UCCM / RCC1.958200.009c

Biological Effects of Small Doses of Radiation in Relation to Diagnostic X-Ray Exposure

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Presented, in less detailed form, in the Symposium on Reduction of Radiation Dose in Diagnostic X-Ray Procedures, at the Thirteenth Annual Meeting of the American Association of Physicists in Medicine, Houston, Texas, July 6-9, 1971.

As I understand my assignment this morning, I am to try to give some sort of general background on radiation exposure at low levels of dosage, how the radiant energy interacts with the tissues and cells of our bodies, what effects it may cause there, and what relation such radiation may have to the health of mice and men. I think the best thing for me to do is to describe very briefly some of the findings made in laboratory experiments and in clinical studies wherever possible. We need consider only those dosage levels expected to be received in medical diagnostic x ray exposure which may be of biological and medical significance. At the same time I want to raise a number of questions relating to low dose exposure of the developing ovum and fetus, because from studies on external radiation in the dose range which is more relevant to our discussion, these experiments and clinical studies are perhaps more widely or better understood in terms of cellular injury during proliferation and differentiation. There is abundant radiobiological evidence that the delayed mutagenic effects of various ionizing radiations of external or internal sources or of different LET are not necessarily dissimilar, and while differences in degree and kind may be observed, the implications are that at the level of fundamental biophysical processes in cells and tissues, the responses ultimately share common mechanisms. And lastly, I would like to conjecture with you on the importance of reduction of unnecessary diagnostic x ray exposure in medical practice, to try to get you to stand up and argue with me and with members of this symposium, or preferably argue with others in this room.

The Concept of Small Dose

At the outset it is important to provide some concept of small doses of ionizing radiations --- this is not easily defined, since what constitutes a small dose in given experimental or clinical circumstances can hardly be the absolute magnitude of the absorbed dose. For example, a dose which causes very few mutations in, say, a bacterium such as *E. coli* will cause many more of them in a mammalian cell, for example, a HeLa cell in culture. Further, the criterion of a small effect is not satisfactory, since the smallness of an effect is frequently difficult to define in quantitative terms. The matter becomes further complicated when a measurable effect which requires a small dose of one radiation may involve a relatively large dose of another radiation. To the cellular radiobiologist, it is always possible to cite pertinent examples of low dose effects in those situations where abnormalities of anatomical structure or physiological function are formed which are sufficiently striking to attract attention. But in such instances, the precision of the optical or electronic equipment, and particularly of automated equipment, or the endurance of laboratory personnel in scoring the experimental data invariably set the limit for the demonstration of radiation effects.

The Scope of the Problem

Insofar as this symposium deals with problems of medical diagnostic x ray exposure, I have chosen, for practical reasons, to discuss a number of selected topics in human and mammalian radiobiology relating to cases where only tens of rads, or even much less, are needed to produce measurable somatic or genetic effects. Occasionally, nevertheless, there will be reason to

discuss effects of higher doses, when it seems likely or possible, that the same effects occur, although with a low probability, following small doses. The nature and scope of the excellent papers which you heard yesterday, and which will continue today, have made it necessary for me to omit from discussion many relevant problems in radiation protection --- such as long-term irradiation at low dose rates and shortening of the life span in mammals, biophysical radiation effects concerned with the response of nervous tissues and sensory organs and behavioral studies in mammals, and the effects of radionuclides in cells and tissues of the body. I have chosen to limit my comments, therefore, primarily to the effects of relatively small doses of ionizing radiations on the reproductive biology, growth and development and neoplasia in the mammal --- and the human wherever possible --- to discuss those areas which are most interesting to me and to quote those experimental and clinical studies with which I am most familiar. This has necessitated some repetition and some omissions --- and I ask that these frailties be forgiven due to a limited experience rather than to insularity.

I should like to begin our discussion with three arguments which I consider to be central to our thesis on medical diagnostic x ray exposure. Each may be refuted, but none can be denied. The first is that it is essential to minimize unnecessary radiation exposure of the patient while obtaining the clinically necessary information, and to minimize the doses that could be considered safe for radiological personnel to receive regularly in the course of their normal work. The second is that medical x ray diagnostic exposure of members of the public has become a much more complex problem with

increasing evidence that occasional harmful effects occur even at low doses or dose rates. Therefore, it has now become important to establish levels of radiation exposure which are not absolutely safe, but rather those which are considered as appropriately safe for the medical circumstances in which they need to be received. And thirdly, the essential problems remain quantitative and quantitative questions require quantitative answers. This becomes apparent when the question is on the level of dose which, to a high degree of certainty, may result in detectable impairment of hematopoietic, testicular, ovarian, visual, or any other tissue function. Thus, information on the magnitude of risk from radiation is of practical value for defining exposure criteria only if it refers to the very low doses which can be considered appropriate levels for the patient, for the radiological worker, for the individual or for the population at large. The task of constant review of existing data and for obtaining new knowledge arises from the need to assess the biological effects of these low doses of radiation encountered in the delivery of radiological health care.

Medical diagnostic x rays represent by far the largest man-made source of radiation exposure to the general population at the present time. In 1964 in the United States, 506 million x ray exposures were given to 108 million persons, or to approximately 60% of the population (1). By 1970, an estimate of approximately 70% of the population would be conservative. Of particular concern is the annual genetically significant dose received by the population as a whole since this will determine the rate at which genetic mutations are introduced into the population pool. From this standpoint it is the total population dose that is important. From a recent survey

of x ray exposures during radiographic examinations, it was estimated that the average annual genetically significant dose from diagnostic x rays to the entire population of the United States for the middle-aged groups was approximately 55 mrads per year, or about half the natural background exposure. This has been considered as a conservative underestimate, and could be off by a factor of two. At present, exposure from therapeutic radiation and diagnostic radioactive isotopes in medical practice affect only a relatively small fraction of the population. Their importance, however, is steadily increasing. In the future, medical radiation exposure to the world population as a whole will probably increase significantly with the development of new radiological procedures and the increased availability of advanced medical care throughout the world.

The evidence which concerns the effects of radiation on an established pregnancy as well as on the maturing human ovum and the zygote is limited. This is understandable, since the techniques required for such experimental studies preclude application to human beings. However, certain valuable information is available which bears on defining the major problems. The target organs concerned are (1) the ovary and the oocyte population of any female of child-bearing age, (2) the ovary or testes of any fetus exposed *in utero*, and (3) the fetus exposed *in utero*. There are two distinct categories of the radiation hazards: the *somatic* hazard which affects only the individual exposed, and the *genetic* hazard which affects future generations. The lines are not clearly drawn here, since both the mother and the fetus may be irradiated. For example, the somatic hazard could be such that

irradiation at a very early stage in pregnancy may lead either to failure of implantation or fetal failure by death of the embryo; this probably would go unnoticed. Or, it may lead to the induction of cancer, in particular, leukemia. On the other hand, the possibility of developmental abnormalities in the offspring, such as mongolism, or trisomy of chromosome 21, is one which gives rise to some concern among patients and physicians. On the basis of existing evidence, it would appear that the risk of such abnormalities arising from doses that are commonly given in diagnostic radiology is somewhat remote. The genetic hazard is not to the developing fetus, but to the gonads of the fetus and to the ovaries of the mother. The genetic risks are not as well documented as the somatic hazards, but appear to be less. From the point of view of diagnostic radiological exposure, however, these risks are not necessarily restricted to pregnant women.

From the radiobiological aspect of somatic hazards, cell <u>killing</u> is important in that (1) the reduction in the number of maternal oocytes may lead to premature sterility, and (2) the death of fetal cells may result in fetal abnormalities. The final outcome will depend on the capacity of the remaining cells to repopulate or repair the damage, to make more efficient use of surviving cells. Thus the cells <u>surviving</u> diagnostic radiation procedures are important, and rather the sensitivity of gonadal and embryonic systems cannot be judged solely by the cells killed. The <u>genetic</u> effects produced in the surviving cells are equally important. <u>Dominant lethals</u> may cause cell deaths, but other effects which result in a genetic detriment to live children can lead to severe fetal abnormalities.

The radiation doses relevant to effects on the developing ovum and fetus are the dose to the ovary and the dose to the fetal bone marrow. There are data on the doses incurred in diagnostic x ray examinations of the obstetrical abdomen and pelvimetry. In these studies in England (2), the average ovarian dose per examination of the obstetrical abdomen was approximately 0.4 rad, and for pelvimetry, 0.75 rad. The corresponding values of the mean fetal bone marrow dose was 0.5 rad and 1.1 rads, respectively. Values for both examinations were spread, but ovarian doses and fetal bone marrow doses of up to 5 rads were recorded, and a large proportion was of the order of 2 rads. No evidence is available for radiation effects of such low doses on adult tissues other than the bone marrow, nor have there been convincing experimental results on mammals reported using the relatively small doses which apply to the diagnostic range. The scale of experiments necessary to detect any somatic or genetic radiation effects from such small doses would be large and cumbersome. There appears to be experimental evidence, however, that there are no threshold levels. Although the expected effects would occur with extremely low frequencies after a few rads, nevertheless cell killing, mutational and teratogenic effects must occur with small doses even if at extremely low frequencies.

When defining the scope of certain of these problems of medical diagnostic x ray exposure in the evaluation of tisks from radiation, at least three important areas must be considered: oogenesis or the maturation of the human ovum, organogenesis in the fetus, and the induction of leukemia and other childhood cancers. A 1965 report of the International Commission on

Radiation Protection (ICRP) (3) included a recommendation that "all radiological examinations of the lower abdomen and pelvis of women of reproductive capacity that are not of importance in connection with the immediate illness of the patient, be limited in time (to the period of the ten day interval following onset of menstruation) when pregnancy is improbable. The examinations that it will be appropriate to delay until the onset of the next menstruation are the few that could without detriment be postponed until the conclusion of a pregnancy or at least until its latter half." This recommendation arises out of the recognition that very real hazards of small doses of radiation to the human zygote, embryo and fetus may exist which could very well affect the public health. The experimental and clinical evidence indicates that the important effect is on the development of individuals, as embryos, male or female, irradiated completely when they are particularly radiosensitive and therefore vulnerable. The doses of radiation of concern are those involved in medical examinations and which under the present rate of increase of diagnostic radiological examinations in the United States, could apply to a relatively large proportion of the adult population. The burden of this message found in the Second Report of the Adrian Committee (2) is that "only essential examinations should be carried out during pregnancy and particular care should be taken to avoid irradiation of the foetus whenever possible. In all women of childbearing age the clinician requesting the examination should never overlook the possibility of pregnancy." The important experimental evidence indicates that there are increased periods of radiosensitivity of the maturing mammalian ovum, the

zygote, and the embryo during the stage of organogenesis. This is shown by embryonic or fetal death or maldevelopment which may follow high dose irradiation at critical periods in the early part of pregnancy. Further, there is no evidence of threshold doses for some radiation effects, such as leukemia. There has also been shown that a causal relationship appears to exist between irradiation in utero at the level of dose used in obstetrical radiology, and the subsequent development of leukemia and other malignant diseases in the children of such pregnancies. Such a relationship may exist for exposures made at a time before pregnancy is even suspected. The relevant radiobiological problems which concern the radiological scientist here, therefore, fall into three broad categories: (1) irradiation of the ovum and during organogenesis; (2) induction of leukemia and childhood malignant disease; and (3) the genetic hazard.

Maturation of the Ovum

After an unknown number of mitotic divisions, the female germ cells, the oogonia, undergo meiosis and enter on their lives as oocytes. Some degenerate and others become dormant in the dictyotene stage of the prophase of reduction division. A large proportion of these subsequently degenerate, so that the stock of germ cells decreases once the oogonia cease mitotic division (Figure 1). The peak number of oocytes in the human ovary is approximately 7 million. This is reached by the fifth month of gestation, and a female baby is born with some 2 million oocytes (Figure 2). Of these, about half show signs of spontaneous degeneration at the time of birth. The number of oocytes in the adult is correlated with age, and although only

approximately 360 follicles are destined to ovulate in the course of a woman's reproductive life, the population of oocytes drops from some 2 million at birth to zero or very few at the menopause. Variability between individuals, even when age is taken into account is very high. The process of reduction division from the dormant dictyotene stage of prophase is resumed just prior to ovulation in the small proportion of the total stock of germ cells which will proceed to ovulation in each reproductive cycle. Ovulation occurs on or about the fourteenth day of the cycle. In a woman ovulating at, say the age of 40, the oocyte concerned will have been in a resting, or dormant and nondividing, but radiosensitive stage, for 40 years.

From studies on experimental mammals, we know that susceptibility to radiation induced cell death depends, in part, on the developmental stage of the germ cell. Sensitivity is high during the period oogonia reach their peak of mitotic activity. The period in the rat corresponds to the developmental stage in the human at the fifth month of gestation, but the development of germ cells is less well synchronized in the human that in the rat fetal ovary (Figure 2).

Radiosensitivity is relatively low during the early stages of meiotic prophase, but increases with the onset of the dictyotene stage, when the oocyte develops into a primary follicle (Figure 3). Primary follicles in the pre-ovulatory stage are extremely sensitive in the rat, mouse and rabbit; but other species of mammal, such as the guinea pig and the monkey, behave differently. In general, radiosensitivity appears to increase just prior to ovulation (4).

The doses of ionizing radiation required to kill a given proportion of the total stock of primary follicles also varies enormously among species. An acute exposure of 10R will kill half the primary oocytes in the mouse, 100 R in the rat, and possibly well over 1000 R in the monkey (5). There is no such information on man, but from radiotherapeutic experience it is known that a single acute dose of approximately 400 to 500 R to the ovaries can cause cessation of menstrual periods in a large proportion of women between 30 and 40 years of age. That is, this dose can destroy the entire follicular apparatus of the human ovary in some women.

Almost all the radiobiological information available relates to data on mouse and rat experiments, and these are, with much caution, extrapolated to situations which may obtain in man. Two important generalizations may be made from extensive rodent studies. First, the oocyte's genetic radiosensitivity in terms of mutational yield increases as its somatic radiosensitivity decreases. Thus, Russell (6) has found in mice that acute irradiation of the mature oocytes gives a high frequency of recessive mutations, but this falls to practically nil with immature oocytes, that is, in later litters. Fetal oocytes seem to have an intermediate sensitivity. Second, the radiation induction of dominant lethal mutations, which result primarily from chromosomal breakage and loss, increases greatly as oocytes pass out of the resting stage, and radiosensitivity reaches a peak soon thereafter, that is, in the first meiotic metaphase, when 100 rads of acute irradiation to mice or rats induces about 50% dominant lethals. Sensitivity remains high until after fertilization.

Those who are not impressed with the similarities between mice and men

must not make hasty judgments that such animal studies have little relevance to problems in clinical diagnostic radiology. Comparable in vivo studies certainly cannot be made in man. But dissimilarities exist. At present, for example, radiation genetics research deals with species with a short gestation period, such as the mouse or rat, but the effects of radiation on the mouse and the doses and dose rates involved are of little help in quantitating with some degree of precision the genetic risk to human offspring. In addition, the radiation effects and genetic risks to primitive oocytes differ in the rodent and in the primate, in part, because of species differences, but also because the arrested meiotic stages are not identical. Further, the susceptibility to radiation induced cell death differs by a large factor, and it may be expected that genetic mutagenesis also differs. It is not known whether primordial oocytes which survive irradiation long enough to continue through growth and ovulation are free from lethal chromosomal aberrations. However, for oocytes in growing follicles irradiated at ovulation, the chances of a mutation getting through to fertilization and subsequent development are high, although some will die as dominant lethals. Those that survive and those irradiated as early zygotes may bear serious chromosomal aberrations.

A number of practical questions arise when an attempt is made to extrapolate from mouse to man. For example, a woman ovulates only some 400 oocytes during her reproductive life, and doses of diagnostic x rays are much less than given to mice under controlled experimental conditions. Can some estimate be given of the chance of any of the live human births bearing

mutations? Second, in mice, 100 rads given in small doses will have little effect on the mutation frequency in offspring, whereas 100 rads given acutely can give a measurable increase. Since women are likely to receive a number of very small doses during repeated diagnostic examinations, should a similar lessening of the genetic hazard be expected? Is the genetic hazard to the zygote or embryo greater or the same than at any other time, and is there an increased radiosensitivity associated with pregnancy? Lastly, can some estimate be given of the harm likely to occur to future generations from irradiation at the dose levels currently used in medical diagnostic radiology?

Organogenesis in the Fetus

The embryological development of man, particularly in relation to the temporal pattern for the induction of developmental errors, is now well known. In mammals, cleavage and gastrulation during the pre-implantation and immediate post-implantation periods are critical phases in development. During the pre-implantation stage irradiation causes a high rate of prenatal mortality; in the mouse 200 R may kill 80% of the embryos (Figure 4). In the post-implantation stage, extensive cell movement and differentiation occur in a delicately balanced situation. During these critical periods in the development of the mammalian embryo, embryonic organ or tissue, teratogenic agents, such as x rays, are more likely to produce structural defects or changes in the physiological mechanisms. Since all organs and tissues do not develop at the same time, a wide range of abnormalities may be produced by a given teratogenic agent. As a general rule, a period of high susceptibility is

usually succeeded by a less susceptible period.

Based on the work of the Russells (6), low dose exposure of pregnant mice damaged the embryo if delivered at certain periods during the stage of organogenesis. In fetal rats and mice, as little as 25 R killed neuroblast cells within only a few hours. They also found the critical sensitive periods to be discrete and quite short, and related to the temporal pattern of organogenesis. For example, when 300 R was given at 8 days, surviving mouse embryos were free of gross malformations, but only 1 day later, central nervous system and facial deformities were frequent after exposure to only 150 R (Figure 5). The earlier the stage of development, the fewer are the cells which comprise the embryo, but such cells are the precursors of all cells of the developing fetus. Damage to chromosomes, which is probably the major effect, can cause cell death or, if such damaged cells survive, can produce developmental anomalies. In general, therefore, it appears that the earlier the stage of development, the more deleterious is the radiation effect in surviving embryos and fetuses. Since neuroblast cells can be destroyed by as little as 25 R, and these embryonic cells are present in the human fetus from about 19 days after conception and are increasing in number and widely distributed until sometime after birth, exposure of the developing human to 25 R is probably hazardous. This level may well be reduced to less than 10R, or possibly even 5 R, with further experimental evidence. There are no convincing experimental data to show that developmental abnormalities are produced by doses of 1 to 5 rads.

Rugh (7) has examined over 300,000 mouse fetuses and has been able to determine the gestation age of greatest radiosensitivity and the range of

threshold which may cause the various congenital abnormalities. Here, the similarities between mice and men are important, since every mouse anomaly produced by radiation is similar to human abnormalities purported in the literature as caused by radiation. Some qualitative inferences may be drawn from these animal studies since the cases of unintentional, accidental, or coincidental exposure of the human fetus are so rare, and never have controls, that the possible causal relationship of radiation and the developmental anomaly cannot be proven. Indeed, some 2.5 to 5% of human live and still births have a gross malformation, even without any prior history of radiation exposure. On the basis of rodent experiments, some controlled monkey experiments, as well as the rare and isolated data from human experience, some valuable information which may relate to human exposure has been obtained (Figure 6). During preimplantation (from 0 to 9 days during the human gestational period) irradiation with sufficiently large doses causes death rather than developmental anomalies. During the period of active organogenesis (from 9 to 42 days), irradiation causes severe structural anomalies, at diagnostic levels of exposure of possibly 25 R or more. During the succeeding weeks of pregnancy, radiation anomalies are more funcational rather than structural, and may not be clinically apparent during the neonatal period.

The human data are limited primarily to fetal irradiation of mothers at Hiroshima and Nagasaki and the Marshallese, and these show an increased incidence of abortions and stillbirths, as well as late somatic damage in the offspring of microcephaly and stunting of growth. The genetic risk, however, may be smaller than that of late somatic effects. Therefore, the significant radiobiological endpoints, such as cell death and cell survival, become very

important when considering radiation hazards to the fetus. Cell killing, on the one hand, or genetic (or chromosomal) damage, on the other, at a certain stage of embryonic development can lead to severe fetal abnormalities. There is still a lack of convincing experimental evidence that radiation with low doses of the order of 1 to 5 rads can damage the human embryo if delivered during pre-implantation, in the early post-implantation stage, or during major organogenesis. In addition, there is no information on how much different the hazard is when irradiation is given to the offspring before ovulation, when it is given around ovulation when the sperm as well as the ovum may be involved, or when it is given before and after implantation when the zygote is at risk.

A recent study of the effect of diagnostic radiation on the human fetus reviewed results on 5,734 women of child-bearing age who had received abdominal x ray examinations in the same hospital; 152 had been irradiated during the first 4 months of pregnancy (8). The conclusions of that study were that no relation existed between the health of the children and irradiation, no teratogenic effect of irradiation was demonstrated, and a somatic effect could not be excluded. Whether any developmental abnormalities can be produced by doses of the order of those given in the course of diagnostic radiography still is uncertain. Some evidence exists, however, which associated with a slight increase in incidence of heterochromatic wedges in the iris of children irradiated *in utero* during the seventh month, and this has been interpreted as a somatic mutation. Most other reports, however, are open to many criticisms and add little, if anything, to the weight of existing evidence.

The Genetic Hazard

The experimental evidence on mice, rats, and dogs exposed continually to gamma irradiation or small daily doses of x rays indicates that normal reproductive function is maintained after daily doses of approximately 2 R. However, the investigations of Russell (9) suggest that there is no threshold dose rate effect for genetic mutation induction in mice. In extensive and elegant studies on the dose rate effects of radiation delivered at 90, 9, 0.8, 0.009, and 0.001 R per minute, Russell examined the distribution of mutations at seven loci on the hereditary genome for mouse spermatogonia. The data demonstrated that the proportion of mutations which was prevented by repair of premutational damage at low dose rates was constant for all loci. This indicated that the irreparable portions of mutations, that is, the mutations that still occur at low dose rates, were probably not qualitatively different from the repairable ones.

The significance of this work requires that this series of experiments deserves careful review. Russell used the technique of induction of specific locus mutations in which mutations at gene loci are produced by irradiating a homozygous dominant mouse and crossing it to a mate homozygous for the recessive mutant allele; the affected progeny will show a mutant character. This technique has provided important information for radiation guidelines on genetic effects; the studies are mainly concerned with the effects of small doses on mutation frequency and the effect of the interval between irradiation and conception on the mutation frequency in female mice. The central issue is that repair of single-hit mutational or premutational (that is, leading to

mutation induction) damage occurs at low dose rates, but at high dose rates, this repair process is either damaged or saturated. In other words, at the higher dose rates, a single-hit mutation will fail to repair because other hits damaged the repair process, or have caused other radiation damage that has saturated the repair mechanisms. A fractionation study on the mutation frequency in female mice exposed to single and fractionated doses of 90 R per minute x radiation demonstrated that the total dose of 400 R delivered in two fractions of 200 R at an interval of 24 hours yielded a mutation frequency similar to that given by a single 400 R exposure. When comparison of mutation frequency was made following exposure to small -- (50 R) and large (400 R) doses of x radiation, it was apparent that the mutation frequency at the lower dose was only one-third of that expected on the basis of a linear relation with the mutation frequency at 400 R. It appeared, therefore, that in oocytes, a large component of the repair mechanism that could occur at the low dose rates could also occur at the high dose rates when the total dose was only 50 R. Russell had observed that 400 R of continuous irradiation delivered at 0.8 R per minute gave a reduced mutation frequency compared with that from a single 400 R exposure of 90 R per minute. He therefore compared the mutation induction of a single large dose of x rays with that delivered in small fractions and demonstrated that when eight 50 R fractions were delivered at 75 minute intervals to a total dose of 400 R, that is, delivered over a period equal to that in the previous study, it was evident that a reduced mutation frequency resulted. And finally, he demonstrated that the interval between irradiation and conception had an effect

on mutation frequency in female mice; he examined the mutation frequency at two intervals after irradiation in female mice, in which the interval between radiation and conception was either up to 7 weeks, or more than 7 weeks. The observed mutation frequency in the later matings was significantly below the rate of early matings.

These and a second series of experiments by Russell are summarized very simply in Figure 7. Here the determinations of the specific locus mutation rates in spermatogonia and oocytes in mice are expressed as the function of radiation dose and dose rate (9). The mean number of mutations per locus per gamete is plotted against the dose of irradiation (upper curve, x rays at 90 R per minute; lower curve, chronic gamma irradiation at 90 R per week); the curves are for spermatogonia, and the experimental points are the mutation rates in oocytes. The evidence suggests that in mouse spermatogonia, mutations increase linearly with dose, and strongly suggest an essentially linear response even at low doses. There are fewer mutations induced at low dose rates than at high dose rates both in irradiated spermatogonia and in oocytes. Whereas the spermatogonia surviving radiation may be synchronized in a mutagenically sensitive stage at the time of the second exposure, a significant degree of synchronization may occur after an initial dose of only 50 R to 100 R.

The greatest concern with the evaluation of the potential genetic hazards of diagnostic radiation is to children and young adults, rather than to older people for a number of reasons. Firstly, children and young adults have many years to accumulate genetic damage from radiation. Since they have not

completed their childbearing period, the genetic damage accumulated may be expressed. Secondly, it is not yet known whether young, somatically, radiosensitive children also have intrinsically greater sensitivity to genetic damage in relation to adults. Further, it is not known whether there is any interaction between radiation and other mutagenic factors in the environment, especially in the sensitive groups.

Thus far, the best quantitative information on human genetic risks comes from the Japanese survivors of the atomic bombings. As yet, there appears to be little direct evidence of genetic damage, except possibly for a suggestive alteration of sex ratio, in the direction expected if radiation induced X-linked recessive lethals were present in increased frequency. However, analyses of the Japanese data are complicated for a number of reasons, and it is still not clear whether any significant deviations in sex ratio were noted.

The information on human genetic risks from the Japanese survivors and from cytogenetic changes in occupationally exposed persons indicate that the present levels of radiation from medical exposure do not necessarily represent a discernible hazard. However, there can be no doubt that radiation is a mutagenic agent. In view of the fact that increased exposures to long lived radionuclides from fallout may persist for many generations, it is of importance to avoid any unnecessary increase in radiation exposures. Clearly, we are witnessing now and in the future a continuation of the steadily increasing level of necessary diagnostic and therapeutic medical radiation exposure.

The significance of the original experiments on radiation mutagenesis in Drosophila and the recent studies in the mouse bear directly on the problem of radiation induced mutation rates in man. Recent concern with environmental hazards of radiation and the estimation of the genetic consequences of radiation exposure in man have led to conservative exposure guides for individuals of reproductive capacity. In an effort to extrapolate to man observations made on the mouse, and information obtained from the few irradiated human populations, such as the Japanese survivors at Hiroshima and Nagasaki, it has been estimated that the dose required to double the mutation rate that occurs spontaneously primarily due to natural background radiation, is of the order of 30 to 80 R with an average of approximately 50 R. The estimates of the spontaneous mutation rate in man is still not precise, so that the doubling dose estimates have varied widely from a few roentgens to over 100 R. Estimates on man, in general, are close to the mutation rates determined for mice; the doubling dose range lies between 30 to 80 rads, but this value is not precise. More information is required on other species before we can depend on extrapolations to man.

Radiation Induced Neoplasia

Stewart and her colleagues (10) carried out a retrospective survey of mothers of some 1200 children in England, and concluded that diagnostic radiological examinations of a pregnant woman increased the risk of subsequent childhood leukemia and malignancy. MacMahon (11) confirmed these general findings from a prospective study based on the records of some 700,000 births in northeastern United States, and indicated that the ratio of incidence in

the irradiated group to that in the unirradiated groups was approximately 1.4 for leukemia, for cancer of the central nervous system and for other childhood malignancies. This would represent an increase of approximately 40% in both leukemia and other cancers following prenatal diagnostic examination. In addition there was some suggestion that the earlier stages of pregnancy may have had increased susceptibility, but these data are not precise, and that leukemia did not necessarily appear to be induced more than the other types of childhood malignancies. There are reliable data that the radiation dose in such radiological examinations is relatively low and within the range of 1 to 5 R. If it is assumed that the dose to the fetus was about 2 R, the incidence of leukemia and for other childhood cancers up to 10 years of age would be approximately 1 per 10,000 irradiated cases per roentgen. The incidence of leukemia in adults over a period of 10 years from exposure, based on data of the Japanese atomic bomb survivors and on radiotherapy patients with ankylosing spondylitis, is approximately 1 per 50,000 or 100,000 per roentgen. This would indicate that the fetus has a much greater susceptibility, possibly of the order of five to ten times, than the adult.

At the University of Chicago, for one year in 1948 every pregnant woman was given an abdominal x ray examination in the course of routine pelvimetry (12). The offspring are now being followed for long term effects. This study will allow some direct comparison between children irradiated *in utero* during that year and children born the year before and the year after when no radiographs were taken. The preliminary results on the 3,024 children,

1,008 of whom received a radiation dose estimated at some 1.5 to 3.0 rads *in utero*, revealed only a slight increase in frequency of hemangiomas in irradiated children, but no increase in leukemias or other malignancies or in anomalies of the eye or the central nervous system. These data have been supported recently by Jablon (13) of the Atomic Bomb Casualty Commission on a survey of leukemias and other cancers in children irradiated *in utero* in the Hiroshima and Nagasaki atom bombings.

Although the epidemiological evidence may be partly convincing, one should place all these statistics in proper perspective, nevertheless. From Stewart's work, the natural child death rate from malignancy before the age of 10 in England and Wales is about 1 in 1,200, whereas children having been irradiated as fetuses *in utero* have approximately twice the chance of dying of cancer before 10 years of age. Of the children dying of malignant disease, less than 13% were irradiated *in utero*, so that for most, the radiation hazard would appear irrelevant. Stewart believes that most childhood leukemias are determined genetically prior to conception, and it has been suggested that this may obtain for at least 75% of all childhood leukemias. Thus, there remains only some 4% of the leukemic children in which radiation may have played some part. The numbers are extremely small and thus the statistics become trivial. We know very little about the 96%, and even less about what conditioning factors, other than radiation, may be responsible for the remaining leukemias in children.

In any attempt to make a realistic assessment of the long term risk of neoplasia in man arising from a given exposure to radiation, it becomes

necessary to have a knowledge of the relative susceptibility of the various tissues of the body to radiation induced cancer, such as leukemia, and of the dose response relationships for given types of tumors. Until much more is known about the nature of the carcinogenic process, however, information about relative tissue susceptibility in man must come from man, and necessarily from those studies involving whole body or at least large volume irradiation. The most valuable investigations are those which concern only a small number of groups, namely, the survivors of the atomic bombings in Japan, the early radiologists, and patients who had ankylosing spondylitis treated by radiation to the spine and joints. The important fact that has emerged from the studies of these exposed human groups has been the increase in incidence of acute leukemia and chronic myeloid leukemia; both these diseases are relatively rare in the normal population. The data are less conclusive for other types of neoplasm. There were early reports of increased incidence of cancer of the stomach and other tumors among exposed Japanese survivors. In general, however, a number of epidemiological analyses, which have been following matched groups of 5,000 persons from Hiroshima and Nagasaki, give recent and important evidence of an increase in other forms of cancer, but much more information is required.

An assessment of the risk of radiation induced leukemia or other neoplasm would require additional information on two important problems, namely, the dependence of tumor incidence on age of exposure and the variation of tumor incidence with time after exposure. A comprehensive answer in human radiobiology would require far more information than is available at the

present time, but there are some valuable data from both experimental and clinical sources on leukemia studies, and a small amount on other malignancies. While the experimental studies, particularly those on mouse leukemogenesis, suggest a close similarity in the age dependence in certain radiation induced and spontaneous tumors, reliable human information on possible changes in age specific tumor incidence after irradiation are still lacking. For the Japanese survivors in Hiroshima and Nagasaki, the peak in leukemia incidence occurred at about 7 years after exposure but there is some evidence that the peak for acute leukemia was earlier than that for chronic myeloid leukemia. From the early data it was not possible to determine whether the age specific incidence for the exposed individuals would eventually return to the control values or would maintain a higher level indefinitely, but recent data suggest that the former situation appears to obtain.

The second important aspect of the problem of the age dependence incidence relates, in part, to the influence of age at the time of exposure on the radiation induced tumor yield. From the analysis of Doll (14) on the irradiated spondylitics in Britain, the increase with age of death from leukemia approximately paralleled that of the general population in England and Wales (Figure 8). In the Japanese survivors, however, the number of deaths from chronic myeloid and acute leukemia demonstrated much less age dependence than in the British study, and, in fact, in certain groups, appeared to be largely independent of age at exposure to radiation. The available evidence suggests, therefore, that a close relationship between radiation induced and spontaneous

incidence of leukemia may very well exist insofar as age dependence is concerned, but information on other malignancies in humans is required for any firm conclusions to be made. From both experimental and clinical studies there is evidence that with leukemia, at least of certain types, the radiation effect appears to be largely exhausted after a given interval.

The most difficult problem for which there is very little quantitative information is that of the dose response relationships for radiation induced human cancer. There has been much concern centering on one form of relationship, generally, a linear relationship, and this has not been a very difficult exercise in view of the lack of precision of the available data on exposure to low doses. The best data in regard to precision of information are again, those from the atomic bomb survivors and ankylosing spondylitis surveys. Nevertheless, the main limitation for determining the dose response relationship is due, in a large part, to the sparceness of clinical information. The data on the ankylosing spondylitics (15) are consistent with many forms of dose relationship (Figure 9); it has been suggested that a linear dose relationship exists at low radiation doses. However, until more information is available, these results do not necessarily help in estimating the risk at low doses from the data obtained at high doses. It is to a large degree for this reason there has been little alternative in calculating the risk to human populations but to assume a linear dose relationship for all types of somatic effects leading to neoplasia over the wide range of doses involved, and it is recognized that this may lead to a gross overestimate of risk. An estimate can be made of the leukemogenic risks to man of whole body exposure

based on the data from the Japanese survivors and ankylosing spondylitis surveys, provided that such linear dose relationships obtain, and if it is assumed that there is no appreciable effect of dose rate or fractionation. The estimate derived is one to two cases per year per roentgen per million persons irradiated. However, for other types of neoplasia, as yet no figures are available, and therefore, in calculating the risk to humans of whole body irradiation, it must be assumed at present that leukemia appears to be the major risk.

Public Health Considerations

Insofar as present levels of medical radiation are concerned, information on radiation exposure received by the population at present as well as projected exposure in the future is reasonably known. Further, approaches to estimating the attendant risk to the individual and to the population and efforts to put the potential hazards from radiation exposure in context, for example, by comparing population exposure from man-made radiations to that from other well known sources, and by comparing the degree of potential attendant risk with that of other everyday risks encountered in life, can place the concern of hazards to the public health in proper perspective.

The present evidence suggests that in regard to somatic mutations, acute leukemia and chronic myeloid leukemia are probably the long term effects of significance in irradiated human populations. From the data on the dose response relationships, there appears at present no alternative but to assume a linear relationship between dose and effect. For some types of somatic effects there may very well be a threshold dose, but for the induction of

leukemia and of many other types of neoplasm, it is likely that there is a finite risk even at the lowest doses. In other words, as appears to be the case for genetic effects, it has to be assumed that there is no safe dose for somatic effects, such as radiation neoplasia. It follows, therefore, that with the present state of our knowledge, the setting of any maximum permissible radiation level or radiation guide, must necessarily remain essentially an arbitrary procedure.

The ICRP recommendation that all radiological examinations of the abdomen and pelvis of women of reproductive age be limited to the ten-day interval following the onset of menstruation is an extension of that made by the Adrian Committee, namely, that particular care should be taken to avoid irradiation of the fetus whenever possible and that, in all women of child bearing age, the clinician requesting the examination should never overlook the possibility of early pregnancy. These recommendations point up a number of problems, since there are no guidelines to assess the risks to the adult or to the fetus of delaying or omitting certain radiological examinations, particularly where these concern the health of the pregnant and the nonpregnant premenopausal woman in clinical practice. Whereas the evidence indicates that doses as low as 10 rads at critical periods may be responsible for embryonic abnormalities in rats and mice, there are not sufficient data with doses as low as this in mammals more comparable to man. From a very practical point of view, many diagnostic procedures involve a dose to an early pregnancy of only between 0.3 and 1.0 rad. A number of important questions therefore arise in regard to public health recommendations, insofar as

they relate to medical diagnostic x ray exposure of the fetus, the growing child and the adult. (1) Should the radiologist protect a possible pregnancy from a dosage of this order by enforcing the ten-day rule? (2) Since there is a need for accurate menstrual history information from married and unmarried women for each relevant radiological examination, can this frequently indelicate information, if obtained, be considered reliable? (3) To what extent would exposure be diminished by reduction in the number of routine lumbar spine, pelvis and abdomen films permitted at any stage of the menstrual cycle? (4) In the light of our experimental and clinical information, should industry be urged to increase the speed of screens and films without loss of quality and to develop more sensitive methods of intensifying the image? (5) Should there be enforced use of fast intensifying screens and the strict limitation of field size as the most important practical measures by which a significant dose reduction can be achieved? (6) Should there be continued evaluation, control and approval of the radiological methods, much like drugs, weighing the information obtained against the small but recognizable risk involved to the public health? (7) And finally, based on limited knowledge about the somatic and genetic hazards to the developing human embryo and fetus which have been exposed to diagnostic radiological doses of the order of 1 to 10 rads or more, should public health guidelines be established which provide an intelligent approach to family counseling and therapeutic abortion?

Conclusion

The gap between our scientific knowledge required for the evaluation of

risks from radiation and our social demands for improved delivery of health care and living standards is widening, and the practical information necessary is seriously lacking. To the radiation scientist, such problems cannot remain isolated or sequestered in the laboratory -- they are the problems of man and his community. The scientist can provide only a limited amount of precise information -- he can weigh an apple and describe the color of a peach. But these problems he is asked to solve involve complex human variables, and appear as hopeless as to compare the weight of an apple with the color of a peach. Fundamentally, the decision to solve these problems is for the community rather than for the scientist alone, and the community or its spokesmen is constantly making decisions, with some degree of enlightenment, on matters that involve the balancing of incommensurable units of the benefits, and risks of human values -- justifying the costs of a hospital, the accidents to be expected during the removal of our mineral resources from the earth, the value of the transplanted heart, or the price of man's exploration of the universe.

It is now assumed that any exposure to radiation carries some risk of deleterious effects. Radiation and the public health, when it involves the public health, becomes a sociological and political problem possibly to be decided by men of business, government and law, and not just an exercise in statistical theory or laws of chance. Unless man wished to dispense with medical and industrial activities which invariably involve exposure to ionizing radiations, he must recognize that some degree of risk exists. In the evaluation of risks from radiation it is necessary to limit the radiation

dose to a level at which the risk is acceptable both to the individual and to his society, if he wishes to continue to derive benefits from such activities.

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LEGENDS TO ILLUSTRATIONS

Figure 1. Schematic representation of the stages of meiosis. The mammalian oocyte becomes arrested in the diplotene (or dictyotene) phase of the prophase of meiosis. Reduction division is resumed about 12 hours before ovulation.

Figure 2. The numbers of oocytes in fetal ovaries during gestation. In the rat, the peak number of approximately 75,000 is reached 4 days before birth, and decreases within the following week to about one-third. In the human, the peak number of approximately 7 million is reached by the fifth month, and the ovaries contain about 2 million oocytes at birth (T, full term).

Figure 3. Radiosensitivity during oogenesis. Radiosensitivity is low during the leptotene, zygotene and pachytene stages, and increases with the onset of the diplotene stage. Primary follicles are extremely sensitive in the mouse and rat.

Figure 4. Radiation effects during organogenesis in the mouse. Irradiation during the early part of the period of major organogenesis leads to prenatal death, and during the middle period, to neonatal death. A large number of different developmental abnormalities result from irradiation during major organogenesis.

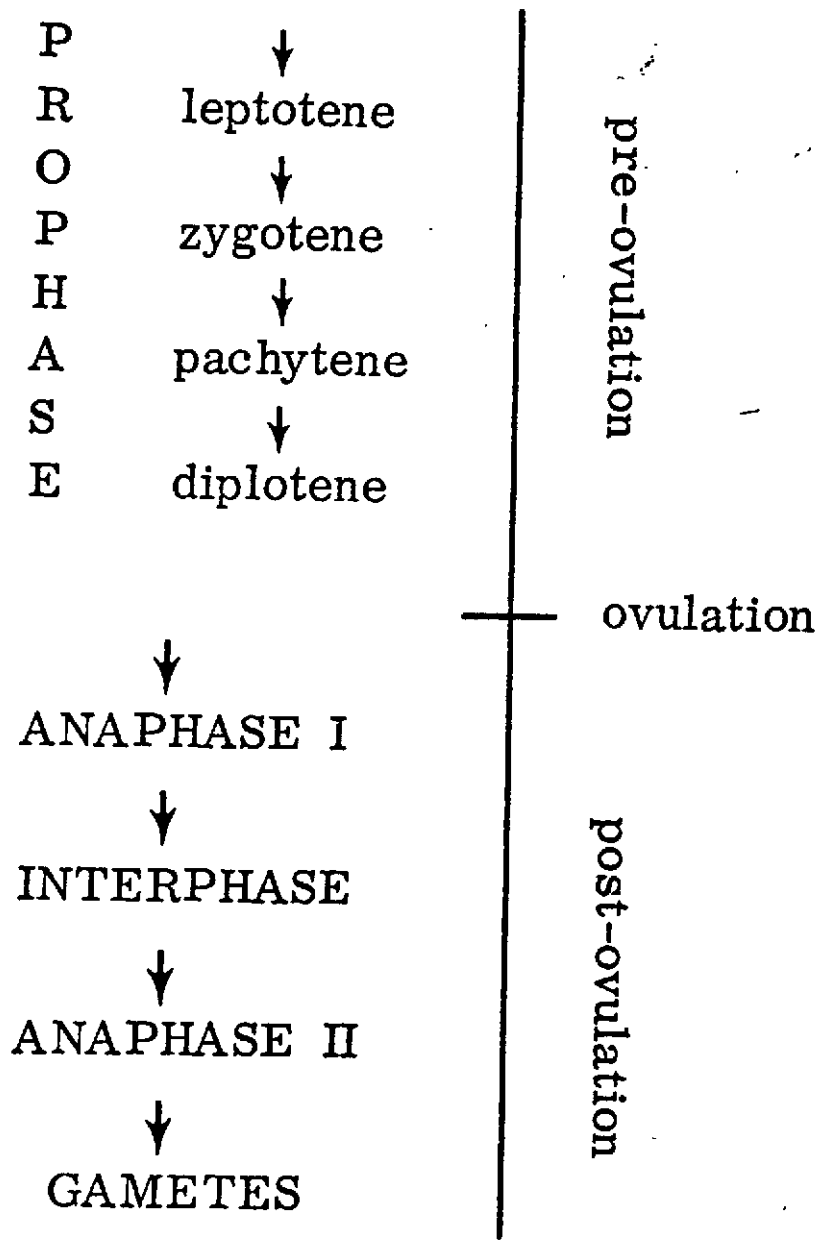
Figure 5. Schematic representation for critical periods of radiation induction of developmental abnormalities in the mouse embryo. The major changes occur in the central nervous system, eyes, skull, and axial and appendicular skeleton.

Figure 6. Diagrammatic representation of the production of prenatal and neonatal deaths and of developmental abnormalities at birth in mice following x-irradiation at different times before and after fertilization. The equivalent periods of embryonic development in man are: pre-implantation, 0 to 9 days; active organogenesis, 9 to 42 days; fetal development, 42 to term.

Figure 7. Specific locus mutation rates (mean number of mutations per locus per gamete x 10^5) in mouse spermatogonia and oocytes for various doses and dose rates. The lines are for spermatogonia; the upper line for high dose rate and the lower line, for low dose rate exposure. The circles and squares are for oocytes; the open symbols for high dose rate and the closed symbols, for low dose rate exposure (see text).

Figure 8. Analysis of age dependence incidence for the induction of leukemia in irradiated (R) ankylosing spondylitics in Great Britain (GB) and Japanese (J) survivors of the atomic bombings. The influence of age at the time of exposure on the radiation induced tumor yield is compared with appropriate control populations (S) in each country (see text).

Figure 9. Dose response relationships for the induction of leukemia in patients irradiated during treatment for ankylosing spondylitis. A linear dose relationship may exist at low doses. The 95% confidence limits are indicated (see text).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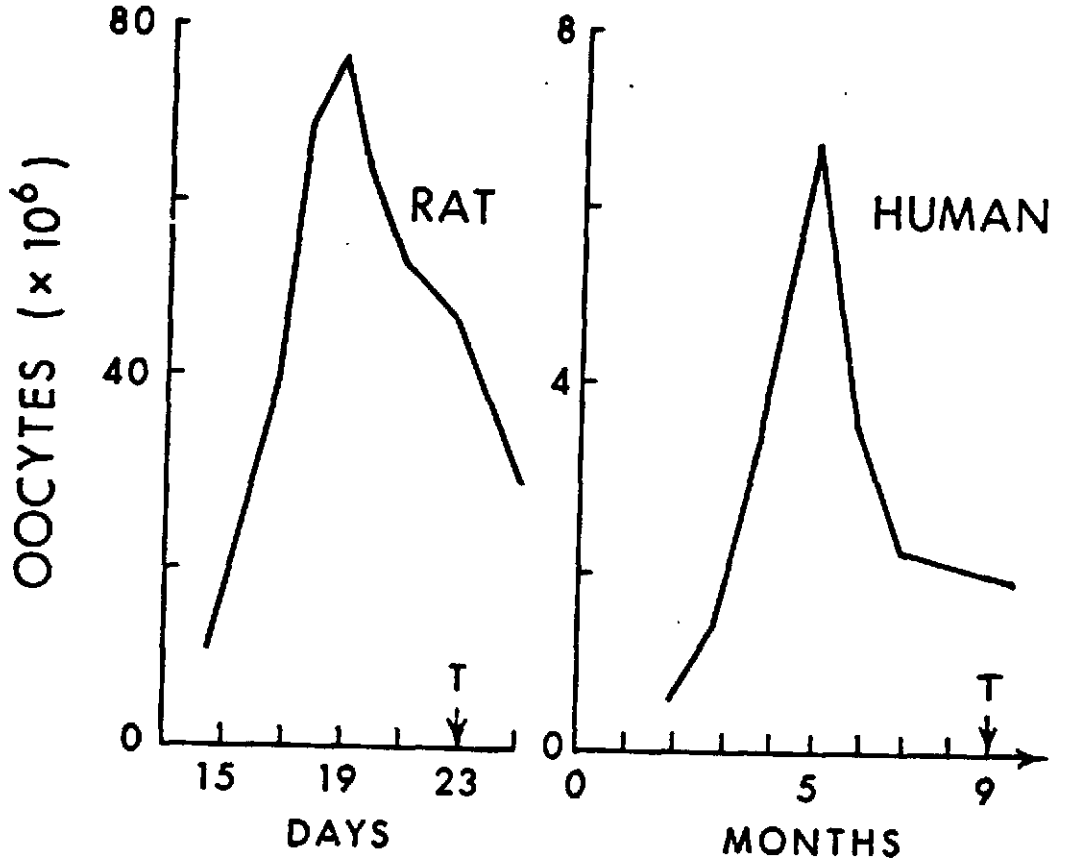
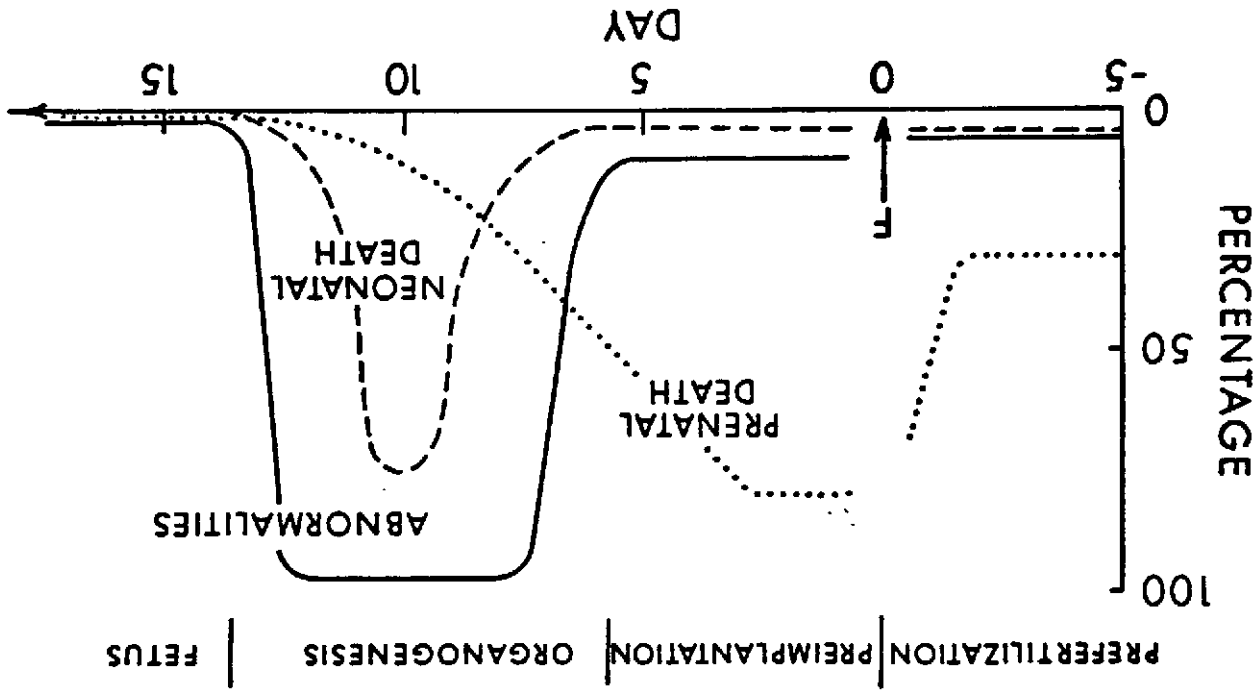


Radiosensitivity During Oogenesis

Stage	Sensitivity
early meiotic prophase	low
↓	↓
late meiotic prophase	increasing
↓	↓
pre-ovulatory primary follicle	high
↓	↓
ovulation	very high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PRENATAL DEATH
NEONATAL DEATH
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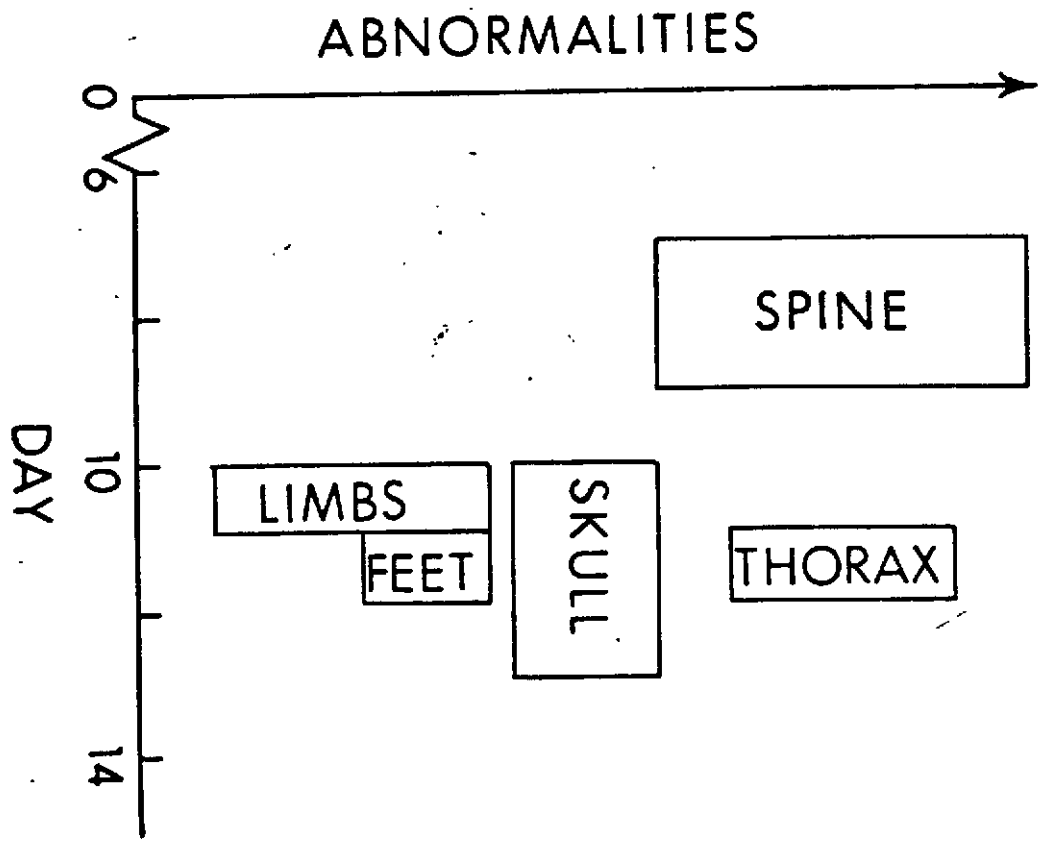
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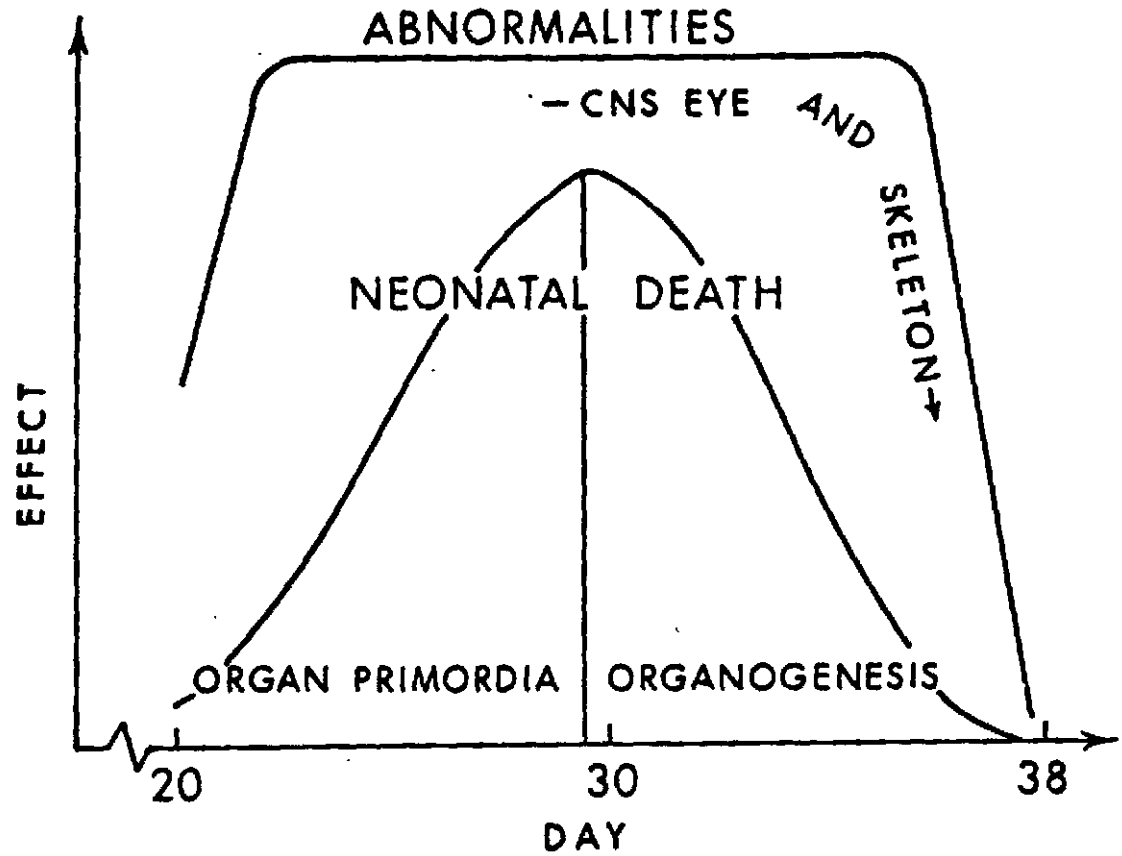
THORAX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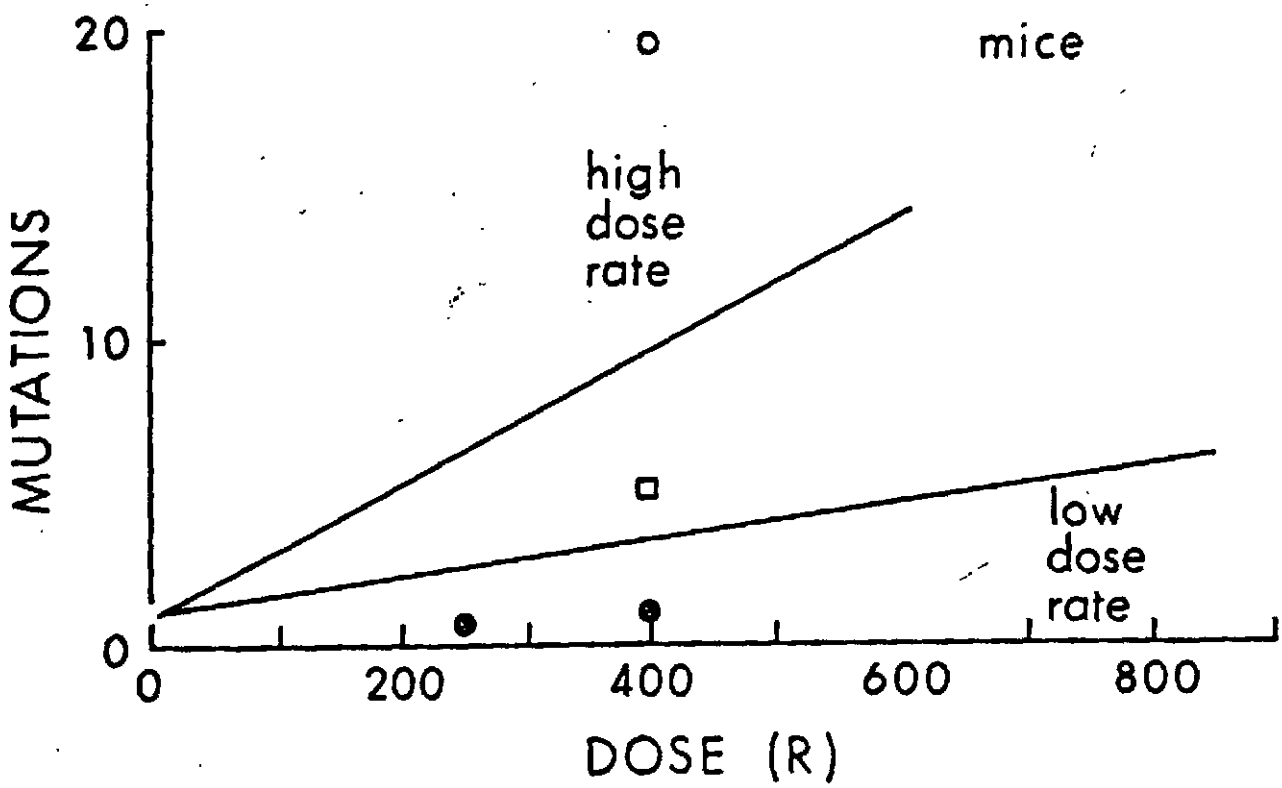
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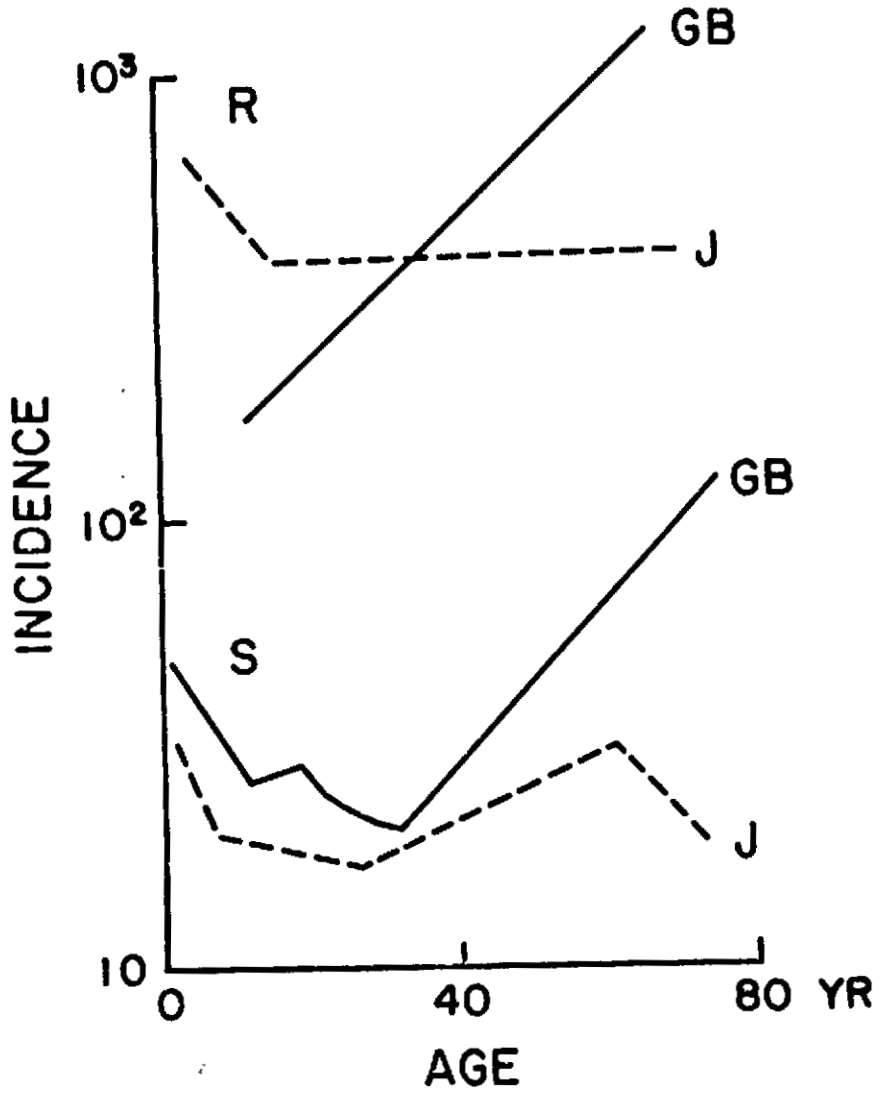
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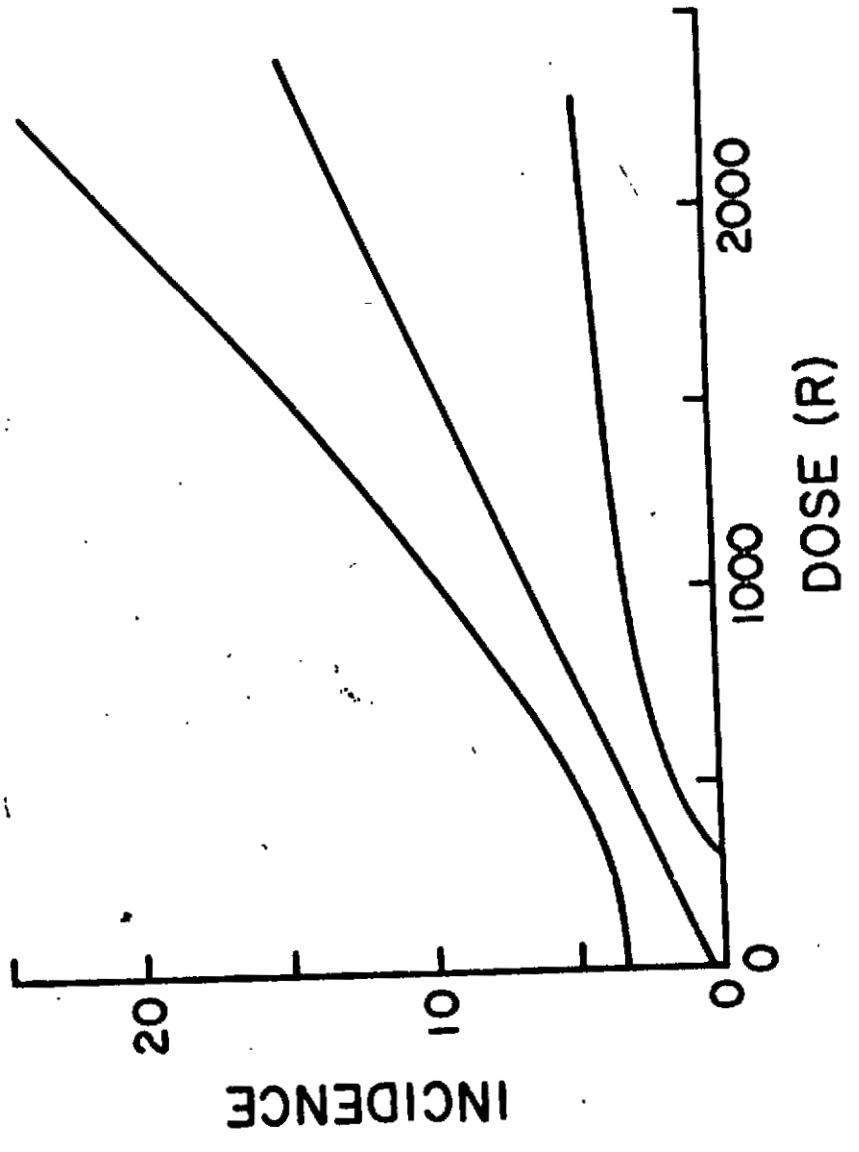
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