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Recovery of Male Fertility After Sterilization by Nuclear Radiation

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This study was planned to investigate the potential fertility in terms of semen quality of eight men 3½ years after they had been exposed accidentally to ionizing radiation of nuclear origin. It had been established that at least five of these individuals received sufficient total-body radiation (236 to 365 rads) to produce symptoms of acute radiation syndrome and that at least five had been found to be virtually sterile within four months after the accident. As determined at intervals by semen quality, a virtually sterile state was maintained for at least 21 months. Disturbances in morphology of the few spermatozoa present in the ejaculate were observed during this time. A reasonable to good level of potential fertility was attained at 41 months after exposure.

ON JUNE 16, 1958, a radiation accident occurred in one of the nuclear plants at Oak Ridge, Tenn. In varying degrees (Table 1), eight men were exposed to a nuclear excursion originating in an enriched (~ 90% U^{235}) uranium-bearing solution, which inadvertently had been transferred by water-flushing into an open tank in their vicinity. Details of this accident and the subsequent medical histories of these men have been covered meticulously in two government reports.[1,2] Those who had received high doses were ill with the acute radiation syndrome characterized by nausea, vomiting, epilation, and typical hematological changes.

The present study is concerned primarily with the potential fertility (as measured by semen quality) of six of these men at intervals up to one year and nine months after the accident, and a final estimation at three years and five months (Nov 27, 1961). The early semen examinations (up to and including April, 1960) were done by technicians at the Oak Ridge Institute of Nuclear Studies Medical Division. The earlier examinations consisted of sperm counts and the preparation of heat-fixed, unstained semen smears, which were stored for future staining. The final urologic examinations and the semen analyses were performed by the authors. The latest semen analyses consisted of measurements of ejaculate volume, sperm motility, sperm counts, and detailed examinations of seminal cytology by standard methods.[3,4] Subjects F and G did not submit semen specimens in the months immediately after their exposure to radiation and one (subject G) could not submit a specimen at any time. Only a study of the present fertility of subject F is possible. This study is concerned, therefore, with data on six men at intervals after the radiation exposure.

Table 1 summarizes the pertinent information on the marital status of the men at the time of the accident. This table shows that, with one exception, all wives were in child-bearing ages and that each marriage had been productive of children. No semen examinations were done before the accident.

When the men were examined by the senior authors 3½ years later, no significant abnormalities were found in the genitalia of the men except in one (subject C). He reported unilateral mumps orchitis at age 21 with partial atrophy. Both testes, however, were about three-quarters normal size, soft in consistency, and located high in the scrotal sac. His body hair was sparse. His semen was devoid of spermatozoa. The cause and duration of his testicular atrophy are a matter of conjecture.

The single man (subject H) was married six weeks after the accident and conception took place six months later. One normal child was born and at the time of his examination was 2½ years old. Contraceptive measures have been used since the birth of the child.

Results

Table 2 presents certain details of semen quality in six of the subjects at intervals up to 41 months after their exposure to the radiation. The ejaculate volumes were not recorded in the examinations preceding the final one in November, 1961, and the sperm motility readings prior to the latter examination lack validity because the semen collections were made in condoms. However, the sperm counts per cubic centimeter were recorded and

Table 1.—Marital Status at Time of Accident

Subject	Age, Yr	Age of Wife, Yr	Years Married	No. of Children
A	40	35	18	2
B	33	33	13	2
C	39	40	21	4
D	51	41	24	1
E	35	33	15	4
F	41	37	21	4
G	56	59	41	8
H	25	Unmarried		

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Table 2.—Effect of Fission Radiation on Human Male Fertility

	Date	Months After Exposure	Sperm Count, Millions/cc	Sperm Morphology, %							Motility % Active
				Oval	Large	Small	Taper	Amorphous	Double Heads	Immature %	
Subject A	July 7, 1958	<1	72	54	21	5	2	8	10	12	60
age 43 yr	Oct. 9, 1958	4	0				all immature cells			100	0
probable	March 20, 1959	9	<1	69	8	11	1	6	5	5	0
exposure	March 4, 1960	21	3	57	6	5	9	10	13	1	25
365 rads	Nov 27, 1961	41	51	73	1	11		9	6	2	75
Subject B	Oct 8, 1958	4	<1	45	35	6	9	3	2	1	0
age 36 yr	March 19, 1959	9	<1				too few cells				0
probable	April 19, 1960	22	8	45	41	2	8	2	2	1	80
exposure	Nov 27, 1961	41	96	81	3	3	5	6	2	0	75
270 rads											
Subject C	Oct 7, 1958	4	0								
age 42 yr	Aug 14, 1959	14	0								
probable	March 4, 1960	21	0								
exposure	Nov 27, 1961	41	0								
339 rads											
Subject D	July 3, 1958	<1	51	64	25	5	4	1	1	0	0
age 54 yr	Oct 9, 1958	4	1	50	22	12	6	8	2	3	5
probable	Aug 17, 1959	14	<1	56	28	12	4			8	0
exposure	Nov 27, 1961	41	218	73	1	10	11	4	1	0	30
327 rads											
Subject E	July 7, 1958	<1	14	14	71	1	2	2	10	10	0
age 38 yr	March 20, 1959	9	<1				not enough cells				0
probable	Aug 17, 1959	14	<1	17	65	2	5	2	9	6	0
exposure	March 4, 1960	21	<1	32	39	4	5	10	10	4	<15
236 rads	Nov 27, 1961	41	35	64	7	5	10	11	3	0	65
Subject F	Nov 27, 1961	41	167	93	3	2	1	1		0	85
age 41 yr											
probable											
exposure											
68.5 rads											
Subject G						No records available					
age 56 yr											
probable											
exposure											
68.5 rads											
Subject H	July 14, 1958	<1	144				no smear				90
age 28 yr	Oct 9, 1958	4	30	75	7	7	2	7	2	1	20
probable	March 18, 1959	9	7	78	8	5	3	5	1	1	10
exposure	Nov 21, 1961	41	121	74	3	3	8	11	1	0	90
22.8 rads											

the seminal smears prepared and fixed in the earlier examinations in Oak Ridge were sufficiently well preserved to allow staining and morphologic study in 1961. The various classifications of the spermatozoal morphology in Tables 2 and 3 may be clarified by reference to Fig 1 and 2. The data in Table 3 present the figures for all parameters of semen quality as determined 3½ years after the exposure to radiation.

It is clear from the data (count per cubic centimeter) in Table 2 that three (A,B, and D) of the four subjects receiving the greatest amount of radiation were sterile or virtually so within four months subsequent to the exposure. Had the semen of subject E been examined at this time, it seems reasonably certain that he, too, would have been found in the same condition. He was sterile in March, 1959. Subject C, who received the second greatest exposure, will be discussed separately, inasmuch as there is considerable doubt that the sterility found in him in all examinations was due to the radiation.

Similarly, in subject H, who received the least amount of radiation (22.8 rads), it is doubtful that the sperm count depression recorded four and nine months subsequent to exposure was due to the radiation. His marriage during this time and the high rate of sexual activity usually associated with the early months of marital life could account for the lowering of the sperm count. In support of this argument, no disturbances in sperm morphology were ever found in his semen.

In terms of sperm count, the state of virtual sterility continued in subjects A, B, and E through March, 1960, nearly 22 months after the accident, although in subject B a sperm count of 8 million per cubic centimeter gave evidence of testicular recovery. No semen examinations were performed

Table 3—Fertility Status of Seven Men Exposed to Nuclear Radiation 3½ Years After Exposure

Subject	Distance From Reaction, Feet	Exposure in Rads*	Ejaculate Volume (cc)	Sperm Count Millions/cc	Total Count	Motility Quality	Motility % Active	Sperm Morphology, % O	L	S	T	A	D	Immature	Lowest Sperm Count Recorded to March 1960, Millions/cc
A	6	365	2.1	51	102	3	75	73	1	11		9	6	5	0
C	17	339	1.0	0	0		0								
D	16	327	2.0	218	436	3	30	73	1	10	11	4	1	0	<1
B	15	270	2.2	96	211	3	75	81	3	3	5	6	2	0	<1
E	22	236	4.0	35	140	3	65	64	7	5	10	11	3	0	<1
F	Above subject E	68.5	1.0	167	167	3	85	93	3	2	1	1	0	0	none done
H	50	22.8	1.4	121	169	3—	90	74	3	3	8	11	1	0	7

*A rad is the amount of ionizing radiation that imparts 100 ergs of energy per gram of irradiated material.

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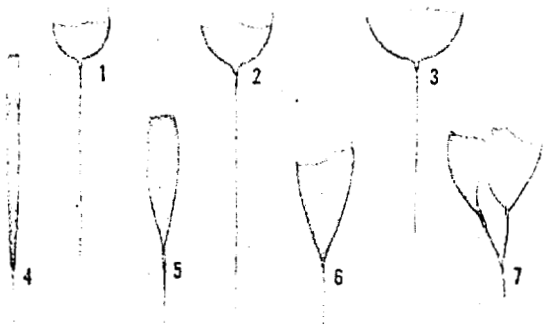

Fig 1.—Variations in shape and size of human spermatozoa include: 1. small form; 2. normal size and shape; 3. megalo; 4. acute taper; 5. moderate taper; 6. tendency to taper; 7. duplicate. From Hotchkiss' classification modified by MacLeod to include "immature forms."

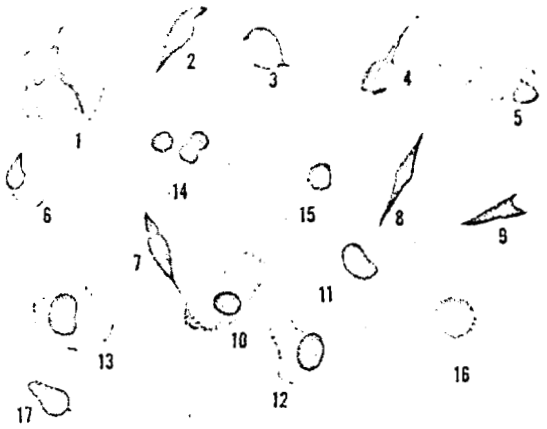

Fig 2.—Abnormal spermatozoa and exfoliated cells of germinal line: 1. immature cell (distorted chromatin); 2-6. abnormal spermatozoa; 7-9. "tapering" spermatozoa; 10-13. immature exfoliated cells (large spermatids); 14. three spermatid nuclei in single cytoplasm; 15-16. "ghosts" of spermatids (nuclei extruded); 17. amorphous.

on any of the subjects between April, 1960, and November, 1961. At the latter time, the potential fertility in terms of sperm count of all of the subjects examined was within normal range. When this level was reached after April, 1960, can only be estimated, but it is reasonable to assume that the fertility of the four subjects receiving the greatest amount of radiation (236 to 365 rads) was severely impaired for at least 30 months following the exposure.

Seminal Cytology

The seminal cytology in man in the presence of a patent duct system is an accurate reflection of the normal morphologic function of the germinal epithelium and a most sensitive indicator of changes in that function.[5,6] Indeed, it can be said that the seminal cytology is to the kinetics of the germinal function of the testes as the peripheral blood cytology is to hematopoiesis in the bone marrow. While human spermatozoa may display a wide variety of head shapes and sizes, the pattern of spermatogenesis, as manifested in the ratios of head shape and size, is remarkably constant over protracted periods in the same person in health. However, in certain illnesses, some seemingly innocuous, these ratios may change markedly; if the trauma is severe enough these disturbances in testicular function may be manifest by the appearance in the ejaculate of immature cells of the germinal line. An analogous situation in the peripheral blood would be the appearance of normoblasts or of myelocytes. In the normal range of human male fertility, one would not expect to find more than 40% of the mature spermatozoa with deviations in head shape or size, nor would one expect to find more than 2% of the total cellular content of the ejaculate as immature cells of the germinal line.

We have used here the arbitrary classification of head shape and size adopted by Hotchkiss and modified by MacLeod by the addition of a category for "immature forms" (Fig 1 and 2). The Papanicolaou staining technique was used throughout. Thus, the "oval" forms in the tables should be considered as "normal" in size and shape. The "megalo" forms are normally shaped cells one to two dimensions larger than "normal" size. Conversely, the "small" are one to two dimensions smaller than the "oval" but otherwise normal in shape. The "tapering" forms may or may not be "normal" spermatozoa depending upon the degree of "taper," but these cells definitely are elongated in head shape and may be acutely tapered in certain toxic conditions. The "amorphous" forms comprise all spermatozoa that do not fit into these categories and definitely show aberrations in head shape (Fig 2). This classification contains a wide range of aberrant types. The "immature forms" (Fig 2) usually appear as spermatids and often are cells in which several spermatid nuclei are present in a single cytoplasm.

The essential feature of the disturbance in mature sperm morphology seen in the four subjects (A, B, D, and E) subsequent to the exposure was the appearance of a rather high percentage of "megalo" forms in the semen of subjects A, D, and E at 21 days. They also were present in subject B in the first postexposure examination done on this man four months after the accident. These forms diminished in the semen of subject A thereafter, but persisted in the other three subjects at least through March, 1960. They were not present to a

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significant extent in any of the subjects in the final examination made in November, 1961, nor were they ever present to a marked degree in the semen of subject H, who received the least amount of radiation.

In subjects A and E, the bicephalic forms appeared to be increased 21 days postirradiation and in subsequent examinations, but it is possible that this deviation in mature sperm morphology is a normal characteristic of the semen of subject A (see the percentage for Nov 27, 1961).

Immature forms (spermatids) were present in significant numbers in the semen of subjects A and E 21 days after exposure and were the only cells of the germinal line in the semen of subject A four months postexposure. These cells continued to appear in the ejaculate of all four subjects during the period of their virtual sterility. Their presence, along with that of an occasional mature spermatozoon, in the ejaulate indicates that while spermatogenesis was almost completely inhibited for an extended period (21 months) following the radiation exposure, some degree of maturation to the spermatid level and beyond was present at all times.

It should be noted that the sperm morphology of subject H, who received the least amount of exposure, was not affected at any time even though there appeared to be a severe depression in the sperm count at four and nine months after the accident. This fact would tend to confirm the suggestion made above that the sperm count depression in this case was not due to radiation.

Motility

Virtually all the semen specimens collected by these men before November, 1961, were obtained and delivered in condoms. Therefore, only an occasional figure on sperm motility recorded before November, 1961, has validity. For example, a good percentage of spermatozoa of subject A on July 14, 1958, retained motility, suggesting that the radiation had not affected the mature spermatozoa already in the duct system. In subjects A and B during the early stages of recovery of spermatogenesis (March 4, 1960, and April 19, 1960), the new generations of spermatozoa showed a considerable degree of motile activity.

In November, 1961, the spermatozoa of all the men examined, with the exception of that of subject D, showed activity that ranged from good to excellent and, in conjunction with the sperm counts and morphologies, is representative of good potential fertility. The low percentage of active cells seen in subject D probably was due to the long period of continence (several months) which preceded the obtaining of this particular specimen. If the semen of subject F ever was affected by the relatively small amount of radiation he received, the only examination made (November, 1961) gave no such indication. His semen was good in all respects.

Comment

Reports of the subsequent fertility of survivors of radiation accidents are sparse. Ten men were involved in the first such accident in this country which occurred at Los Alamos within a year of the first military use of the atomic bomb.

Hemplemann and associates [7] have studied these cases in great detail. One of the survivors had received a dose (estimated) of total-body irradiation amounting to 390 roentgens (r) of 80 kv x-rays and 26.4 r of gamma rays. His sperm count 37 days after the exposure was 5 million per cubic centimeter (the figure was given as 5 million per millimeter, but we feel sure that centimeter was intended), about 1.5 million per cubic centimeter at 80 days, and he was sterile at seven months. Fifty months after the exposure two sperm counts were 10 and 16 million per cubic centimeter respectively and he initiated conception of a normal child about this time.

This case was studied further by Oakes and Lushbaugh,[8] particularly in relation to testicular morphology. Three testicular biopsies were done, the first at 10 months after the exposure and the others at 20 and 50 months, respectively. At 10 months, severe damage to the germinal epithelium was recorded, with only moderate improvement at 20 months. Even at 50 months, considerable atrophy of the germinal epithelium still was present at a time when the sperm count was between 10 and 16 million per cubic centimeter. However, since neither his potential fertility in terms of semen quality nor the state of his testes was known before the accident, one cannot be certain that the seminal and testicular deficiencies seen at 50 months were caused by the radiation. Indeed, it is doubtful that this man received any more radiation than that received by the men in our study and in whom the semen quality had shown good recovery at 41 months.

Two other survivors of the Los Alamos accident received only minimal amounts of radiation. No semen examinations were done on one, but he had two normal children after the accident. In the second man, the sperm count four months after the exposure was reported as within "normal limits."

Hasterlik and Marinelli [9] studied four men who had been exposed to total-body irradiation of neutron and gamma rays at levels between 12 and 190 rem. These amounts are considerably below those received by subjects A, B, C, D, and E in our study. Nevertheless, depressions in the sperm count were found in all. One man was sterile at 10 months with recovery at 20 months.

A well-documented single case history in terms of semen quality and testicular morphology is recorded by Robinson and Engle.[10] A 26-year-old

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man was exposed to a neutron bombardment lasting less than one second. Nevertheless, epilation did occur and his blood level fell. No spermatozoa were found in the ejaculate only three weeks after the exposure, and a testicular biopsy nine months later showed only a few spermatogonia in the tubules. At 10 months no spermatozoa were found in the semen, but at 15 months a sperm count of 21 million per cubic centimeter was evidence of a sharp resurgence in spermatogenesis. The sperm count did not improve appreciably during the next ten months. The extraordinary features of this case, in which the amount of radiation received could not be determined, are the complete absence of spermatozoa in the semen at only three weeks after the exposure and the apparently very rapid recovery of spermatogenesis (within five months after almost complete destruction of germinal elements). Even though spermatogenesis had been halted abruptly at the moment of exposure it would take several weeks, if not months, to completely empty the duct system of the mature spermatozoa present before the radiation.

In the nuclear excursion that is the subject of this paper, shortly after the accident extraordinary measures were taken at the Oak Ridge National Laboratory and the Medical Division of the Oak Ridge Institute of Nuclear Studies to determine the amount and type of radiation to which these men had been exposed. Only the estimates finally reached have pertinence to this study. Five of the subjects (A, B, C, D and E) were considered to have received dangerous but not lethal amounts, both in terms of the calculated dose of radiation (236 to 365 rads) and the subsequent clinical findings. Subjects F and H, receiving 68.5 and 22.8 rads, could not be considered as suffering injuries producing significant symptoms of the acute radiation syndrome.

It is clear from the data in the tables that, with the exception of subjects E and H, all the subjects submitting semen specimens were sterile or virtually so four months after exposure.

However, at 41 months, the semen quality of all the men (except subject C) ranged from satisfactory to excellent as measured by all available standards (volume, sperm count, sperm motility, and morphology).[11,12] In particular, the sperm morphologies were good. These morphologic findings, of course, do not preclude the possibility that mutations have occurred.

The case of subject C is an enigmatic one. His semen was devoid of spermatozoa in the first examination which, unfortunately, was not done until nearly four months after the accident. No spermatozoa have been found in all subsequent examinations. Had a semen examination been done on this man within three or four weeks after the exposure and spermatozoa found at that time, we could say with some assurance that the present sterility was due to the radiation. Mumps orchitis, whether bilateral or unilateral is not certain, occurred when he was 21 years old, but since two of his four children were born several years subsequent to the orchitis, it is clear that he was not sterilized by the mumps. Nevertheless, we are not convinced that he was sterilized as a result of the radiation.

Within the limits of the data we have presented here, it is clear that, as measured by semen quality, evidence of recovery of spermatogenesis may be expected within 21 months, although the sperm counts at this time probably will not be consonant with a reasonable level of fertility. The latter state may be reached within 41 months and it is quite likely that a satisfactory level of fertility may be attained by 30 months .

Finally, review of the male fertility data on the recorded cases of sublethal nuclear radiation accidents has clearly shown that relatively small amounts of radiation will produce pronounced effects on the testes, but that ultimate recovery of some degree of fertility is possible in most, if not all, of such cases.

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