of injury when present. Since a complete blood record can be obtained almost as simply as a lymphocyte count alone, and because blood changes other than that of the lymphocyte count will give additional information, it would seem proper to define the tolerance dose for whole body exposure simply with respect to blood changes. In the case of local injury, such as on the hands, blood changes would probably have little meaning. Hence, it is necessary to use a different effect here, and it is suggested that sustained faint skin reddening be used, such as that which appears at the base of the nails of radium workers, since this is one of the first signs of damage and fairly easy to detect.

Thus following the pattern used by Taylor, we suggest that "tolerance dose" be defined as the amount of X-ray or gamma ray energy that a person can receive continuously or at repeated intervals without suffering changes in the blood when the whole body is exposed, or reddening of the skin when local areas are exposed.

SUMMARY

1. The history of protection from injury caused by X-rays and gamma rays and of the tolerance dose and the trends in protection have been discussed.

2. As a consequence, it becomes clear that practically all of the discussions on protection have pertained to the physical aspects of the problem with the result that the nature of the injuries to be protected against and the significance of the biological factors involved have been almost completely overlooked.

3. By taking account of the information now available, it is possible to point out that the previous concepts of protection do not apply to one kind of effect, the radiogenetic.

4. The term "tolerance dose" as used before can apply only to threshold-type reactions—ones for which safe exposures exist. The radiogenetic type of injury, as manifested in lower forms, is shown to have no threshold of safety. The problem, therefore, is one involving probability of action or injury.

5. Thus the question of whether the genetic injury produced by 0.1 r/day is tolerable is obviously an arbitrary matter. Unfortunately, not enough data are available for human beings to allow any satisfactory statement as to how much genetic damage is produced by this exposure; but by analogy from the condition in lower forms, this appears to be more than we should prefer to tolerate.

6. Because of the non-threshold character of the radiogenetic reaction and because of the far-reaching influence that it may have, the significance of this irradiation effect has been stressed.

7. The tolerance dose (for threshold-type reactions) is more specifically defined as the amount of X-ray or gamma ray energy that a person can receive continuously or at repeated intervals without suffering changes in the blood when the whole body is exposed or sustained redness of the skin when local areas are concerned, the assumption being that if these effects are protected against, all other types of injury will be cared for automatically.

8. Much more information is needed before the adequacy of 0.1 r/day as a safety standard can be stated. Accordingly, available information pertaining
to persons (especially groups of persons) who have been exposed to known or reasonably well estimated amounts of radiation for known periods of time, and whose health records contain information about blood and skin changes, reproductive potencies, etc., should be published at the earliest opportunity. Likewise, records should be kept where possible in order that future tabulations can be made.

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