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ACTION OF RADIATION UPON HUMAN SPERMATOGENESIS*

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The reproductive system of men offer four features which are advantageous for the study of the effects of radiation.

1. The testis is the only internal organ that can be successfully *isolated* for exposure to radiation without appreciably affecting other bodily functions.

2. Thus *known graded dosages of radiation*, of whatever composition, can be administered and the results studied. At the moment this is limited to single or intermittently applied doses of radiation.

3. The human testis may prove to be the most *radio-sensitive tissue* available for study.

4. Radiation effects are not delayed but appear at all time intervals after radiation. *Immediate* effects are observed upon the cytology of the spermatogonia within 3 to 6 hours. '*Early*' effects are observed on other cells of the germinal series from that time forward. The 'immediate' effect upon the spermatogonia are reflected as 'early' effects in the seminal fluid some 46 to 70 days later as a drop in sperm count. The *late* effects are sterility which, although dose-dependent, may endure for years or perhaps permanently. The *late*, *late* effects on chromosomes of the germinal epithelium may not be discernible for several generations if indeed there are such effects.

Inferences regarding the effects of radiation upon human male reproduction emanate from three general sources:

1. Nuclear explosions and accidents (where dosage can only be estimated, observations generally are random and antecedent control data is unobtainable);

2. Extrapolation from animal experiments (with all its built-in hazards—for example, 800 r hardly affects the bull; whereas we have found, 15 r has a marked effect on man), and

3. Direct exposure of the testes of normal men to *known* graded doses of radiation. The latter offers the advantage that each pertinent parameter may be studied during a normal control interval. Thus each subject may serve as his own control.

The former two categories are discussed in the literature. The latter has been made feasible by two circumstances:

1. The cooperation of inmates who volunteer at the Oregon State Penitentiary; and

2. The recent unravelling of the process of spermatogenesis in man. For the first time, all the cell types have been defined. The stages of the germinal epithelium have been recognized and defined. The time of each cycle of spermatogenesis has been determined as well as the total duration of spermatogenesis (Clermont; Heller and Clermont, 1963).

Each of the inmate volunteers is vasectomized at the end of the experimental period and before their release into the general population. Only volunteers who desire to be sterile are

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accepted into our program. The vasectomy is performed in order not to contaminate the population with potentially abnormal chromosomes.

The following observations of the effects of ionizing radiation upon man are from an incompleted current investigation. To date, the testes of 24 inmate volunteers have been exposed to single doses varying from 15 r to 600 r.

Azoospermia is produced by exposure to a single dose of ionizing radiation at 100, 200, 300, 400 and 600 r within circa 10 weeks.

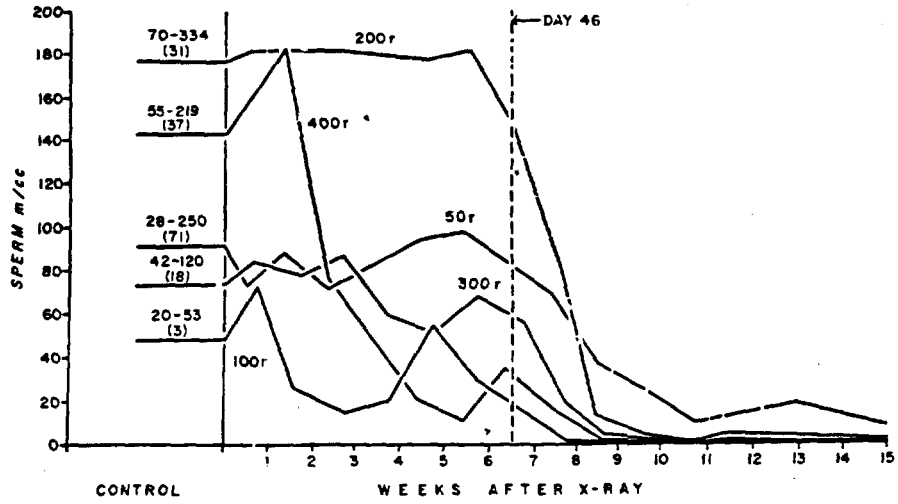

Fig. 1. The response of seminal spermatozoa to graded doses of ionizing radiation. Radiation exposed was administered at the time zero designated by the solid vertical line.

Decrease in sperm count is not detectable before 46 days elapse (the time of development from preleptotene spermatocyte to spermatozoa) at 100, 200 and 300 r. The decrease is detectable earlier at 400 r and 600 r. (A more mature germinal cell is hit).

100 r appears to be the threshold dose for azoospermia in that a few spermatozoa (in 7 subjects) continue to be detectable.

50 r results in marked oligospermia.

20 r results in moderate oligospermia.

15 r results in moderate oligospermia.

Necrosis and distortion of cellular elements, as revealed by testicular biopsy specimens, are apparent in 4 to 6 hours. The cells involved at 300 r and below are Type A pale, A dark (Fig. 2) and B spermatogonia. Many of these cells have disappeared by 12 hours. The more mature cells, from preleptotene spermatocyte through the reduction division process and including the spermatids, are unaffected at these lower dosages. These cells go on to develop into normal-appearing spermatozoa at the same rate as in unexposed individuals.

Denuding of the entire germinal epithelium occurs at all doses—some complete, 200 r and above (Fig. 3), and some incomplete, 100 r and below.

Recovery experiments are in progress. In general, the lower the dose the more rapid the recovery. Recovery has begun at doses up to 400 r.

Urinary gonadotropins are significantly and unequivocally elevated in any instance where denuding of the germinal epithelium occurs. This reflects the lack of utilization of the hormone and parallels the time and degree of the denudation.

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Fig. 2. Testicular biopsy obtained four hours after exposure to 400 r. Cellular association I. Note type A dark spermatogonia (the large cell next to the basement membrane) is pyknotic, distorted and undergoing dissolution.

Fig. 3. Testicular biopsy obtained 40 days after exposure to 400 r. Cellular association I. Note the only normal remaining germinal cells are the mature spermatids, absent are pre-leptotene, leptotene, zygotene, pachytene, secondary spermatocytes and immature spermatids. Sertoli cells are exposed and normal. The remaining spermatogonia is degenerating.

Libido and potentia are unaffected up to and including 600 r. More sophisticated measures of Leydig-cell function are being undertaken. Total estrogens and total 17-ketosteroids are unchanged. Leydig-cell morphology (inspection only) is unchanged.

Individuals exposed to doses of 600 r and 200 r, for whom urinary testosterone measurements have been made, show a marked reduction in testosterone following radiation. Recovery to control values is distinctly more rapid at the lower doses than for higher doses.

Conclusion

Graded doses of ionizing radiation when administered directly to human testes evoke graded biological responses in sperm count, testicular biopsy and rate of recovery. Urinary gonadotropin output rises in direct proportion to the degree of denuding of the germinal epithelium. This finding confirms the validity of the Utilization Hypothesis. This hypothesis states that the more active the germinal epithelium the more gonadotropin is utilized and therefore less is excreted in the urine. Conversely, as the germinal epithelium becomes denuded, less germinal cell activity is present, hence less gonadotropin is utilized and it accumulates and spills over into the urine. This accounts for the rise in urinary gonadotropins.

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