the two countries, but they were of comparable importance, and no other country can claim any substantial share in the credit. The recent advances in anaesthesia are, however, divided between Canada, the United States, and Germany. The change in our country's position is regrettable. I would suggest that what is needed is an organization of the methods of study of anaesthetics that will permit the accurate estimation of the value of new methods, which, even if they do not provide any sensational advance, yet may be a significant improvement on established methods.

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H. C. Ling, L. Greene, and S. E. Pai (*Chin. med. J.*, 1938, **54**, 177) record two fatal cases of diphtheria gravis bacteraemia. The first, which is only the second example of the condition to be reported in China, occurred in a boy aged 12 who had a severe attack of faucial and nasal diphtheria and died after about ten days' illness. The gravis type of diphtheria bacillus was isolated from the blood. The second case was that of a girl with grave faucial, laryngeal, and bronchial diphtheria, who died after four days' illness. The gravis type of diphtheria bacillus, together with a non-haemolytic streptococcus, was cultivated from the heart blood seven hours after death.

RADIOTHERAPY IN NON-MALIGNANT UTERINE HAEMORRHAGE*

BY

B. WINDEYER, M.B., B.S., F.R.C.S.Ed., D.M.R.E.

Medical Officer in Charge, Meyerstein Institute of Radiotherapy, Middlesex Hospital

Diagnosis

The first point to be considered in cases of abnormal uterine haemorrhage is the question of diagnosis. Only too frequently do we see patients who have complained of irregular or excessive bleeding at or about the menopause for which no attempt has been made to discover the cause. Many patients believe that such irregular bleeding is a normal phenomenon and do not seek medical advice; but in some cases they do so, only to be reassured, and to be told to wait for a month or two, when the bleeding will stop, no vaginal examination or other investigation being made. It is from cases such as these that a large proportion of patients with advanced carcinoma of the cervix eventually come for treatment, after a delay of months and when the prospect of cure is very considerably reduced or it is impossible. It cannot be emphasized too strongly that when such symptoms appear the patient must be examined immediately and thoroughly for the possibility that the symptoms may have causes other than menopausal dysfunction of the ovaries, and especially must a thorough pelvic examination be made, to exclude malignant disease.

Apart from this all-important question of diagnosis I do not propose to deal with the vast subject of malignant disease of the uterus, but to consider those types of non-malignant uterine haemorrhage in which radiotherapy is employed. These cases fall into three categories: (1) bleeding at or near the menopause; (2) bleeding associated with fibroids; (3) bleeding in young subjects.

How Radiotherapy Acts

The manner in which radiotherapy acts in the treatment of these cases has been the subject of considerable discussion. It is generally agreed that when external irradiation by x rays is the method employed the production of amenorrhoea is due to the destructive effect on the more mature follicles of the ovary. Much experimental research has been carried out on this subject, and Regaud and Lacassagne (1927), describing the effects of radiation on normal tissue, give a clear and concise account of the changes that occur. All ovarian follicles can be destroyed if the dose of radiation is large enough; but there is a very great difference in their radiosensitivity, depending on the stage of maturity. Immature ovarian follicles have little radiosensitivity, and escape apparently unscathed even after heavy irradiation. As they develop, their degree of radiosensitivity increases, until finally the mature follicle is very radiosensitive and is destroyed by only a small amount of radiation. In the ovary of a woman at the end of her reproductive life and approaching the menopause the follicles which remain are either mature or approaching maturity, and therefore are highly radiosensitive. In such cases permanent sterilization can be brought about by moderate doses of radiation. With the young subject, however, this is not the case: some follicles are approaching maturity and are therefore radiosensitive; but the majority have not begun to develop, and need much greater doses for their destruction. A frequent

* Read in opening a discussion in the Section of Radiology at the Annual Meeting of the British Medical Association, Plymouth, 1938.

result of radiotherapy in a young patient is temporary sterilization, with the return of more or less regular and normal menstruation after a period varying from a few months to one or two years.

There is less agreement as to the action of radium placed in the uterine cavity, and two views are commonly expressed: (a) that radium acts on the ovaries as in the case of external irradiation by *x* rays; (b) that amenorrhoea is produced by a fibrosing action on the endometrium and underlying blood vessels. The usual argument in favour of endometrial action is that, by the physical laws governing the distribution of radiation, the intensity received on the ovaries from radium placed in the uterine cavity can be only a small fraction of that received on the endometrium, and that the dose received by the ovaries would not be sufficient to cause sterilization. Forsdike (1922-3), who strongly supported the theory of endometrial action, has produced evidence of destruction of the endometrium with underlying fibrosis but with demonstrable effect on the ovaries. On the other hand, Corscaden (1935) has demonstrated that in the uterus which had received a sterilizing dose of radium a portion only of the endometrium was obviously affected. Clark and Norris (1927) have observed the destruction of ovarian follicles with regeneration of the endometrium. Actually, assuming that in the average case the ovary is 4 cm. from the endometrium and that, including the thickness of the container, the endometrium is 0.5 cm. from the radium, the dose received from 2,400 mg.-hours filtered by 1.5 mm. platinum with an active length of 4 cm. would be between 10,000 and 20,000 *r* on the endometrium and between 500 and 1,000 *r* on the ovary, depending on their position in each individual case. This is a very heavy dose on the endometrium, and undoubtedly will produce some destruction; but the dose on the ovary, comparing it with the *x*-ray dose given for sterilization, should be sufficient to destroy the follicles.

Again, amenorrhoea produced by intra-uterine radium is almost always accompanied by the menopausal symptoms of hot flushes (86 per cent. in Moore Patterson's (1933) series). A recent article by Corscaden, Kasabach, and Lenz (1938) points out also that examination of blood and urine of women made amenorrhoeic by radium or *x* rays has shown the characteristics found in the spontaneous menopause—absence of oestrone and increase of prolan.

I think the weight of evidence is definitely in favour of action on the ovaries being the main factor in the production of amenorrhoea by radium, but that changes in the endometrium are probably contributory. Abnormal position of the ovaries may account for the small percentage of failures.

I. Irregular Haemorrhage at or about the Menopause

Radiotherapy is undoubtedly the treatment of choice in this condition. In the joint discussions held by the Sections of Radiology and of Obstetrics and Gynaecology at the Royal Society of Medicine in 1933 and in January of 1938 there was general agreement on this question. The advantages of radiotherapy over surgery in this condition are that the same result can be obtained by irradiation with less risk and with a much shorter and almost negligible period of convalescence. The treatment can be carried out either by *x* rays or by the insertion of radium into the uterine cavity. Whatever the method, a preliminary dilatation and curettage is advisable; if radium is inserted the treatment is completed and the patient returns home with scarcely any more delay than from

curettage alone, while for the actual *x*-ray treatment she need not even be hospitalized.

Mr. Leonard Phillips (1938) collected from twenty authors over 7,000 cases of menopausal menorrhagia and of fibroids treated by irradiation, with a 95 per cent. cure rate. He estimated that over half of these were cases of menopausal menorrhagia. The mortality rate given by twelve authors was under 1 per cent. for each series and averaged 0.25 per cent. for the whole. The report of the Radiumhemmet in Stockholm (1937) shows 282 cases of this condition, with only one death from intercurrent disease and only two cases which were not cured.

The mortality rate from *x* rays is negligible, while the few deaths recorded from radium have been almost entirely due to an occasional embolus. Moreover, in the very small number of failures of radiotherapy subsequent surgery is not rendered any more difficult. The only contraindications in patients about or over the age of 40 would seem to be the presence of an associated prolapse or cervical laceration, which could be cured at the same time by surgical intervention, or the presence of a previous pelvic inflammation; but even this latter need not be a contraindication if *x* rays are employed and the treatment is given slowly and carefully.

An analysis of sixty-one consecutive cases of menopausal menorrhagia which I have treated at the North Middlesex County Hospital gives the following data:

No. of Cases	Result	Remarks
57	Successful	37 had no further bleeding 13 had one subsequent period 7 had no subsequent periods
1	Partially successful	Periods for 18 months at regular intervals, but very scanty in amount
1	Unsuccessful	Hysterectomy 4 months later for a recurrence of bleeding
2		Subsequent history untraced

COMPLICATIONS AND SEQUELAE

The complications arising from treatment were not serious. The most frequent one was a watery discharge, which was present in twelve cases and persisted from one to four months. The discharge is undoubtedly due to the destruction of a portion of the endometrium by the intense irradiation which it must receive if a sufficient effect is to be obtained on the ovaries. The heavy filtration of 1.5 mm. of platinum and a rubber cover is used to minimize this effect as far as possible. With less filtration one might expect a higher proportion of cases with discharge, and this possibly accounts also for the cases of pyometra which have been described in other series.

Cases of ulceration or cicatricial stenosis of the vagina have been reported after radium treatment, but these have undoubtedly been due either to insufficient packing of the vagina, so that the radium has slipped out of the cervix, or to the use of irritating chemicals in the packing. Corscaden and others have reported cases where a loop of small intestine adherent to the uterus has been damaged by intra-uterine radium and old pelvic inflammation has been lighted up by this treatment, but none of these complications occurred in my own series. In the large number which Phillips collected there were several deaths from embolism, and, as I have said previously, the mortality for the whole series was only 0.25 per cent.

THE CHOICE OF RADIUM OR *x* RAYS

In my own series of cases radium has been used almost exclusively, and the complications have all been due to radium insertion. Such complications have not been

reported after the use of x rays alone, and the production of amenorrhoea has been just as certain. The main arguments which have been advanced in favour of radium are: (1) That it is necessary to make a thorough examination under an anaesthetic, with dilatation and curettage in cases of menopausal haemorrhage, and that it is very convenient to insert radium at the time; the whole treatment thus being completed in a few days. (2) That the action of radium may be on the endometrium and may cause less depression of ovarian activity. As I have said, I think the weight of evidence is opposed to this theory.

In favour of x rays it may be said that: (1) there are no complications such as discharge due to endometrial destruction; (2) in cases of diabetes, cardiac disease, etc., when a diagnostic curettage must be omitted, no anaesthetic is necessary; (3) there is no danger of embolism or damage to an adherent loop of intestine; (4) even in cases of pelvic inflammation x rays can be used if given slowly and carefully; (5) there is no reason why x rays should not be employed after a preliminary dilatation and curettage. In addition, radium causes a varying degree of discomfort, nausea, and perhaps vomiting during the time it is in the uterus. This is avoided by the use of x rays, although such symptoms may also occur if x -ray treatment is carried out too quickly—for example, in a single treatment.

To sum up, I think that when both methods are available x rays are to be preferred.

TECHNIQUE AND DOSAGE

Radium.—In England probably the most common method is the one I have described—namely, the use of an intra-uterine applicator containing 50 mg. for forty-eight hours, giving a dose of 2,400 mg.-hours, with a filtration of not less than 1.5 mm. of platinum or its equivalent. Variations of this have been 75 mg. for thirty-six hours or 100 mg. for twenty-four hours, with the object of reducing the time the radium is in the uterus and thereby curtailing the nausea and discomfort. I think, however, that the greater intensity of radiation is more likely to increase the symptoms while the radium is in position. In America the doses have usually been somewhat smaller, but the filtration has been less; 1,800 mg.-hours with 1 mm. platinum filtration is about the maximum. Norman White (1933) showed that recurrence may arise after this dosage, and advised as much as 3,000 mg.-hours with 1.5 mm. platinum, or equivalent, filtration. In our series 2,400 mg.-hours was successful in all but two cases, and these patients were big women, both only 38 years old. In France it is common to use radium packed into the lateral fornices of the vagina as well as the intra-uterine dose, which is considerably decreased. This may be advantageous in that the radium is placed closer to the ovaries and the sequelae of endometrial destruction are diminished; the disadvantage is that vaginal contraction may occur.

X Rays.—Many varieties of technique have been described that aim at the production of amenorrhoea in cases of menorrhagia, and all have met with a high percentage of successes because sterilization in women approaching the menopause can be achieved by a very moderate dose of radiation received on the ovary. This in some cases has resulted in the use of the lower kilovoltages for this purpose, even though the majority of therapeutic x -ray machines in this country are capable of working at about 200 kV. A kilovoltage of 150 or even lower will produce amenorrhoea with a fair degree of certainty, but the dose necessary is close to the skin

tolerance, and there is more danger of causing skin damage than with an adequately filtered beam generated at 200 kV. Sterilization can be produced in women over 35 by an irradiation carried out in one day, but, as previously stated, this may give rise to a considerable amount of nausea and vomiting, which will be entirely avoided if the dose is fractionized and spread over a week to ten days. The effect is also more certain if the period of irradiation is prolonged. A method which we have found suitable is to use 200 kV with a Thoreux filter and a focal skin distance of 50 cm.; to irradiate three fields, one anterior and two postero-lateral, each about 10 by 15 cm.; and to treat daily, giving a dose of 300 r to each field in succession for a total of nine treatments—that is, three treatments of 300 r measured on the skin to each area. This results in a dose of 700 to 900 r to the ovaries. In very big women it may be necessary to increase the surface dose.

Menopausal symptoms such as hot flushes follow the production of amenorrhoea by either radium or x rays, and have been investigated by various workers—Donaldson and Moore Patterson (1938), Malpas (1937), Miss Martindale (1938). There is general agreement that they do not vary either in nature or in severity from those accompanying either the natural or the surgically produced climacteric.

II. Bleeding Associated with Fibroids

In uncomplicated cases of uterine haemorrhage associated with fibroids occurring in women about or over the age of 40 radiotherapy is the treatment of choice. Bleeding is controlled as rapidly and with the same sureness as in menopausal menorrhagia, and the fibroid decreases markedly in size in two to three months. In the case of large fibroids which may not entirely disappear the remnant causes no symptoms. The treatment is carried out in the same way as for menopausal menorrhagia: there are the same indications for the choice of x rays or radium, except that, in the case of fibroids, x rays seem to be more definitely indicated because the distortion due to the tumour may cause the ovaries to lie at an increased distance from the endometrium, with consequent diminution of the dose received from the intra-uterine radium.

Radiotherapy should not be used in the treatment of fibroids in young women unless there is some factor, such as cardiac disease, which makes the risk of surgery too great. The results are uncertain, and successful treatment invariably produces menopausal symptoms. Other contraindications to radiotherapy for fibroids are: (1) pressure symptoms—for example, interference with micturition through pressure on the urethra when a very rapid result is necessary; (2) evidence of degeneration of the fibroid; (3) very large fibroids. These latter tend to show incomplete regression and are more likely to undergo degeneration. Many radiotherapists do not agree that the size of the fibroid is a contraindication. Finzi (1933) in particular states that some of his most striking results have been in cases with very large tumours, in which operation would have meant considerable risk and prolonged convalescence.

III. Menorrhagia in Young Subjects

This is a field in which the indications for radiotherapy are much more debatable. In the past it has been accepted generally that these patients should be treated by hysterectomy, with preservation of the ovaries, if more conservative treatment has failed. A considerable amount of work has been done, however, the object being to produce a temporary cessation of bleeding by giving a

dose of radiation which would destroy the mature Graafian follicles but would not be sufficient to damage the undeveloped follicles; so that menstruation would become established after a period of amenorrhoea lasting for some months, and there would be a possibility of future pregnancy.

Phillips has tabulated the records of 165 patients, in 128 (77.5 per cent.) of whom normal menstruation was restored. These were mostly adolescents and young women under the age of 25. The treatment was by radium in every instance, and a small dose averaging under 500 mg.-hours was given. It would appear that this treatment is still in the experimental stage, and that the dosage cannot yet be expressed numerically with accuracy. The question as to the liability to subsequent normal pregnancy is even less clearly defined.

Corscaden, Kasabach, and Lenz (1938) record sixty-nine further cases which received a substerilizing dose of radium or x rays for menorrhagia, fibroids, or dysmenorrhoea. Eleven pregnancies occurred among six women in this series: five patients aborted; four children lived beyond infancy, and two died at the age of 6 weeks and 6 months. This is only a small series, and the larger numbers of Murphy and Goldstein (1929) and of Miller *et al.* (1936) indicate that preconceptional irradiation should have no harmful effect on subsequent pregnancies, and that certainly it does not cause any increase in the percentage of abnormal children and monsters. It may be thought that the four surviving children in Corscaden's series are sufficient indication that this method of treatment is of value; it is obviously much to be preferred to the alternative of hysterectomy in those cases of severe bleeding which sometimes occur at puberty. It should only be used, however, when all else has been tried, and patients should be warned of the possibility of permanent menopause which may result (with the present state of our knowledge) in a certain proportion, especially of those aged 30 and over.

Further, if one accepts the action of radium as being mainly on the ovary—and it appears that this is, the only way that the greater difficulty in sterilizing young women can be explained—it would seem advisable to use x rays rather than radium: the dose to the ovaries can be assessed with greater accuracy and there is less damage to the endometrium, with consequently a greater chance that an impregnated ovum can be retained.

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Small-pox has become an extinct disease in Poland, where the law on compulsory vaccination and revaccination is strictly enforced. Complications of vaccination are rare, and no cases of post-vaccinal encephalitis have so far been reported in Poland. In many towns where immunization against diphtheria is also compulsory protection against the two diseases is carried out at the same time.

THE TREATMENT OF NON-MALIGNANT UTERINE HAEMORRHAGE*

BY

BEATRICE M. WILLMOTT, M.B., F.R.C.S.,
D.M.R.E.

Honorary Surgeon and Radium Officer, Birmingham and
Midland Hospital for Women

The treatment of non-malignant uterine haemorrhage in women approaching the menopause—the only class of case which I propose to consider—calls for a nicety of judgment which is, I think, ideally to be expected of the gynaecologist with special training in radiotherapy. Those in whom the surgical instinct predominates habitually subject women to major operations which, as I hope to show, can be avoided in many cases by the substitution of radiotherapy. Radical operation entails a primary mortality which is inseparable from hysterectomy; moreover, in every practice there occur, not infrequently, cases which for one reason or another are bad surgical risks—heart and lung disease, obesity, and so forth. On the other hand, the indiscriminate use of radiotherapy will in some cases involve the retention of a dangerously unhealthy uterine cervix, and in other cases, notably submucous fibroids, a liability to sloughing, with the possibility of catastrophe.

It is my practice to use total abdominal hysterectomy in all cases showing an advanced degree of chronic cervicitis, in the presence of large fibroids causing symptoms, unless myomectomy is indicated, and in those judged to be submucous. I avoid sterilizing operations so far as possible by trying medical treatment and sometimes curettage in women who desire to add to their families. In all other cases, including bad surgical risks, I prefer to use radium. Deep x rays are not at the moment available for my patients, so in the field of radiotherapy radium for me is Hobson's choice.

My impression has been that radium is most valuable in suitable cases, and for the purposes of this discussion, and with the permission of my colleagues of the Birmingham and Midland Hospital for Women, I have investigated the results of cases treated in that hospital during the years 1935 to 1937. These results I propose to present here.

Analysis of Cases Treated with Radium

Of 226 patients presumed to have been reached by a questionnaire 199 replied. I have felt justified in assuming that those who failed to reply are a fair sample of the whole; probably any woman with a grievance would have seized this chance of airing it.

Diagnosis.—The cases are classified as follows: subinvolution seven, metropathia haemorrhagica twenty-two, fibroids twenty. Two cases are included in which radium was applied to bring about sterilization. The remaining 148 cases I have not attempted to diagnose scientifically, but have used the term "chronic metritis."

Dosage.—A single 40-mg. or 50-mg. needle was used, with screenage equivalent to 1 mm. of platinum. The needle was left *in situ* for from twenty-four to forty-eight hours, in a few cases for seventy-two hours. The dosage of radium element varied from 960 to 3,600 mg.-hours, the great majority receiving about 2,000.

* Read in the Section of Radiology at the Annual Meeting of the British Medical Association, Plymouth, 1938.