REVIEW ARTICLE

THE TREATMENT OF FEMALE STERILITY WITH X-RAYS TO THE OVARIES AND THE PITUITARY*

WITH SPECIAL REFERENCE TO CONGENITAL ANOMALIES OF THE OFFSPRING

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BECAUSE ONLY ABOUT 6.10% of women with delayed menstruation spontaneously became pregnant, all sorts of methods have been tried to aid the remaining large number of infertile women to conceive. In 1926, Rubin[1] called attention to the fact that, because x-ray therapy was capable of regulating menstrual irregularity, it also was successful in producing favourable responses in cases of sterility associated with habitual amenorrhœa. In 1944, Mazer and Greenberg[2] reported on 330 cases of amenorrhœa treated by low dosage irradiation; 71% responded favourably and an examination of the children born to these women indicated no deleterious effect on them. Drips,[3] at the Mayo Clinic, also found irradiation effective and harmless for the treatment of female sterility. In 1951, Mazer and Israel[4] advocated x-ray therapy for female sterility because it had proved successful in most instances where used, and because "no one has reported adverse effects on the patient and her immediate offspring". In a very complete and careful report, based upon his experience over a long period of time, Israel[5] in 1952 stated that even though irradiation in the treatment of infertility was used on an empirical basis, it might safely be employed in properly selected cases and was also effective for the treatment of secondary amenorrhœa. Playfair and Booth[6] also found x-ray therapy effective in the treatment of secondary amenorrhœa and at the same time stated that it has never been proved that, cytologically, x-rays have permanently damaged either the pituitary gland or the ovaries, provided the x-rays were properly applied.

In 1952, Rubin[7] again advocated irradiation for the treatment of female sterility, for in a follow-up of such treated women he had found no deleterious effect from the x-ray treatment in the women so treated, their offspring or the children of these offspring. Siegler[8] in 1952 also stated that for the treatment of anovulatory menstruation, x-ray therapy to the pituitary and the ovaries was the most effective procedure. Based upon a long experience in the treatment of female infertility with x-rays, I presented a report in 1953[9] at the Seventh International Congress of Radiology, in which I demonstrated that there was no abnormal effect on the third-generation progeny of irradiated women. Again in 1954,[10] I reported on a larger group of sterile women treated by irradiation, and on their grandchildren, and from these observations reiterated my previously published conclusion that irradiation, when properly employed for the treatment of female sterility, is harmless to the woman so treated, her children and the offspring of such children.

Just how x-ray therapy to the pituitary and to the ovaries produces the favourable response is still a moot question. Arnold[11] states that the hypothalamus exerts a considerable influence on the pituitary; since the pituitary is presumed to be quite radioresistant, a favourable response in ovarian function following irradiation to the pituitary is in all probability due to the action of the x-rays on the more sensitive adjacent hypothalamus.

Because the pituitary plays an important part in the normal functioning of the ovary, Kotz[12] says that dysfunction is not a primary ovarian fault but secondary to pituitary failure; x-ray therapy, by acting on the pituitary, corrects the condition.

In the case of ovarian response to x-ray therapy, we are not definite as to the action of the x-rays. If it is believed that the sterility is due to inability of the ovary to extrude an ovum each month, the x-rays, by activating the ovary, cause it to extrude an ovum which may then become fertilized in the usual manner. If the anovulatory sterility is associated with a persistent corpus lutem, irradiation may be the factor which activates the resolution of a persistent corpus luteum, permitting normal menstrual function and subsequent conception. It is known that cystic ovarian involvement may be the basis of sterility. It is believed that x-ray therapy destroys or affects such cysts in a manner similar to surgery, and thus relieves the sterility. Where the lining of the uterus is improperly prepared to receive the fertilized ovum, irradiation of the ovary may activate the latter to stimulate correction of the endometrial condition and permit safe conception. In many instances, however, irradiation is used empirically, and, because it produces satisfactorily the result we seek, it is acceptable as a proper therapeutic procedure for the relief of female infertility.

Today there is no longer any doubt that x-ray therapy is properly recognized as a useful, essential and effective therapeutic procedure for the treatment of amenorrhœa and sterility.

During the past 31 years there were referred to me a very large number of married women who had failed to respond to all other forms

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of therapy for the relief of amenorrhœa and sterility. In all instances the diagnosis of sterility was made by the referring gynæcologist. Treatment by me was limited solely to the administration of low-dosage x-ray to the pituitary and the ovaries of the referred patient. In this period there were referred 754 married women, 15 of whom were not treated because they had closed tubes, were over suitable age, or had some anatomical defect. Some of these patients failed to report for treatment after discussing possibilities. Some failed to return after one treatment. Of the 739 treated, I am unable to trace 175. Of the balance of 564 women treated, I have a record of 26 definite failures of response; though these had adopted children, none have subsequently borne children of their own. One woman died a year following treatment, of leukæmia not previously recognized. There were 538 women who responded to treatment and resumed normal menstruation; of these I have a definite record of 311 women who have become pregnant 513 times. In this group there were 6 ectopic pregnancies; 2 have subsequently borne normal children. There were 409 children born to these women—191 boys and 218 girls, including five sets of twins. Sixty-seven women miscarried, some more than once, and of these I have a record of 40 who became pregnant again and bore normal children; the balance of 27 have not reported subsequent pregnancy, though all are not traced. In a few cases of miscarriage, the cause was accidental trauma, automobile smashes, bicycle falls and other mishaps. Some miscarried because, as Kleegman[13] suggested, conception occurred too soon after x-ray therapy. The percentage of miscarriage in this series of cases, however, is not as great as that noted in the normal group of pregnant women.

At the present time, in July 1955, there are 13 pregnant women.

It is of interest to mention that in my hands treatment of infertile Negro women has not been successful in any of the five cases referred to me. These women had not responded to any other form of therapy before reporting for x-ray treatment.

As to the question of abnormalities in children born of irradiated mothers, almost all the dire pronouncements of such harmful effects on the progeny of women treated by x-rays have been promulgated mainly by those who base their assumptions solely on animal experimentation. Should an abnormality occur in the progeny of an irradiated woman, in practically every case it is due to the effect of x-rays on an already existing fetus in the uterus, an entirely different condition from that associated with irradiation of a non-ovulating ovary. Russell,[14] in observing the effects of irradiation in mice, noted that the critical period in the development of progeny abnormalities occurred at a time which in man corresponds to six weeks' gestation. Even a small dose of irradiation at this critical time, says Russell, may produce changes in an existing embryo in an irradiated mother's womb. He does not, however, report any such subsequent abnormalities in progeny of animals irradiated in a non-pregnant period. Hicks also noted deleterious neural effects on the progeny of irradiated mice, but only when an animal already pregnant received irradiation.

Such pronouncements, however, while correct when considering the employment of x-rays in the treatment of an already pregnant woman, have no valid status when irradiation is to be employed solely for the treatment of the infertile woman. In this procedure irradiation is not administered to a pregnant uterus with its existing fetus but to a non-pregnant woman. It is a matter of record that no one has as yet conclusively demonstrated any harmful effect in a child born of an irradiated infertile woman. Although Muller[15] has demonstrated transmitted genetic effects to progeny of irradiated flies, no such genetic abnormalities have been noted or reported as having been observed in the children or grandchildren of infertile married women properly treated with x-rays. This is significant too because Muller[16] also states that it is in the first generation born of irradiated forebears that the mutations are most likely to show. He also says that spontaneous mutations are not less harmful than radiation mutations, and that nature through natural selection controls the effects on the race. Therefore I do not believe that radiation mutations are less controllable by nature and that they are more apt to contribute any more harmful effect on the human race.

It is a matter of record that abnormalities are found in newly born children even where no x-rays have been administered and such abnormalities occur spontaneously. In a study of 5,964 pregnancies observed at the Babies Hospital and The Sloane Hospital for Women in New York City, over a period of five years, Rustin McIntosh[17] and his co-workers in 1954 reported that 7% of the children born of these pregnancies were abnormal. In my series which I now report,* there were 739 women given radiation therapy for infertility, and 512 pregnancies followed such treatment. In this group there were only 3 cases of child abnormality.

One of these children I reported on in 1932[18]; I believe the abnormality resulted from irradiation of an already existing fetus *in utero*. In the second case, after having borne a perfectly normal child following irradiation, the woman conceived a second time and produced a child which seemed normal but developed intestinal trouble diagnosed as Hirschsprung's disease, and unfortunately succumbed at operation six weeks after birth. In

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the third case, I am at a loss to explain the occurrence but do not believe it was due solely to the x-rays. This mother began to menstruate late, at age 16, was always irregular and for a long time menstruated only after hormone injections. She married at age 24, and irregularity continued. She was referred in September 1953 for x-ray therapy at age 27, was given treatment to the pituitary and ovaries in the usual manner, responded well, menstruated normally, conceived, and was delivered by low forceps of a full-term baby girl on February 2, 1955. This child was abnormal—hydrocephalus, brain injury, club foot, spina bifida. I still doubt that the x-rays administered more than two years previously were the cause of this mishap.

In this series there were two stillbirths, not an unusual percentage. Three children were born dead because the umbilical cord was knotted about the neck and could not be removed in time to save the children, who were otherwise physically normal. Two children died, one at age 2 from accidental drowning and one at the age of 6 of tetanus infection. The other 409 children born of irradiated mothers are all healthy, physically and mentally. In this group there are 191 boys and 218 girls. There are five sets of twins.

One of the basic assumptions of the radiation antagonist is the fear that mating of human progeny from an irradiated mother with one from an irradiated father would produce defective offspring as noted in animal experiments. The chance, however, that such marriages would occur in a population of more than 150 million people is very small, because at the present time there are probably not more than a few thousand offspring of irradiated mothers in the United States. Irradiation as a method of therapy for male infertility has rarely been utilized and has as yet not proven successful. In animal investigation, however, it is the effect of irradiation of the male gonads that has revealed the mutation abnormalities quoted by the geneticists and the radiation antagonists.

Slatis[19] says that were man to be poisoned by irradiation so that his mutation rate were doubled, it would be several generations before the accumulation of new mutations would amount to much. Although the frequency of the gene would build up to a more rapid frequency, the increase would be so minor that with such small changes it would seem unlikely that doubling the mutation rate would pose a serious problem to the life of the species, and it might go almost unnoticed.

The type of damage due to gene mutations, says Slatis, "requires that two individuals descended from the same irradiated person shall marry and have children. Since our customs and laws forbid such incest, it will be at least another three or four generations before we have any families in this category." It is my opinion, based upon the large number of women irradiated and reported upon by me, that in all probability it will require many more generations of progeny of irradiated mothers for the possibility of intermarriage of these children to occur.

Evans[20] says that when experimental organisms are irradiated at a low rate, no induced mutations have as yet been observed in organisms studied (fruit flies and mice). This suggests that the effective average radiation sensitivity of immature sperm and eggs may be less than the sensitivity of mature sperm and eggs. He says further, "From the appropriate mathematical theory, and the experimental data now available, it seems safe enough to conclude that no detectable increase in hereditary abnormalities is likely to result, even after many generations, if a small fraction of the population receives radiation doses up to 0.1 roentgen per day." It should be emphasized that the radiation dose used in the treatment of human female infertility is never as large as that utilized by Evans for his calculations in estimating the x-ray effect for producing new mutations.

It is a genetic fact that where irradiation is lethal, progeny is rarely produced. Lea,[21] in summing up his discussion of x-ray action on *Drosophila*, states, "We may say that there are strong indications that lethal chromosome structural changes play a major part in accounting for the failure of eggs to hatch after the irradiation of the sperm or egg prior to fertilization, or of the egg soon after fertilization. The evidence is, however, circumstantial."

Neel[22] and his co-workers, in studying the effect of irradiation from the atomic bomb in Hiroshima and Nagasaki, stated that the rate of mutations was probably the same in man as that observed in the experimental mouse. They also stated that they did not observe any significant difference during the first year of life in children conceived after the bombing where one or both parents were exposed to the radiations, and children born subsequently to suitable control parents. Their investigation revealed no indication of any unusual sensitivity of human genes to irradiation. This too was concluded even though the exposure of the mothers was to a radiation dose far in excess of that used in the therapy of infertile married females.

My report covers only the history of infertile females treated by irradiation and then bearing children to their non-irradiated husbands. So far all of the resultant children, except in three instances, are normal in every way.

So much for the second generation. What about the third—that is, the grandchildren of the originally irradiated women? It is quite readily understandable that it is no easy task to trace women treated 20 or more years ago, whose children should at present be of marriageable age. I am fortunate in having located 19 such women whose children have married and have already borne 25 normal children, that is, grandchildren of the originally treated women. Some of these children are again pregnant and additional grandchildren are on the way. All of these grandchildren are perfectly normal, physically and mentally. I have records of several additional children at present engaged but not yet married.

Rubin[7] properly states: "The long span of time between generations obviously makes it difficult to give an absolute answer to the theoretical question of the ultimate harmful genetic effect of irradiation on the human race. But the long interval between the births of a first and

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second generation would warrant the assumption that whatever harmful effects may have been produced by the x-ray irradiation to the ovaries of a grandmother would have been dissipated over the years. No acquired lethal effects on the genes have been observed in hundreds of babies born following this treatment for the relief of infertility and delayed menstruation."

It required 20 years of waiting before I could report in 1950[23] on the birth of grandchildren of irradiated grandmothers, and the present recording of the birth of 23 normal grandchildren* certainly lends no support to the claim of some that low-dosage x-ray irradiation to the pituitary and the ovaries produces harmful effects in the progeny of women so treated.

CONCLUSIONS

I agree with Professor Muller[24] that "The saving of life does not automatically justify its production of offspring, for the chief criterion on which to base decisions in the planning of parenthood would be the welfare of the descendants themselves."

I believe my work meets this criterion and, therefore, as a result of more than 30 years in the employment of x-ray therapy for the treatment of amenorrhœa and sterility in the infertile married woman I am, I believe, justified in stating that, when properly administered, x-ray therapy to the pituitary and the ovaries is effective and is harmless to the mother, to her children, and to her children's children. Any adverse reports are based solely on animal experimentation that definitely cannot be interpolated for human results.

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*November 1956. I now have records of 32 grandchildren and 2 on way.

PUBLIC RELATIONS FORUM

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PUBLIC ATTITUDES TOWARDS DOCTORS. IV.

THIS IS THE FOURTH ARTICLE in a series reviewing findings of a public opinion survey conducted for the American Medical Association. Views of special publics are discussed.

VIEWS OF SPECIAL PUBLICS

Certain individuals, because of the nature of their work or their daily association with doctors, are in a strategic position to alter or shape the attitudes of the general public towards the medical profession. For this reason the views of these "special publics" about doctors are particularly important.

To determine what such opinion leaders think about the medical profession, 100 interviews each with editors and commentators and lawyers were included in the public opinion survey. In addition, 300 allied medical people—100 druggists, 100 nurses, and 100 executive secretaries of state and county medical societies—were also polled.

Four of the five special publics think as highly of their own family doctors as the general public does, or even more highly.

In rating their family doctors' likability, intelligence and capability all special groups but the druggists give them the same scores as the general public, or even better. All the secretaries, nine out of ten editors, 97% of the nurses and 96% of the lawyers say they like their family doctors. Ninety-six per cent of the general public by comparison say they like their family doctors. Almost identical percentages of the special groups, except druggists, consider their family doctors highly intelligent and even higher percentages say he is very capable.

In rating family doctors in regard to whether or not he takes enough personal interest, once again all but druggists give more favourable replies than does the public: editors, 88%; lawyers, 95%; nurses, 93%; secretaries, 97%; public, 87%; and druggists, 83%.

On other questions, too, four out of five of the special publics reflect more favourable attitudes towards their own doctors than the public does, or equally favourable attitudes.

	Editors	*Lawyers*	*Nurses*	*Secretaries*	*Public*
Deny that he thinks he is always right	80%	81%	86%	80%	71%
Say that he is frank enough about illnesses	85%	90%	87%	86%	80%