ARM2.950149.001

ARMY MEDICAL RESEARCH LABORATORY

FORT KNOX, KENTUCKY

REPORT NO. 175
2 February 1955

ADAPTATION TO IONIZING RADIATION*

*Subtask under Biological and Medical Aspects of Ionizing Radiation AMRL Project No. 6-59-08-014, Subtask, Effects of Ionizing Radiation.

RESEARCH AND DEVELOPMENT DIVISION
OFFICE OF THE SURGEON GENERAL
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Army Medical Research Lab. Project No. 6-59-08-014 Report No. 175

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A. T. Krebs and J. B. Storer

17 pp & i 2 illus. 29 December 1954

UNCLASSIFIED

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ADAPTATION TO IONIZING RADIATION*

by

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and
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from

RADIOBIOLOGY DEPARTMENT
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FORT KNOX, KENTUCKY
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*Subtask under Biological and Medical Aspects of Ionizing Radiation AMRL Project No. 6-59-08-014, Subtask, Effects of Ionizing Radiation

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ABSTRACT

ADAPTATION TO IONIZING RADIATION

OBJECT

To review the available literature on the subject of acquired radioresistance in mammilian systems and to present data on experimental studies performed in the laboratory.

RESULTS

It is well established that a variety of human and animal tumors as well as certain normal tissues have the ability to adapt to the effects of ionizing radiation. It is not known with certainty whether or not an entire animal can adapt and thereby raise the dose required to produce lethality. In the experimental studies in this laboratory there was no evidence of ability of mice to adapt to total-body radiation, nor was there evidence of adaptation in testicular tissue.

CONCLUSIONS

Adaptation can occur in certain tissues. Information is meager as to the extent of adaptive ability and no information is available with respect to many tissues.

RECOMMENDATIONS

A systematic study employing quantitative methods for measuring radiation effect should be initiated to evaluate the extent, mechanism, and possible application of the adaptation phenomenon.

Submitted 29 December 1954 by:
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ADAPTATION TO IONIZING RADIATION

I. INTRODUCTION

Man and experimental animals have been shown to have the ability to adapt to wide deviations from their normally encountered environmental conditions. The physiologic adaptation to altitude is well known (1). Blair and Dimitroff (2) have demonstrated a remarkable ability of rats and rabbits to acclimatize to extreme cold. Examples of adaptation to the toxic effect of drugs are common (3-6). Tolerance to atropine, arsenic, and organic arsenicals can be increased by repeated administration to animals (6). In commenting on human drug addicts Bamford(5) states: "The fact that addicts can, with apparent safety, take daily doses of poisonous substances in quantities which are much more than enough to kill ordinary people is well known, but has never been satisfactorily explained."

Since the development of tolerance or an acquired resistance to various noxious agents is a relatively common occurrence in animals it would appear relevant to the problem of radiation hazards to consider whether or not a similar adaptation to the effects of ionizing radiation can occur. The present report consists of: - a brief review of the available literature on the subject; a preliminary report of studies in this laboratory; and, a discussion of some of the factors to be considered in future research.

II. DEFINITIONS AND CRITERIA

Before proceeding with further consideration of the problem it is essential that adaptation to radiation be rigidly defined and that criteria be established for evaluating whether or not adaptation has occured. It is proposed that adaptation to radiation (acquired radioresistance) be defined as that status arising from changes induced in an organism by radiation exposure(s) which result in a diminution in the magnitude or duration of the response to subsequent radiation exposure(s) relative to the response to be anticipated if no prior radiation treatment had been given. From this definition it can be seen that adaptation is a relative term and for practical purposes is measured in terms of effect on an unadapted or control organism(s). The control observation most frequently reported in the literature consists of the extent of response induced in the biological material following the initial dose of radiation. The response to

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subsequent doses of similar size is then compared to the initial response. This type of control might be designated as an "internal" control. Another type of control which has been used might be called the "external" control. In this case a number of biological test objects (mice, rats, plants, etc.) each of which are as homogeneous (with respect to genetic constitution, age, size, sex, etc.) as is feasible to obtain are divided into two groups. One group receives "adaptive" doses of radiation and then both groups receive a "test" dose. Difference in the response to the test dose are then evaluated to determine whether adaptation has occured. Either type of control is acceptable.

Certain specific criteria should be met before data are accepted as demonstrating the occurence of adaptation. These criteria may be summarized as follows:

1) The radioresistant state must have been induced by radiation exposure. A number of chemical agents are known which produce a state of relative radioresistance in experimental organisms. This resistance, strictly speaking, is an acquired radioresistance but will not be considered as adaptation in the sense used in this report.

2) The total extent of or duration of the response must be less in the "adapted" organisms than in the controls (whether internal or external controls are used). In other words the incidence of lethality, extent of atrophy, loss of cellularity, depression of function, etc., must be less even though the total dosage (sum of the adaptive and test doses) is greater in the adapted group. If, for example, a tissue has become depleted of cells due to the adaptive doses and the test dose produces little further depletion, this finding will not be considered to indicate adaptation unless the total depletion is less than that found in the control series which has been given only the test dose.

3) Simple lack of complete cumulation of effect of repeated or continuous doses of radiation will not be considered to indicate adaptation since such results may usually be explained on the basis of repair times. Consideration of this phenomenon is beyond the scope of the present report.

III. LITERATURE REVIEW

A. Evidence for Adaptation

A considerable amount of evidence has been presented, especially in the clinical literature, that suggests that adaptation

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of certain tissues to radiation may occur. The majority of the reports are concerned with resistance of neoplasms (7-18) and there can be little doubt in this case that there is true adaptation, otherwise the cure rate from radiation therapy would be substantially higher. The evidence with regard to neoplasmas has been summarized very well by Windholz (17) who has written:

> "Experience shows that malignant tumors of various microscopic structure which respond to initial irradiation may lose their radiosensitivity in part or whole during or after radiation therapy. Thus, they acquire radioresistance, which, in the opinion of many observers, is one of the main causes of failure of radiation therapy."

Wintrobe (19) further indicates that in the case of chronic leukemias, radioresistance eventually develops in all cases so treated.

Adaptation of normal tissues is less well established. One of the difficulties encountered in the case of normal tissue is that the end point for evaluation of effect is rather vague in comparison with tumors. If a tumor begins to enlarge despite continued radiation treatment, whereas it initially showed a diminution in size, then there can be little doubt that it has become radioresistant. A normal tissue, which does not show such variations in size, may become resistant to radiation but in this case the evaluation depends on a subjective impression as to whether it appears healthier, shows less histological damage, etc. Despite this difficulty it seems well established that normal tissues may become adapted. Healing of radiodermatitis (15, 20) and damaged mucosal epithelium of the mouth, pharynx, and larynx (15, 17, 21) has been reported to occur even though radiation exposures were being continued. Connective tissue is also said to differentiate and repair in the presence of continued exposures (20, 22).

The foregoing discussion has been based on clinical observations in patients treated with radiation. There are considerably fewer reports available which were based on experimental studies in animals. Studies on experimental animal tumors support the conclusion that tumors in general have definite adaptive ability (13, 23, 24, 25). Acquired resistance to beta (13), gamma (13, 24), and x-irradiation (25) has been demonstrated in the Jensen rat sarcoma following repeated doses of these radiations. The criterion used in each case was the dose required to prevent successful transplantation to an unirradiated recipient rat. A similar resistance has been demonstrated in a "slow rat sarcoma" (13). Freyman (26) has recently reported that if Yoshida ascites tumor cells are repeatedly exposed to x-irradiation there is a progressively smaller effect on the mitotic index of these cells. It is not clear in this case, however, whether or not this phe-

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nomenon can be considered as adaptation since the report consists of a brief abstract and complete data on cell counts, etc., are not given.

Bloom (27) has apparently presented the most extensive data on adaptation in a variety of normal tissues from experimental animals exposed to repeated or continuous radiation dosages. In summarizing the findings of the various contributors to his report he points out that:

> "... (in experiments) in which mice were exposed to 80 r per day, the intestinal mucosa, spleen, thymus, bone marrow, lymph node, and testis all showed damage after one or a few doses. The testis and splenic white pulp became progressively more depleted throughout the six-week duration of the experiment. The thymus and bone-marrow, though not entirely recovered showed little further depletion after the first three weeks. The intestinal mucosa and ectopic myelopoiesis in the splenic red pulp looked normal after 24 treatments. Lung, adrenal, kidneys, and other resistant tissues were not affected. In short, except in the testis and splenic white pulp, there was no effect as a result of these repeated exposures or there was some evidence of acquired resistance to irradiation."

Bloom goes on to say that in guinea pigs given 8.8 r per day there was a cumulative effect on the testis but the spleens "...of some specimens that had accumulated 700 r could not be told from the controls." A similar lack of effect on splenic red pulp was found in animals injected with certain isotopes that normally accumulate in high concentrations in the spleen.

Not all of these findings fulfill the criteria previously set up for establishing that adaptation has occured. The lack of damage to the spleen by 8.8 r/day, for example, may be due to repair occuring at a rate sufficient to prevent the appearance of damage. In other words simple lack of cumulation does not necessarily indicate adaptation. The lack of further depletion of the thymus and marrow after the first three weeks similarly does not necessarily indicate adaptation. Repair and damage may have reached a balance at a certain point of depletion without the cells being adapted. On the other hand it seems almost certain that the intestinal mucosa and the ectopic myelopoietic cells of the spleen were adapted in view of their normal appearance at the end of the experiment compared to the damaged produced after the first few doses.

Adaptation of the intestinal mucosa has been confirmed by Margaret Bloom (28) in a thorough study on mice. Using histological

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criteria such as amount of cellular debris, extent of mitotic inhibition, etc., she was able to show definite evidence of adaptation. Earlier reports by Warren and Whipple (29), and Friedman and Warren (30) are in agreement with this conclusion.

There is no similar degree of agreement in the case of the testis. As indicated above, Bloom (27) has reported a continued depletion of cells as radiation was continued. This finding appears to be supported by the recent study of Carter et al (31) which indicated that gamma ray doses of only 1.64 r/week produced reduced fertility in male mice after an accumulated dose of only 40 r. Langendorff and Langendorff (32) and Lorenz et al (33) also found deleterious effects on the testes from repeated small doses of radiation. Ferroux et al (34), Pape (35) and Trautmann et al (36), on the other hand, found histological evidence of resistance to the effects of a single large dose of radiation in rats exposed to repeated low radiation dosages.

Since adaptation can apparently occur in various individual tissues it would seem reasonable to suppose that adaptation of the entire animal might also be possible. There are few reports indicating that such is the case, however. Raper (37), in studies on the additivity of effect of total-body beta radiation, found that under certain conditions a previous dose of beta radiation increased the tolerance to a subsequent dose of beta radiation. Cronkite et al (38) exposed mice to weekly doses of 144 r of x-radiation for three weeks and on the fourth week exposed them to 703 r. Survival was significantly higher in this group than in the "unadapted" control group, Apparently this interesting experiment has not been repeated or if so it is unreported. Incidental to their study on the testes, Trautmann et al (36) found an increased survival time in their "adapted" rats.

In summary it is apparent that many human and animal tumors as well as certain normal tissues have the ability to adapt to the immediately damaging effects of ionizing radiations. Among the normal tissues which may acquire radioresistance are skin, mucosal epithelium of the upper respiratory tract, intestinal epithelium, connective tissue, and splenic red pulp. It has not been satisfactorily established whether or not bone marrow, thymus, lymph nodes, and testis may adapt. No information is available with respect to normally resistant tissues such as liver, kidney, adrenal, nerve tissue, and bone. In an admittedly incomplete survey of the literature only three reports were found which suggested that animals could adapt to the lethal effects of radiation (36, 37, 38). Because of the lack of data, no general conclusion can be drawn concerning this phenomenon.

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B. Theories of Mechanism of Adaptation

Various theories of mechanism of adaptation of tissues in general and tumor tissues in particular have been advanced. The principal of these theories, which have been discussed by other authors (17, 25), may be summarized as follows:

1) A tissue is composed of cells showing all degrees of sensitivity to radiation. Radiation destroys the most sensitive cells, leaving resistant cells to proliferate. The radioresistance is passed from one generation of cells to the next, thus producing a resistant tissue by a process similar to natural selection (10, 34).

2) Radiation produces an essentially new and radioresistant cell type by the induction of a mutation (18).

3) Repeated radiation doses do not affect the resistance of the tissue cells per se but alter the supporting stroma (connective tissue, blood vessels, etc.) in such a manner that the tissue becomes resistant(12, 14). There are at least two theories as to how this resistance is brought about. It has been suggested that in the case of tumors the resistance is apparent rather than real since damage to the stroma might impair the natural defenses of the host and allow uninhibited growth of the tumor. A second possible explanation would be that the stromal damage alters the "metabolic state" of the tissue (reduced blood flow, lower oxygen tension, etc.) so that it becomes resistant.

While these theories might apply to certain specific examples of adaptation, there are a number of objections to accepting them as a general explanation of the phenomenon. For example, if the first theory were correct then radioresistance in tissues would be permanent. It may well be in the case of certain tumors, but M. Bloom found that resistance in the duodenum was lost if the time interval between the last adaptive dose and the test dose exceeded one week. The rapidity with which adaptive changes occur as well as the lack of permanent resistance renders the mutation theory untenable. The specific mutation required for radioresistance could not be expected to occur in more than a few cells (a very optimistic estimate) and the time required for these cells to repopulate a tissue would be considerably greater than the time usually required to induce adaptation. The development of resistant strains of microorganisms might be due to a mutation but this explanation almost certainly does not apply to mammalian tissues. Changes in the supporting stroma leading to radioresistance of tissue might occur in certain specific in-

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stances following radiotherapy to tumors. It is well extablished that decreased oxygen tension renders a tissue relatively more resistant to radiation. If obliteration of vessels in a tumor occurred as a result of radiation therapy then the decreased oxygen tension might result in resistance to further treatment. It is difficult to see how this explanation would apply to normal tissues which may adapt as a result of small doses of radiation. Connective tissue and blood vessels are relative resistant tissues and histological evidence of damage is not usually present following small doses. There could, of course, be alterations of function produced which do not parallel histologic changes. For this reason the theory cannot be entirely rejected. It cannot be considered a general explanation, however, since the studies with transplantable tumors indicated that resistance persisted even though transplantation to an unirradiated host was performed (13, 24, 25). The supporting stroma of transplantable tumors is generally believed to arise from the host rather than the tumor. If stromal damage were responsible for resistance then the resistance should be lost in an unirradiated host. The transplantation studies also rule out the theory that impairment of the animal's defense mechanisms is responsible for continued growth in the presence of continued radiation exposure.

In addition to the above theories the rather vague concept of "establishment of alternative metabolic pathways" should be considered. If radiation blocked a particular vital metabolic function of the cell then cellular damage or death would result. It is conceivable that the cell might find some new metabolic pathway to circumvent the damaged one. If this new pathway were resistant to radiation then adaptation would have occurred. This concept is not new and has been discussed by biochemists for years. At present, however, knowledge of cellular metabolism and effects of radiation on this metabolism is insufficient to allow a critical evaluation of this theory.

Another equally vague but interesting theory might be formulated as follows. It is is assumed that cells divide in response to an external stimulus of some sort then a prolonged period of depressed mitotic activity might result in a potentiation of this stimulus. If the stimulus became sufficiently strong then division might occur despite continued exposure to radiation and a normal level of mitotic activity or a healing of a damaged tissue might occur. This notion would appear to be supported by the finding that regenerative hyperplasia in bone marrow induced by treatment with phenyl hydrazene renders the marrow somewhat radioresistant (39).

From the foregoing discussion it can be seen that no generally acceptable theory of the mechanism of adaptation has been estab-

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lished. It is possible that there is no general explanation and that for different conditions different theories apply. At the present time the phenomenon of adaptation has not been sufficiently studied and characterized to permit more than general speculation as to mechanism of effect.

IV. EXPERIMENTAL STUDIES

Three experimental studies were performed in this laboratory in an attempt to demonstrate acquired radioresistance. Two of these studies consisted of attempts to lessen the lethal response of mice by previous exposures and the third consisted of an attempt to demonstrate acquired resistance in a normal tissue.

A. Methods

A total of 176 mice were used. Of these, 120 were adult CF-1 females, 2 to 3 months of age. 31 were adult C3H males 3 to 6 months of age, and the remaining 25 were C3H females of similar age. Prior to and following radiation exposures the mice were maintained on Purina laboratory chow and water ad libitum.

X-rays were delivered from a Kellikoett deep therapy model machine operated at 200 KVP with added filtration of 1.0 mm Al and 0.5 mm Cu. The tube current and target-specimen distances were varied depending on the output desired. Calibrations were performed in each case with Victoreen thimble chambers and the radiation doses represent those measured in free air and include backscatter.

B. Experiment I

The work of Cronkite et al (38) on adaptation of mice to the lethal effects of x-rays was repeated. One hundred and twenty CF-1 mice were randomly divided into three groups of 43, 43, and 34 mice, respectively. Groups 2 and 3 were then given 3 exposures of 144 r, each, at weekly intervals. One week after the last exposure groups 1 and 2 were given a single exposure of 703 r. The survival was then followed for 30 days.

The results of this study are shown in Table 1 and Figure 1. Twenty-three per cent of the animals receiving 703 r with no prior exposure survived for 30 days while 28 per cent of those receiving 703 r after 3 weekly exposures to 144 r survived for 30 days. This slight difference in survival is of no significance. Neither was there

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a significant difference in survival times (Figure 1).

C. Experiment 2

Since no evidence of adaptation was obtained in the first experiment it was decided to vary the procedure for giving the "adaptive" doses of radiation. It seemed reasonable to assume that continuous exposure to low dose levels might be preferable to 3 relatively large fractionated doses. It was not feasible to expose the animals continuously so repeated daily exposures were used as a substitute. Twenty five adult female C3H mice were divided into 2 groups of 12 and 13 mice each. Group 1 was then given doses of 1 r/day, 5 days a week, for 6 weeks (accumulated dose of 30 r). Group 2 was handled identically, being put in the exposure cage and placed in the x-ray room, except that no exposure was given. At the end of the 6 weeks both groups were exposed to 720 r and the mortality followed for 30 days.

The results are shown in Table 1 and Figure 2. There were no significant differences in either survival time or total survival at thirty days.

D. Experiment 3

Because neither of the previous experiments gave any evidence for adaptation to lethal effects it was next decided to attempt to produce adaptation in a tissue. It has been reported that excellent protection (using a histological evaluation of results) of the testis of rats occured when the rats were exposed to repeated low doses prior to the final large dose of radiation (34, 35, 36). To test for an adaptation in the testis by using a quantitative rather than a qualitative end point, the following experiment was performed. Adult male C3H mice were divided into 2 groups of 16 and 15 mice each. Group 1 was then exposed to daily doses of 1 r/day, 5 days a week, for 6 weeks. At the end of this time both groups were given 150 r total-body x-irradiation. Four weeks later, at a time when testicular atrophy was maximal, they were killed and the wet weight of the testis obtained. To compensate for slight differences in body weight the testicular weights were expressed as mgm/gm of body weight.

The results are shown in Table 1. The mice in which adaptation was attempted showed a greater degree of testicular atrophy than did the "unadapted" controls, the mean testicular weights being 4.25 and 4.72 mgm/gm of body weight, respectively. On t-testing it

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was found that the greater atrophy in the "adapted" group was significant at the 2% probability level.

E. Discussion

No evidence of adaptation or acquired radioresistance was demonstrated in the present studies. No increase in survival was obtained in either of the experiments in which lethality was used as the biological end point nor was there evidence of adaptation in the testis when testicular weight was used as an endpoint.

Reasons for failure to duplicate the results obtained by Cronkite et al (38) require consideration. It should be pointed out that whereas Cronkite used White Swiss mice as experimental animals, CF-1 mice were used in the present study. The strain difference, however, probably does not account for the divergent results since adaptation phenomena have been described in a wide variety of animals. It seems more likely that a freak statistical occurence either in their data or in ours accounts for the differences. Cronkite obtained data indicating less than 1 chance in 20 that the values obtained were due to chance. Either their data showed a significant difference entirely by chance (the odds being greater than 20 to 1 against it) or by a similar chance happening our data did not show a significant difference (the odds in this case not being calcuable). Further study is, of course, required to resolve these differences.

The failure to find adaptive resistance in the testis is in agreement with the findings of Bloom (27). The spectacular degree of acquired resistance reported by other authors (34-36) is unexplained. There were differences in the methods of giving the "adapting" radiation doses, however, which must be investigated before it can be categorically stated that adaptation does not occur in the testis.

TABLE 1

RESULTS OF ATTEMPTS TO ADAPT MICE TO RADIATION.

EFFECT ON SURVIVAL AND TESTICULAR WEIGHT.

Animals	'Adaptive' Dose	Test Dose	Result
43 CF-1 female mice	144 r/week for 3 weeks	703 r	12/43 or 28% survival at 30 days
43 CF-1 female mice	None (controls)	703 r	10/43 or 23% survival at 30 days
34 CF-1 female mice	144 r/week for 3 weeks	None	34/34 or 100% survival at 30 days
13 C3H female mice	1 r/day, 5 days a week, for 6 weeks	720 r	0/13 or 0% survival at 30 days
12 C3H female mice	None (controls)	720 r	1/12 or 8% survival at 30 days
16 C3H male mice	1 r/day, 5 days a week, for 6 weeks	150 r	Mean testicular wt. 4.25 mgm/gm body wt.
15 C3H male mice	None (controls)	150 r	Mean testicular wt. 4.72 mgm/gm body wt.

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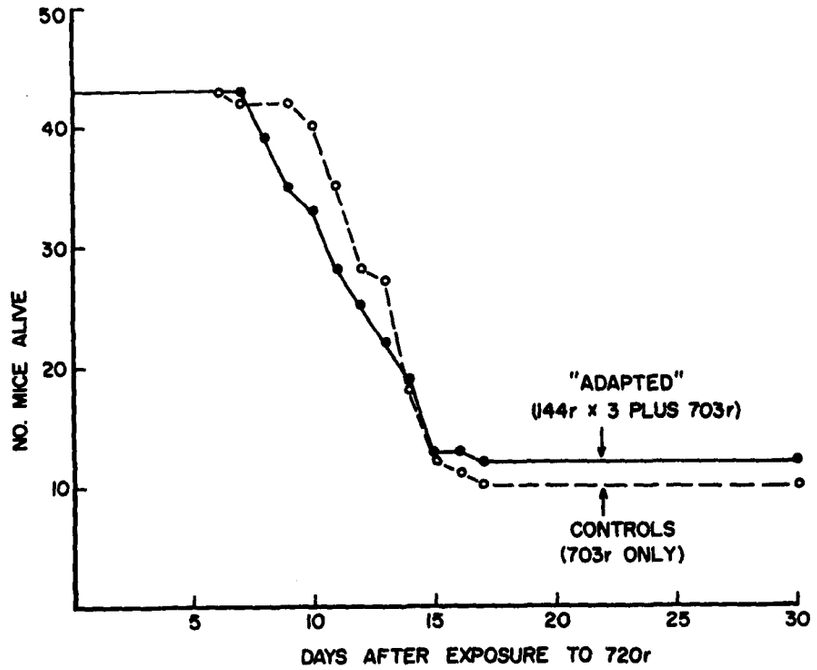

FIGURE 1. SURVIVAL OF CONTROL AND "ADAPTED" MICE AFTER 703r. "ADAPTED" MICE RECEIVED 144r AT 3 WEEKLY INTERVALS PRIOR TO EXPOSURE TO 703r.

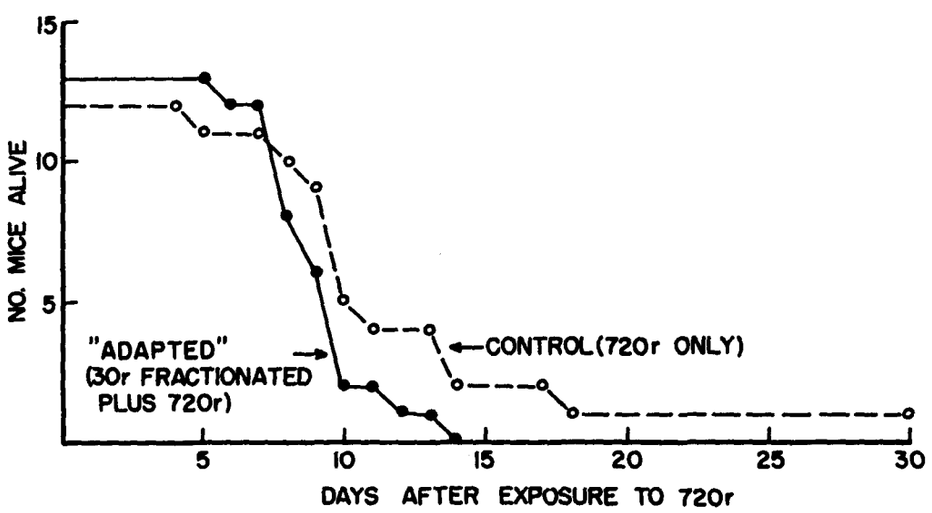

FIGURE 2. SURVIVAL OF CONTROL AND "ADAPTED" MICE AFTER 720r TOTAL BODY RADIATION. "ADAPTED" GROUP RECEIVED 1r/DAY, 5 DAYS A WEEK, FOR 6 WEEKS PRIOR TO 720r EXPOSURE.

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V. FACTORS TO BE CONSIDERED IN FUTURE RESEARCH*

At first glance it would appear that in studies on adaptation there are nearly an infinite number of variables to be controlled. Among the problems facing the investigator are the choice of animals, end point for evaluating the effect, tissue to be studied, magnitude and spacing of the adaptive doses, and the time interval for and size of the test dose. Failure to obtain positive results in an experiment might be blamed on any or all of these factors. Further consideration of the problem, however, indicates that the choice of experimental conditions can be narrowed and that certain approaches are more likely to lead to definitive results than others.

The choice of experimental animals should make little difference. If adaptation of biological material to radiation is a general phenomenon then one species should be as good as another. Whenever possible the end point for evaluating results should be amenable to quantitative estimation. Much of the data presented in the literature is difficult to evaluate since the results were measured in terms of a subjective estimate on the part of the investigator. Storer and Langham (40) have summarized elsewhere some of the methods for quantitative evaluation of radiation effect on mammalian systems. Among the quantitative end points available are: lethality; extent of atrophy of the spleen, thymus, testis, and intestine; duration of depression of mitotic activity; and degree of depression of radioiron uptake by red cells. All these end points are quantitatively related to radiation dose and, depending on the one chosen, radiation doses as low as 5 r or as high as 100,000 or more r may be employed. If quantitative differences in response of one of these test systems could be established in "adapted" and control animals there would be no difficulty in evaluating results.

The tissues most likely to show adaptive phenomena appear to be the spleen and intestine, judging from data available in the literature. Other tissues should be studied since the establishment of lack of adaptive ability would also be of value. Since there are likely to be differences in adaptive ability of various tissues it may not be possible to adapt the entire animal to radiation exposure. If some vital tissue, e.g., the bone marrow, is unable to adapt then

*The following section was written primarily for guidance in studies in this laboratory. It is included since it may be of general interest to other radiobiologists.

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no lessening of the lethal response may result even though other tissues such as the intestine may have become adapted. For this reason it might be advisable to shield certain tissues during exposure to the adaptive and test doses of radiation in order to determine if the remaining tissues are more resistant to lethal effect. Total-body exposures should also be made, of course, since it is still uncertain whether adaptation of the entire animal can occur.

The question of the optimum size of the adapting doses is the most difficult to answer. On the basis of the encouraging results obtained by W. Bloom (27) and M. Bloom (28), it appears that daily doses of less than 100 r might serve well as a starting point.

The optimum time between the last adapting dose and the test dose appears to be about one week or less for normal tissues. This variable along with the size of the adapting doses requires considerable investigation. The test dose should apparently be kept relatively low in the case of tissues although a lethal level is necessarily required for study of adaptation of the entire animal.

In summary the following specific recommendations are made for purposes of guidance in the design of studies on adaptation:

1) Quantitative end points for evaluating results should be used. Among the quantitative end points available are determination of the weight of the spleen, thymus, testis, and intestine; tabulation of survival time and ultimate lethality; measurement of degree of depression of the uptake of iron by red cells (using isotope technique); and determination of duration of depression of mitotic activity by repeated counts of the mitotic activity.

2) Adaptive doses should probably be given daily for one to three weeks. The size of the dose should be less than 100 r. Since M. Bloom obtained adaptation with 50 r/day this level might be used at the start.

3) The test dose should be relatively large compared to the adaptive doses but should be less than lethal, except in studies using the lethality end point. Since all the other end points (except mitotic depression in some instances) are quantitatively related to dose in the region of 200 r, this dose might be advantageously used.

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4) One week or less should elapse between the final adaptive dose and the test dose.

VI. CONCLUSIONS

It is well established that a variety of human and animal tumors, as well as certain normal tissues have the ability to adapt to the effects of ionizing radiation. It is not known with certainty whether or not an entire animal can adapt and thereby raise the dose required to produce lethality. In the experimental studies in this laboratory, there was no evidence of ability of mice to adapt to total-body radiation. No evidence of adaptive ability was demonstrated in testicular tissue.

It is concluded that the field of adaptation has been inadequately explored and that further studies are indicated.

VII. RECOMMENDATIONS

A systematic study employing quantitative methods for measuring radiation effect should be initiated to evaluate the extent, mechanism, and possible application of the adaptation phenomenon.

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