Gonadal Irradiation

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SUMMARY

A brief account is given of the circumstances under which gonadal irradiation may be expected to occur. The non-specific tissue effect and the hormonal and sterilising effects are considered. Genetic implications are mentioned.

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For the general practitioner inexorably implicated in the management of the patient suffering from malignant disease, a basic knowledge of the effects of ionising irradiation on the human organism is desirable. This is probably even more so in the specific instance of gonadal irradiation effects. There is little justification in ignoring or underplaying the psychological trauma and the anxiety experienced by the patient who knowingly submits to radiation exposure. Furthermore, the practitioner should be in a position to warn the patient of the real risk of sterility or castration. For this reason the radiotherapist must lean heavily on the support of his general practitioner colleague in the management of the patient (and his spouse) when recommending treatment with ionising irradiation.

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RADIATION EXPOSURE

The circumstances of exposure include:

1. Accidental or occupational exposure to radiation. When this occurs the effects will be dependent on over-all radiation dose and duration of exposure.
2. Radiation therapy for malignancies of the primary sex organs and closely related neighbouring structures. Those tissues directly in the radiation volume will receive a full cell-killing dose of irradiation.
3. Radiotherapy administered for disease of remote regions. The dose will be the consequence of scattered irradiation and will depend on distance from the primary beam.[1] Considering a treatment field of 20 by 15 cm the scattered dose at 5 cm $\simeq$ 5%, at 15 cm $\simeq$ 0,7% and at 25 cm $\simeq$ 0,5%. For example in a woman receiving 5 000 rads to a mediastinal field the dose to the ovaries would be 20 rads. In the case of the male receiving 5 000 rads to retroperitoneal nodes the testicular dose would be as high as 150 - 200 rads. This will result in some degree of temporary aspermia. (Doses above 600 rads will cause permanent sterility.)[2]
4. Radiation as an alternative to surgical castration. As discussed later, this is only practical in the female.

5. Radiation from circulating radioactive isotopes used therapeutically, as in thyroid disease. The dose to the gonads is small and can be disregarded.

RADIATION EFFECTS

The effect of gonadal irradiation can be considered in three different contexts: (*i*) the non-specific tissue effects; (*ii*) the sterilising effect and its hormonal consequences; and (*iii*) the genetic effects.

Non-specific Radiation Change in the Primary Sex Organs

The non-specific response of the pelvic structures, like that of other tissues, depends on a number of factors, summarised as follows:

Radiation factors: These include the total dose administered; total treatment time; the volume of tissue treated and the radiation distributed within that volume.

Use of adjuvants, such as chemotherapeutic agents (potentiators) and hyperbaric oxygen.

Patient factors, including age; race; nutritional state; the tissue oxygenation (degree of vascularity and the haemoglobin concentration); and previous treatment (surgery or radiotherapy) received.

It is therefore often difficult or unreliable to anticipate a given reaction in a given patient or to assess tolerance prior to curative therapy such as may be used in a treatment programme of 5 500 rads given over 5½ weeks in equal daily fractions.

Specific Radiation Changes in Primary Sex Organs

Cervix and Corpus Uteri

The tissues composing the cervix and uterus are able to tolerate very high doses of radiation, much more so than any other comparable volume of tissue anywhere else in the body. The epithelium of the uterus and cervix appears to possess a remarkable ability to recover from radiation injury even at doses of 15 000 to 20 000 rads from an adjacent radium source. This is well in excess of a tumorocidal dose and it is for this reason that the small cervical carcinoma is so readily controlled by use of intracavitary radium.

Indolent postirradiation ulcers of the cervix and vaginal vault can be expected to develop 6 - 12 months later in a small percentage of patients. These ulcers, however, most often follow on the successful treatment of what were large ulcerating cancers. They are often asymptomatic and difficult to distinguish from persistent or recurrent disease. Months may be required for re-epithelisation, especially where there is repeated coital trauma. There is also a real danger that such ulceration may develop into vesicovaginal or rectovaginal fistulas. Conservative management usually proves successful.

The Testes

The testicle, because of its accessibility and variety of cell types of widely varying radiosensitivity, has for many years been a favourite site of study among radiobiologists. In spite of this the data on the radiation effect on spermatogenesis in man is very scanty.

Such information as we have is largely based on semen counts done on patients undergoing radiation therapy for some malignant disease, while data derived from accidental exposure[3] and incidents such as the Hiroshima bombing, were based on reproductive performance. Semen counts have been so poorly documented as to be useless for analyses. We must therefore rely on the results of animal experimentation and the assumption that these can to some degree be extrapolated to humans.

The three cell types involved in normal spermatogenesis are: (*a*) the cells of Leydig or the interstitial cells, which are responsible for testosterone and the control of the secondary sex organs and characteristics; (*b*) the syncytial cells of Sertoli, which are responsible for the support and nutrition of the developing sperm; and (*c*) the germ cell.

The spermatogonia which derive from the gonocytes of the fetus and infant are the stem cells of the adult seminiferous tubules and are seen as the basal cell layer comprising the cell column of the tubule. They divide by mitosis, resulting in the next layer of cells — the primary spermatocytes. These then undergo reduction division, called meiosis, by which the normal diploid number of 46 chromosomes is reduced to the haploid number of 23, and so are transformed into secondary spermatocytes. These in turn undergo a normal mitotic division to form two spermatoids, which mature by a series of morphological steps to spermatozoa. The duration of this entire process has been estimated as being about 40 days in the mouse and 64 days in the human.

What happens when these tissues are irradiated depends on where in the spermatogenic pathway the particular cell is, because the degree of radiosensitivity varies throughout the sequence of the maturation process. In terms of the cell-killing effect of irradiation, those cells undergoing division either by mitosis or meiosis show the least degree of radiation tolerance.

This can be readily demonstrated histologically. Two hours after irradiation the spermatogenetic cell column starts to shrink because of a reduction in the number of spermatogonia, some of which are undergoing abnormal mitosis.

Four days later we find the more mature elements, the spermatozoa and spermatids, unchanged. This means that the process of maturation has continued without replacement by the stem cell or spermatogonia, which have disappeared, resulting in a depletion of primary spermatocytes which also show abnormal division. Associated with reduction in cell population is a more marked shrinkage of the cell column. Eight days after irradiation all primary spermatocytes have disappeared and some secondary spermatocytes show abnormal mitosis, with further reduction of the cell column.

Three weeks after irradiation no spermatocytes are left and a few of the spermatids show abnormally-shaped heads. The cell column is further reduced. At 5 weeks no

spermatids are left and all that remains are the Sertoli cells and new spermatogonia showing that recovery has begun. This has been shown to occur as late as 2 - 3 years after radiation exposure in the human testes.[3]

It follows, therefore, that sperm production will continue for some time after testicular irradiation, but that this will be followed by a period of aspermia which may be complete or incomplete, of short or long duration, depending on the total radiation dose. When repopulation occurs it takes approximately three times as long as normal spermatogenesis.[4]

It must be remembered that neither the severity of nor the rate of recovery from the radiation effect is altered by hormone administration before, during or after exposure. During the period of aspermia neither the interstitial hormone-producing cells nor the syncytial cells of Sertoli appear to be affected. In the fetus or infant, however, these interstitial cells are still undergoing proliferation and because of their immaturity are more sensitive to the effects of ionising irradiation. As a result their growth is suppressed, and the adult will be hormonally deficient.

In the adult, however, even in the presence of complete or permanent aspermia, there is no gross regression of secondary sex characteristics. This emphasises the difference between surgical and X-ray castration. A difference based on the fact that although spermatogenesis is hormonally controlled (by the pituitary and by the androgen production of the Leydig cells), the germ cells themselves play no part in the production of testosterone. Clearly, therefore, a disruption of spermatogenesis will produce no effect on the output of androgens.

This is in contradistinction to the female gonad where the germ cell development and hormone production are closely interrelated.

The Ovary

The germinal epithelium in the ovary, by creating the primordial follicle, accounts for both the ovum and the cells producing oestrogen and progesterone.

The normal cycle within the ovary commences with the ingrowth of a group of cells from the germinal epithelium. These develop to form the primordial follicle containing the oöcyte and the membrana granulosa and theca interna. The latter are responsible for the production of oestrogen, which is partly secreted into the circulation and partly stored in the liquor.

The mature or Graafian follicle, after rupturing and expelling the ovum, develops into the corpus luteum — the progesterone factory. The early development of the germ cells is by a process of mitosis up until the formation of the primary oöcyte. During this period of mitotic activity, sensitivity to irradiation is high. The primary oöcyte which undergoes reduction division by meiosis is also considered radiosensitive, to a degree which varies from species to species. Its tolerance in humans is not known.

As the ovum ages into the Graafian form, it becomes more resistant to the injurious effects of irradiation. This is not true of the granulosa cells which appear to be more sensitive in the Graafian follicle than in the primordial follicle.[4] Most of these data are derived from work done on rabbits, where a single dose of 1 200 rads is sufficient to arrest oögenesis. The minimum dose required to produce the same effect in the human is uncertain but is known to depend on the age of the woman. While a dose of 400 - 500 rads may be sufficient to produce permanent arrest of the menses in a 40-year-old woman, a dose of 1 200 - 2 000 rads will be required to give the same result in a young female.

Therefore, ionising irradiation applied in relatively low doses to the female pelvis will result in a twofold effect of radiation castration, comprising both sterility and premature menopause. This is complete, as can be demonstrated by urinary excretion studies which show a reduction of oestrogen after irradiation which is not further affected by surgical oöphorectomy.[5] While this is obviously a disadvantage for women subjected to radiotherapy where the ovaries, by virtue of their anatomical location, cannot be shielded, it can be of benefit to the patient with advanced breast carcinoma, where surgery is contra-indicated.

We have seen that the gonads are composed of tissues of widely varying radiosensitivity, the extremely sensitive and the more tolerant, a distinction of great importance to the radiotherapist. Tumours arising from these tissues appear to inherit a similar degree of radiation response, making both the seminoma and the dysgerminoma a group of tumours readily curable by radiotherapy.

The Genetic Effect

The genetic effect of irradiation and its risk to mankind presents, in theory anyway, disturbing possibilities. The study of this subject is too involved and cannot fall within the scope of this discussion. Perhaps one might mention that observations on the mutagenic effect of irradiation in man have been directed at a number of groups,[6] viz.: radiologists; survivors of the Hiroshima and Nagasaki bombing; French men and women receiving X-ray therapy for sciatic neuralgia and other ailments; and women treated for sterility by ovarian irradiation.

The yardsticks used to elicit genetic effects included altered sex ratio in the offspring; congenital malformations; fetal and infant mortality; infant birth mass; and anthropometric measurements.

Little reliable evidence of a genetic effect of radiation has emerged from these studies. Animal experimentation, however, definitely demonstrates a mutagenic effect. In the testes, the early spermatids appear to be most susceptible to genetic damage. In the ovary it is the oöcyte which is least tolerant, but fortunately at a dose which almost certainly induces sterility and so the risk is unlikely to manifest in the offspring.

It would be foolhardy to expect that man is an exception to this observed effect. Until such time as sufficient evidence accumulates to permit adequate appraisal of the problem, we would be wise to take whatever steps are necessary to reduce the prevailing rates of exposure.

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