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The Use of low-dosage irradiation to the pituitary and ovaries in the treatment of amenorrhea and sterility in women

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THE USE OF LOW-DOSAGE X-RAY IRRADIATION TO THE PITUITARY AND OVARIES IN THE TREATMENT OF AMENORRHEA AND STERILITY IN WOMEN

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INTRODUCTION

Numerous reports have now accumulated in the literature concerning the satisfactory employment of low-dosage x-ray irradiation to the pituitary and ovaries in the treatment of sterility due to amenorrhea and certain other functional menstrual disorders. Although beneficial in some cases, estrogenic and gonadotropic therapy alone has not proved to be the answer to the reestablishment of regularity of the menses in the treatment of sterility. The use of x-ray irradiation to the pituitary and ovaries has been shown to produce much better results in these cases.

Halberstaedter (1) in 1905 called attention to the fact that roentgen rays have a selective action on the ovary. Clinically, Van de Velde (2) reported in 1915 the return of normal ovarian function after the application of small doses of x-rays over the ovaries. Rongy (3) in 1924 was the first man in this country to describe the beneficial effects upon secondary amenorrhea and sterility from x-ray stimulation of the pituitary and ovaries. Rubin (4) and Hirsch (5) in 1926 reported good results in the treatment of depressed ovarian function and sterility with these methods.

MODE OF ACTION

It is still a point for debate just how irradiation works to correct these functional menstrual disorders and subsequently

sterility. Rubin (6) is of the opinion that the relief of amenorrhea and sterility following roentgen irradiation is probably a general reaction to a stimulating effect based on Halberstaedter's selective action findings. Taylor (7) agrees with this theory of a stimulative effect by roentgen rays. Drips and Ford (8) believe in the stimulative effect of roentgen irradiation on the ovaries and pituitary and found this method of treatment especially applicable to cases in which there was either a pituitary gonadotropic deficiency or a primary ovarian deficiency. After examination of rat ovaries which had been given low-dosage irradiation, they concluded that apparently a congestion of the ovaries was all that was produced and assumed the release of a hormone, presumably estrin. Mazer et al (9) state that irradiation therapy has a stimulating effect and is a valuable means of therapy in amenorrhea where there is pituitary or primary ovarian dysfunction. Mazer and Spitz (10) point out that true stimulation is evidenced by the restoration of ovarian function and menstrual periodicity and that this is in contradistinction to the improvement in genital function that occasionally follows destructive irradiation of pituitary or adrenocortico adenoma.

However, these investigators have based their arguments of a "stimulative" effect only upon biological and physiological sequences following irradiation. It is very feasible, as Tamis (11) points out, that the "stimulating" effects following the use of roentgen therapy are due to the destruction of some

inhibitory force. He states that it is erroneous to think of x-ray irradiation as a "stimulating" agent, because it is always a destructive force. It has been shown with experimental animals that there is a selective sensitivity of the various structures in the ovaries of mature rabbits and dogs to x-rays, the most sensitive structure being the maturing follicle, and the least sensitive being the corpus luteum, following the rule that the more immature the cells the more radiosensitive they are.

It is generally known that cystic ovaries tend to inhibit proper menstruation, and that when these cysts are mechanically ruptured, menstruation should follow. Stein and Leventhal (12) believe that low-dosage irradiation produces a hyperemia with subsequent swelling of the tissues and in this way perhaps mechanically causes rupture of an existing ovarian cyst. Rock et al (13) and Desjardins (14) are also of the opinion that the beneficial effects of low-dosage irradiation in the treatment of amenorrhea and dysfunctional uterine bleeding result from the destruction of a persistent corpus luteum or of an abnormally large Graafian follicle which had failed to rupture spontaneously. This theory would seem plausible on a hyperemic basis with subsequent mechanical rupture, but when a destructive action, per se, by the x-rays is assumed, the escape from damage of the remaining essential and more vulnerable elements of the ovaries would have to be explained. Usually this opinion has been stated as an impression only, and has not been supported by clinical evidence.

By following the hormonal excretion pattern before, during, and after irradiation therapy, Rakoff (15) attempted to provide evidence indicating whether the effect was primarily on the pituitary or on the ovary, so that the modus operandi of response could be determined for several types of menstrual dysfunction. His results were not sufficiently indicative to warrant conclusions in this regard, but certain observations suggested possible underlying mechanisms. In one patient with a primary ovarian deficiency who showed some improvement, there was a simultaneous fall in the gonadotropins and a rise in the estrogens. He surmised that in this instance the effect of irradiation was primarily on the ovary, producing a rising titer in the estrogens. The fall in gonadotropins was believed to be a secondary effect rather than a direct depressing effect of the x-rays upon the pituitary. This would appear to be only an analysis of the end result of irradiation and would not explain the basic fundamental action of the x-rays in producing this result.

In view of these seemingly conflicting clinical and experimental observations the understanding of the action of low-dosage irradiation to the pituitary and ovarian glands must take into account the independence of the functional results from indiscernible structural changes in the cells. Rubin (6) believes that it is conceivable that the action of the x-rays upon the ovaries may change the molecular structure of the ketosteroids which are stored in granulosa and theca cells of the ovary and which are

inert. X-rays may alter these more or less inert steroids so that an active alpha estradiol, which is analogous to the conversion of ergosterol activated by ultraviolet rays to form vitamin D or calciferol, may be produced. He leaves this research problem to the biochemists.

It is now generally acknowledged that there is a definite interrelationship of the pituitary, thyroid and ovaries in bringing about the menstrual phenomenon. The menstrual cycle is dependent upon the harmonious interaction of the gonadotropic hormones of the basophilic cells of the anterior pituitary lobe and the estrogenic and luteal hormones produced by the ovaries. The follicle stimulating hormone of the anterior pituitary must be present to insure the maturation of the ovarian follicle and the normal secretion of estrin. The luteinizing hormone of the anterior pituitary must also be present in a proper amount to maintain the physiological development of the corpus luteum of the ovary and production of its hormone, progestin. If sufficiently pronounced, any disturbance in the integrity of this chain of endocrine factors will affect the intimate relationship and result in menstrual dysfunction and possibly sterility. Functional amenorrhea probably results from a defect in the synchronism of the pituitary, ovary, and uterus, with thyroid activity depending chiefly on the balanced action of the pituitary. At the present time it will probably be best to consider a dose of roentgen rays too small to produce even microscopic changes in

the cell, yet capable of modifying its functional activity, possibly through indiscernible effects, with the end result being the correction of the defect in balanced activity of the endocrine system.

SAFETY OF THE PROCEDURE

Most of the writers on this subject believe definitely that the small doses of therapeutic irradiation applied to the ovaries and pituitary for amenorrhea and sterility, when properly administered, will not produce harmful effects upon either the mother or her offspring. The fear that this form of treatment will have deleterious effects upon the fetus or offspring if pregnancy should follow is twofold. Murphy (16) showed that massive doses of x-ray during pregnancy may lead to fetal abnormality and destruction. This observation has been substantiated many times since by other investigators. However, this would not seem to be applicable to this form of therapy because only small doses and not massive doses, are used; and pregnancy is a definite contraindication to the use of this form of treatment and is meticulously ruled out before low-dosage irradiation is given.

Secondly, it is feared that roentgen rays may produce mutations within the genes which will be transmitted to the offspring and result in the increased production of undesirable characteristics within the species. Intensive investigations into the effects of irradiation on genetics were started when Muller (17)

first noted in 1927 that roentgen rays were able to induce mutations in the fruit fly, Drosophila. The induced mutations from x-rays were indistinguishable from those occurring spontaneously, but the rate of mutation was much greater than that of the natural appearing ones.

Friedman and Seligman (18) have shown that the litter and succeeding generations of irradiated mice differ both in quantity and quality from those of controls, even when the x-ray dosages used were kept very small. These authors hold that the changes in inherited biologic characteristics produced by irradiation are in the mutations which are markedly increased by irradiation of the genital glands. It is correctly stated that not all genetic effects of irradiation on experimental animals can, as yet, be translated to man; but, on the other hand if a normal child is born of an irradiated mother, one cannot conclude that the possibility of injury to the hereditary factor has not taken place. The long life span of human beings, the small number of offspring, the difficulty of controlling experiments, lack of knowledge of the specific dose received, and inability to determine the proportion of genetically produced fetal abnormalities complicates this genetic study when applied to man.

Mutations in dominant genes may be detected in the next generation, while recessive mutations may go undetected for several generations. Since the majority of mutations, both natural and radiation, are recessive, little change can be expected

in the first generation; and, being recessive, the probability that they will manifest themselves in succeeding generations would seem to be relatively small. Robert Hugh (19), a geneticist and Associate Professor of Radiology at Columbia, prepared a paper which would seem to bolster the arguments of those not too enthusiastic about this method of therapy. It is quoted here. "Ionizing radiations are the most effective form of activation which brings about hereditary changes, no matter how small the dose. The effects of radiations on genetic material are cumulative. Most effects are harmful and therefore undesirable. A total dose of 50 r. doubles the rate of the spontaneously-appearing mutations in the animal. The effect is long delayed and is never seen in the first generation. It will, however, eventually cause a genetic death. It is conceivable that any exposure to ionizing radiations of the gonads carries some hazard. If 20,000 people are exposed so that their gonads receive 150 r. x-rays, 1,000 will eventually die a genetic death and several thousand will be maimed. For each 100 r. to which the human sperm are exposed, 10 per cent of the subsequently fertilized eggs will die in utero and 0.5 per cent of the live-born children will show structural abnormalities, and many of them will prove to be sterile or semisterile as adults."

At the present time it is impossible to determine the complicated chain of electrochemical events which operate within the genes to produce mutations, and therefore, the observation of

the ultimate results of these events, the study of cell morphology, must be the only means for interpretation. Observation of many succeeding generations of irradiated patients is necessary to prove that the hereditary characteristics of the offspring have been altered. Kaplan (20) has recently reported a follow-up of thirty-four children whose mothers were irradiated twenty or more years ago. Twenty of them have already married and up to the present time have produced fourteen normal living children, that is, third-generation children, or grandchildren, of the women originally treated with x-ray therapy for sterility. All of these grandchildren have been proved to be normal in every respect and no adverse genetic effects are noticeable in either the second or third generation of such irradiated women.

It seems that the enthusiastic proponents of this form of therapy take the short range view that "it is results that count;" and on this point published results would certainly seem to leave no room for argument, for the irradiation plan seems to be more frequently effective in the treatment of many cases of amenorrhea and infertility than is possible from endocrine or constitutional therapy. As to the long range effects upon subsequent generations which the geneticists emphasize as the real hazard, there is really no evidence available; the few scattered reports on children and grandchildren of patients thus treated seem to be of no statistical significance. The hypothetical objection to low-dosage irradiation on the basis of its harmful effects upon succeeding

generations can not, as yet, be relevantly argued. The concept that x-rays invariably cause structural, and consequently functional deterioration of human cells is partly responsible for the reluctance of the profession to use this effective means in the treatment of amenorrhea and sterility. The published clinical results of many gynecologists and radiologists refute this belief. Where pituitary irradiation alone is employed successfully, the problem of influencing heredity can be avoided.

Frank (21) and others have reported a prolonged or permanent amenorrhea with or without menopausal symptoms in a few cases following low-dosage irradiation therapy. Of 480 patients treated Mazer and Israel (22) state that only seven experienced an aggravation of the amenorrhea. They rightly warn, however, that in ovarian irradiation the margin between harmless and harmful doses is limited. Mazer and Greenberg (23) state that in 28 regularly menstruating women the alteration was only temporary and that none of them became amenorrheic.

Hoffman (24) warns that in the treatment of functional menstrual disorders irradiation is applied to subnormally functioning ovaries which may be further depressed by a dose of x-ray which might leave the normal ovary unharmed. First (25) has found a large number of sterility patients who have not had treatment but abort within a few months after becoming pregnant; and patients who, after a great deal of endocrine therapy, go to term, but deliver an abnormal fetus--evidence of so-called low reproduc-

tive efficiency or poor germ plasm. He believes it is illogical to refuse to treat sterility patients because of these remote possibilities. The large number of sterile women who have delivered healthy children warrants trying all the means available to cure them. Since a higher incidence of blighted ova is to be expected in these women regardless of the type of therapy employed, there is no justification in fearing to use low-dosage irradiation. Most authors agree that satisfactory clinical observations warrant the use of radiation, and as yet the problem can not rationally be approached on the basis of theory or animal experimentation.

Of the numerous statistical reports in the literature on the clinical effects of low-dosage irradiation of the pituitary gland and ovaries, not one is unfavorable. Irradiation of the pituitary even with massive doses does not seem to have a deleterious effect. Crooke (26) has found no changes in the pituitary gland attributable to treatment with x-rays for inoperable brain tumor, the doses being usually about 1,600 r. direct to the brain base. The pertinent studies of Hartman and Smith (27) on the effects of low-dosage irradiation to the pituitaries of anovulatory monkeys failed to reveal any significant beneficial or harmful effects. Randall (28) recently stated that roentgen irradiation of the pituitary body, the ovaries, or both, has been used safely and effectively at the Mayo Clinic for eighteen years. Further benefit, both in the treatment of menstrual dysfunction and fertility, has occurred from courses of irradiation given for the second or

even third time with no ill effects, although the dangers of such repeated courses have been stressed. It is the consensus of opinion that these small doses of preconception x-ray, when properly administered to the pituitary and ovaries, will not produce unfavorable effects upon either the patient or first generation offspring.

SELECTION OF CASES

Drips (29) distinguished two groups of the amenorrheic type clinically. By amenorrheic type is meant that menstrual dysfunction in which there is a tendency to longer than normal intervals between the menstrual periods and a decrease of flow or complete absence of menstruation. One group of patients had no symptoms associated with amenorrhea, aside from the complaints of menstrual irregularity and perhaps a tendency to gain weight during these periods of amenorrhea. These cases were thought to be on a basis of pituitary failure. The second group had many complaints associated both with the periods when they had them and with the periods of amenorrhea. These symptoms of which they complained were similar to those which women experience during the early climacterium when there is physiologic ovarian failure. This group was classified as cases of primary ovarian failure. These observations were later substantiated by laboratory studies determining the amount of gonadotropic hormone from the anterior lobe of the pituitary and estrogenic substances in the urine.

This investigator states that cases of ovarian dysfunction due to pituitary failure outnumber those due to primary failure of the ovaries. Pituitary failure was classified as exogenous and endogenous. The exogenous type was disturbed pituitary function brought on by general systemic conditions, including changes in dietary habits as well as disease states, and most frequently by emotional upsets more prone to occur in young women. This exogenous type of pituitary dysfunction is easily remedied by general hygienic measures, administration of thyroid extract, and cyclic administration of estrogens and progesterone, if the concomitant amenorrhea has not lasted long enough to bring about much atrophy of the uterus.

The endogenous type of pituitary failure is due to lack of functional development of the gland or to some disturbance of undeterminable etiology. For this type of pituitary dysfunction and amenorrhea low-dosage irradiation over the pituitary and ovaries is used. Administration of potent estrogens cyclically for a few months following irradiation was found to enhance the action of the irradiation and effect a longer period of menstrual regularity. The incidence of abortions following pregnancy which occurred soon after irradiation was also decreased by administration of potent estrogens.

In the cases of primary ovarian dysfunction when administration of thyroid extract, pelvic heat and estrogens fail to improve ovarian function, low-dosage irradiation is given over the ovaries

only, as a rule. If the woman is not having hot flushes, it apparently does no harm to irradiate the pituitary, but it is thought that little is gained. These clinical observations are presented in a very logical manner and are supported by laboratory studies. It has application in the determination of which gland is primarily at fault and serves as an indication as to where irradiation should be directed, as well as what causes may benefit by additional treatment with estrogens.

Drips believes that the goal to be sought in the treatment of young married women complaining of menstrual irregularity and sterility is the establishment of regular periods until pregnancy can occur. No patient ever comes directly to the radiologist for roentgen-ray treatment for sterility. Practically every case is referred from a gynecologist because every other available treatment has proved unsuccessful. Kaplan (30) believes that any woman who desires a baby and who has failed to respond to other therapeutic measures should have a trial with irradiation.

It must be determined that the husband is not infertile before x-ray therapy is used. Some investigators advise charting of the basal temperature record, which will indicate the time of ovulation or the presence of pregnancy when, of course, irradiation is not indicated. In almost all amenorrheal women subjected to low-dosage irradiation a biologic test is performed to exclude the possibility of pregnancy, unless the patient happened to have had a menstrual flow within two weeks preceding the onset of

therapy. The patient is usually instructed to abstain from intercourse until the course of treatment has been completed.

Patients are selected after a careful history and physical examination show no evidence of constitutional debilitating disease, diabetes mellitus, or thyroid malfunction. A careful pelvic examination and study should eliminate the possibility of uterine fibroids, the absence or destruction of the generative organs or tubal closure. As a rule patients under sixteen or over forty are not treated, as in the former the ovaries are presumably immature and more sensitive to x-ray, and in the latter, are naturally declining in function.

TECHNIQUE OF IRRADIATION

Some investigators are inclined to attach prime importance to the treatment of the pituitary body in correcting the menstrual dysfunction. Kotz and Parker (31) restored normal menstrual function in 56 per cent of their patients by irradiation of the pituitary body alone. But, as Campbell (32) points out, although pituitary irradiation alone appears to be efficacious many successful results have followed radiation of the ovaries alone. Since normal genital function of the female depends on the proper correlation of the endocrine activity of both the pituitary and ovaries, it seems logical that the best results follow selective roentgen therapy to both structures. Clinically, with the perfection of technic, combined treatment has considerably improved the results.

Most radiologists employ the technique of Edeiken (33) or Kaplan (34) with uniformly good results. Edeiken's technique may be described as follows: One hundred thirty-five kv., and 5 ma. at a distance of 35 cm., filtered through $\frac{1}{4}$ mm. Cu. and 1 mm. Al. administered so that the pituitary receives 50 to 90 r. air units through a 5 x 5 cm. temporal portal at weekly intervals for three weeks, and each ovarian pelvic area receives 50 to 90 r. air units weekly for three treatments through alternating anterior and posterior 10 x 12 cm. portals.

Kaplan's technique consists of using the factors of 200 kv., 4 ma., 0.5 mm. Cu. plus 1 mm. Al. filter, with a target distance of 30 to 40 cm. Treatment is directed through the anterior and posterior right and left pelvic fields, using 9 x 12 cm. to 12 x 15 cm. portals, and to the pituitary area through a 3 x 3 cm. temporal field. A dose varying from 75 to 150 r. measured in air is given weekly for three weeks. The pelvis is irradiated anteriorly the first week, posteriorly the second week, and anteriorly the third week. The pituitary is given similar dosage at the time the pelvis is treated anteriorly.

Approximately the same total roentgen dosage is delivered in both of these methods, in general, about 35 to 50 tissue roentgens being the total dosage reaching the ovaries and pituitary. Campbell (31) states that in cases which show clinical signs of definite pituitary insufficiency, the total dosage to this gland may be safely increased to several times that mentioned above for a

greater stimulating effect and because of the high resistance of the anterior lobe to destruction by irradiation. It has been found that close adherence to these techniques avoids the occurrence of ill effects. Variation in dosage and method of application would seem to be confusing insofar as determination of final results is concerned.

CLINICAL RESULTS

All of the workers in this field are highly enthusiastic about their results and believe that organotherapy is far less effective than irradiation of the affected endocrine glands in the successful reestablishment of menstrual regularity. If a favorable response is obtained, menstruation returns within six weeks to be followed by normal menstrual cycles, and with associated sterility, pregnancy usually follows immediately or at least within a few months after administration of irradiation. As yet there is no satisfactory way of determining before treatment which cases will respond.

Over the course of twenty-three years a total of 402 married women have been treated by Kaplan (35) for amenorrhea and sterility. Of these, ninety-five were not traced, sixty-four failed to respond to treatment, and 242 were cured of amenorrhea. Of these 120 became pregnant, 98 went to term, 22 more than once. These patients gave birth to 125 normal living children, 58 boys and 67 girls, with one set of twin girls. There were 32 pregnancies following

irradiation without living children. Of these 24 miscarried, several a number of times, and of these 10 subsequently gave birth to normal children. There were two ectopic pregnancies. One patient had a stillbirth and three had normal births with the children dying a few hours after birth. There was one abnormal child and one case therapeutically aborted. Two cases were treated with two courses of roentgen therapy and both gave birth to a second normal healthy child. Two women who did not respond adopted babies and one of these women later became pregnant. There were eight cases still pregnant at the time of publication of his paper.

Mazer (22) in 1943 reported on ninety-two cases. Ten of these had no menses from sixteen months to six years, and five are now regular in from one to five years of observation. Twelve of the ninety-two cases menstruated on six-month cycles. Eight of these are having normal menses. Sixty-eight of the ninety-two had oligomenorrhea with two to four month cycles. Fifty-two, or 76.5 per cent of these have been menstruating normally from one to five years. A second course of therapy was given to ten of the ninety-two cases. Three of these were restored to normal function following the second dose. Mazer points out that the percentage of cures is inversely proportional to the severity of the amenorrhea. Thus, those who had menstruated at intervals of two to four months yielded the highest number of successes. Thirty of fifty-four infertile women conceived at variable intervals after the

the completion of the treatment. Twenty-eight delivered normal infants and the remaining two aborted during the first trimester. Twenty-one of thirty conceived within four months after combined low-dosage treatment, and a few without any intervening menstrual flow. Complete restoration of the menstrual function for over one year in nineteen of the twenty-one women who conceived soon after treatment implies that conception was the result of stimulated ovarian activity. Two successful pregnancies followed a second course of irradiation given after the first course failed to completely restore menstrual function. Of Mazer's ninety-two cases sixty-two per cent are menstruating normally.

Reidenberg (36) reports a long-term survey of 136 patients followed for three to thirteen years. Restoration of normal menstrual function occurred in 71 per cent of fifty-one women with amenorrhea, 78 per cent of thirty-seven with oligomenorrhea, 57 per cent of seven with hypomenorrhea, 59 per cent of twenty-seven with menorrhagia, and 50 per cent of ten with metrorrhagia. Four patients with primary amenorrhea were unaffected. The percentage of cures for the whole group was sixty-six. Forty-four were either unaffected or only temporarily improved. The return of menstrual function in fifty-seven patients with associated sterility materially aided in conception of thirty-four cases. Of ninety pregnancies in fifty-four women, eighty resulted in full-term healthy offspring.

Edeiken (33) in 1933 reported on a series of 56 amenorrheic patients. In 40 there was a return of normal menstruation. There were 33 cases of associated sterility with the amenorrhea. Of these there resulted 15 pregnancies in fourteen patients. Drips (29) reports on 123 young married women treated with low-dosage irradiation. Thirty-four, or 27.6 per cent, had become pregnant directly after treatment. Eighty-two women stated that their normal menstrual periods were definitely more regular after treatment and of these, 45 became pregnant and have had 67 full-term pregnancies; one patient gave birth to a monster after a full-term pregnancy.

Payne (37) states that thirty-two (65 percent) of 49 women treated by pituitary and ovarian irradiation demonstrated improvement in basal body temperature curves and endometrial biopsy patterns. Nineteen patients conceived. There were 29 pregnancies; 15 full-term, seven miscarriages and seven patients now pregnant. The incidence of abortion and miscarriage was 24 per cent. Of thirty-one patients treated by Siegler (38) with x-ray therapy, six had ovulated previously with hormone therapy. Of the remaining twenty-five, 20 (eighty percent) became ovulatory, and five (20 per cent) remained anovulatory. Fifteen (48.4 per cent) pregnancies resulted. Of these two were miscarriages, one at five months, the other at three months. Of 25 patients who remained anovulatory with both hormonal regimens twenty developed ovulatory cycles following irradiation. Small doses of estrogen

were concurrently given following x-ray therapy for the stimulating action on the uterus. Many other series of cases have been recorded in the literature with equally good results.

It has been reported repeatedly that the best results have occurred in women with secondary amenorrhea of relatively recent origin, although some favorable results have occurred even after prolonged periods of amenorrhea. Primary amenorrhea is usually not amenable to this type of therapy, probably because it is a manifestation of genetic deficiencies in the uterus or ovaries. Younger women are generally more responsive than those in the later years of reproductive life, but again there are many exceptions. Patients with excesses of bleeding of functional origin do not respond as well as those with secondary amenorrhea, oligomenorrhea, or hypermenorrhea. Poor results are generally obtained in women with normal or relatively normal menstrual cycles so far as fertility is concerned. Patients with hot flashes and other manifestations indicating a primary ovarian deficiency generally do not respond as well as those without these symptoms.

SUMMARY

This paper is a presentation of irradiation therapy as it is used for the correction of amenorrhea and sterility. The modus operandi of this form of treatment is still a moot question. Clinical observations would lead one to suspect a stimulating action, as the end result at least, but would not eliminate the possibility of the destruction of some inhibitory force. The understanding of the action of low-dosage irradiation to the pituitary and ovarian glands must take into account the independence of the functional results from indiscernible structural changes in the cells.

Clinical investigators agree that small doses of preconception x-ray, when properly administered to the pituitary and ovaries, will not produce unfavorable effects upon either the patient or first generation offspring. Fourteen third-generation children or grandchildren of women originally treated with x-ray therapy for sterility have been reported to be normal in every respect with no apparent adverse genetic effects. The point which a geneticist emphasizes is that once a mutation is produced, and ionizing radiations seem to be the most efficient means of producing mutations, it is permanent so long as it is carried from one generation to another through the gametes and ultimately, if that gene carries a lethal mutation, it will express itself. It may be 100 generations hence. There is enough evidence that this

possibility exists, regardless of whether you use Drosophila eggs, bean shoots, or mice, and it has been shown by many geneticists.

No one has been able to demonstrate the occurrence of genetic abnormalities in the progeny of properly therapeutically irradiated women definitely comparable to the genetic injuries noted in experimental animals following irradiation. In evaluating the genetic injuries from x-rays the geneticist states that lethal injuries disappear immediately. Dormant mutations, if lethal, become evident only when present in sufficient numbers to provide a chance of their coming together in the mating of two individuals carrying them. In a population of nearly 180 million the chance that progeny of an irradiated mother will marry progeny of another similarly irradiated mother is rather slight. It seems more remote if one considers that there exist many potential possibilities for mutations and radiation therapy is unlikely to produce the same mutation in appreciable numbers.

Life, in general, is a calculated risk anyhow and with atomic scientists playing with bigger and better H-bombs, it seems ridiculous to shake a finger at radiologists for irradiating only a very small percentage of the population where there is no inbreeding for this treatment.

If a woman is confronted with a sterility problem and has tried more conservative therapy with no success, then, if one explains the possibility of mutations in two or three, or 100

generations following irradiation therapy, I believe one has done the ethical thing.

There have been no unfavorable statistical reports in the literature on the clinical effects of low-dosage irradiation of the pituitary gland and ovaries. Prolonged or permanent amenorrhea has been reported in a few cases following irradiation but this number is not significant.

Patients are selected after a careful history and physical examination show no evidence of constitutional debilitating disease or anatomical abnormality of the generative organs. Pregnancy is a contraindication, and of course, it must be determined that the husband is not infertile.

Two techniques of irradiation of the ovaries and pituitary have been described. Both deliver approximately the same total roentgen dosage, in general, about 35 to 50 tissue roentgens reaching the irradiated glands. Close adherence to these techniques avoids the occurrence of ill effects.

Favorable responses usually follow immediately or at least within a few months if the therapy has been successful. There is no satisfactory way to determine before treatment which cases will respond.

Clinical results of several investigators have been presented. The results have all been favorable and tend to parallel one another.

CONCLUSION

Low-dosage x-ray irradiation has been proven to be more effective than other methods in the treatment of amenorrhea and sterility.

Small doses of preconception x-ray, when properly administered to the pituitary and ovaries, will produce no unfavorable effects upon either the patient or first generation offspring. Although satisfactory statistical data are lacking at the present time, it seems unlikely that the second generation offspring of irradiated mothers will be adversely affected. The genetic influence of low-dosage irradiation can be determined only after observation of many succeeding generations of irradiated patients, unless some means to determine the complicated chain of electrochemical events which operate within the genes to produce mutations is found.

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