The Use of Radium in the Treatment of Benign Uterine Bleeding.

BY

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DURING the last 25 years radium has been used more and more in the treatment of benign uterine bleeding, and at the present time most gynaecological clinics would be in a position to produce an extensive series of cases. A forecast made by Lockyer¹ in 1914 is interesting and has certainly proved a true one. Discussing the recent developments in the X-ray and radium therapy of fibroids and carcinoma which had been made in France and Germany, he stated that the gynaecologist, who had started by being a physician and had already proved sufficiently adaptable to become a surgeon when surgery was required of him to fulfil his duties, must now similarly betake himself to the study of radiology. It would not indeed be far from the truth to say that at the present day radium finds a greater applicability to the treatment of benign bleeding than of malignant lesions.

The modern technique for the use of radium in the treatment of benign bleeding has developed out of its use in the treatment At the present time, however, fibroids occupy a of fibroids. place secondary to malfunctional bleeding among the indications for radium. For that matter the methods and results of the radium treatment of fibroids do not differ from those obtaining in the treatment of the other types of benign bleeding, subject to certain well-defined conditions which specially apply to fibroids. These conditions, first enunciated by Chéron² in 1909, are now generally accepted, and, subject to their recognition, the presence of a fibroid is merely an incidental factor when the question of the propriety of radium therapy is considered in a case of benign bleeding. Fibroids may, therefore, be best considered, not separately, but among the various other conditions which may limit the applicability of radium therapy.

MATERIAL OF THE INQUIRY.

In Liverpool we have treated 432 cases of benign bleeding with radium, and 200 of these cases have been available for afterstudy. A mere enumeration of the results we have obtained would be, at the best, but a repetition of the many thorough studies already published. For this reason, and also in view of the very success of radium therapy, most attention is given in the present paper to its failures and complications, both those encountered personally and those recorded in the literature.

Supplementing our own findings 37 foreign clinics have contributed personal communications, placing us very much in their debt. Our thanks are also due to our colleagues in Liverpool who allowed their cases and methods to be incorporated in the inquiry.

Free use has been made of the many papers which have been published, notably those shown in the following list, which in the aggregate deal with 2,183 cases.

Author						Year	No. of Cases
Blacker						1923	77
Dannreuther, V	V. T.				•••	1932	109
Donaldson	•••				• • •	1932	202
Forsdike	··· ·				•••	1926	200
Kelly, H. A.	•••					1915	36
Martindale					•••	1933	45
Martius, H.	•••		•••	•••	•••	1934	87
Murray, E. F.	•••		•••	•••		1928	30
McIlroy		•••	•••	•••	•···	1934	55
Naujoks	•••	•••		•••	•••	1934	285
Peightal						1932	600
Phaneuf, L.					•••	1934	150
Smith, W. S.	•••					1932	111
Titus						1920	91
Ward, G. Gra	у	•••		•••	•••	1932	309

TABLE I.

The subject falls naturally into the following sections, which will be considered separately.

- A. The Use of Radium for the Production of Permanent Amenorrhoea.
 - 1. Technique and dosage.
 - 2. Incidence of (a) failure to control bleeding; (b) radium

injuries; (c) menopausal symptoms; (d) post-irradiation carcinoma.

B. The Use of Radium in the Treatment of Menorrhagia with Conservation of the Menstrual Function.

I. Dosage. (Technique similar to that of Group A).

2. Incidence of (a) failures to control bleeding; (b) postirradiation fibrosis; (c) impairment of the reproductive function.

C. The Use of Radium in the Treatment of Post-menopausal Bleeding.

D. The Respective Scope of Radium and X-ray Therapy.

E. The Effects and Action of Radium on the Uterus and Ovaries.

(This section is considered last because any conclusions which may be reached are based on the clinical experiments embodied in the earlier sections.)

A. RADIUM IN THE PRODUCTION OF PERMANENT AMENORRHOEA.

Of our 200 cases 178 or 86 per cent fall into this category. Of these 7.5 per cent were between the ages of 51 and 55, 27 per cent between 45 and 50, 50 per cent between 41 and 45, 8.7 per cent between 36 and 40, 5 per cent between 31 and 35. Only one patient was under 30, a girl aged 29 suffering from mitral stenosis and intractable menorrhagia.

There were no cases of post-operative death in the whole series. There were four failures to control bleeding, a percentage of 2.2, although in three cases a secondary irradiation was necessary. These and other complications are discussed later.

1. Technique and Dosage.

In Table II, I have embodied the technique adopted by a representative series of observers who furnish personal communications. The table shows the close approximation of American and British practice, also the preference of Continental workers for the use of larger doses or for X-rays. At the end of the table are shown the reasons given by the chiefs of six clinics who avoid the use of radium.

W	ethods of	Clinics usin	ıg Radium to	produce Permanen	ut Amenorrhoea (based on personal c	ommunications).
	а 	OSAGE.				
Referenc	Mgms. te R.E.	Hours	Mgm. Hours	Screenage	Reservations and contra-indications	Failures.
America	п.					
Р.1	100	20	2000	Pt. 1 mm.	Only near menopause. Infections, pelvic pathology.	Two secondary hysterec- tomies.
P.16	90	12	100-1500	Br. 1 mm.	Pedunculated fibroids, pelvic in- fection.	Occur.
P.35	1	1	1200-1800	Pt. 1 mm.	Pelvic infection, multiple or pedunculated myomata.	In two per cent of cases.
P.31	100	24	2400	Pt. 1 mm.	Pedunculated fibroids, large fi- broids, pelvic infection.	None.
P.32	50	50	1000	Pt. 0.5 mm.	Not under 40 years, submucous fibroids, pelvic infection, in- testine adherent to uterus.	
P .29	l	I	1500	1	Only near menopause, submucous fibroid, pelvic infection.	
P.33		ł	0061	Pt. 1 mm.	Only near menopause, infection, pedunculated fibroids.	None.
P.26	I	ł	ł	I	Only near menopause, infection, submucous and large fibroids.	Occur.
P.27	80-100	12–36	1200-1800	Br. 1.5-2.0	Ovarian neoplasms, pelvic infec- tion.	Occur.
P.7	75-100		1200-1800	Br. 1 mm. with 0.5 mm. Pt.	Adnexal disease, previous laparo- tomy.	None.

TABLE II.

89

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	Failures.	Rare. Two cases needed hyster- ectomy for recurrent	In improperly selected cases.	Several, including haema- tometra.			None. In some cases of sub-	mucous nbroids. Rare.	In five per cent of cases.	None.
	Reservation and contra-indications	Pelvic infection, endocervicitis.	Only near menopause, pelvic in- fection, pedunculated or large throids	Submucous fibroids, pelvic infec- tion.	Doubtful diagnosis, large tumours, pelvic disease.	Pelvic infection, pelvic pain. Only near menopause.	Degenerating fibroids. Adnexal disease.	Only near menopause, infection. Pelvic infection.	Only near menopause, pelvic in- fection.	Only near menopause.
	Screenage.	Au. 2 mm. Br. 1 mm. Ag. 0.5 mm.	Br. 2 mm.	1	Pt. 1.5 mm.	Pt. 2 mm. Br.	Pt. 1.5 mm. Pt. 0.5 mm.	Pt. 1.5 mm. Au.	Pt. 2 mm.	Br. 1.3 mm.
	Mgm. Hours	1200 2000 m.c.h.	1600-1800	1800	1200-1800	1500 1200	2000 3360	1200 3600–4800	4800	1800-2000
OSAGE.	Hours	12 ation	16-36	24	12-18	15 	33 ¹ ⁄2 168	24 48	96	2022
Q	Mgms. e R.E.	100 Eman	50-100	75	100	100 50-100	60 20	land. 50 75–100 tal.	50	001-06
	Reference	P.5 P.2	P.4	P.24	$P.z_0$	P.11 P.10	P.21 P.25	Vew Zea P.8 P.34 Continent	P.3	P.22

JOURNAL OF OBSTETRICS AND GYNAECOLOGY

TABLE II (continued)

90

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	Q	OSAGE					
Referenc	Mgms. e R.E.	Hours	Mgm. Hours	Screenage	Reserv contra-	vation and indications	Failures
,				Ĩ	F		
F. 13	50	20	2000	Ft. I mm.	Karely used.	A-rays preterred.	None.
	(repe	sated in 14	days				
P.I7	80-120	24-48	2000-9000	Ag. 1 mm.			
				Fe. 3 mm.			
P.14	1800	20	3600	Pt. 1 mm.	Rarely used.		None.
P.23	70	24-48	1500-3200	Br. 1.3 mm.	Majority treate	ed by X-rays.	In one case out of 12 an
							adenocarcinoma found later.
P.12	i	I	1	1	Prefers X-ray	castration because	
					of risk of int	fection.	
P.28	ł	I	1	1	Only patients	near menopause.	
P.9	I	İ	ł		Only patients	near menopause,	One in 20 because of
					always comb	ined with X-rays.	mistaken diagnosis.
P_	-Personal	Communic	cation. P	tPlatinum.	Br.–Brass.	Ag—Silver. Au.	Gold FeIron.
			Clinics av	oiding Use of Rad	lium to Produce A	menorrhoea.	
Clinic.			Surgeon.			Reasons for Avoidan	ice.
Utrecht	(P.30)	de	Snoo				
Upsala	(P.36)	M	estman	X-ray	s preferred		
Genoa	(P.15)	He	enkel, M.	Fear	of inflammatory r	eaction	
Rome	(P.6)	С С	llin	X-ray	rs preferred		
Lund	(P.10)	Es	sen-Moller	Six c	ases of subsequen	t malignant degenera	tion led to abandoning of
				met	thod.		
Hungary	(P.18)	Kc	ovais	X-ray	rs preferred becau	se of risk of post-irra	udiation stenosis.

TABLE II (continued)

91

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The technique which has been adopted in Liverpool, while it has been progressively modified as our experience has grown, does not differ essentially from most of the foregoing techniques. It may be summarized as follows:—

I. Exclusion of inflammatory disease of the appendages. The fact that no instance of pelvic inflammatory reaction has occurred severe enough to call for special comment or treatment, shows that either our selection of cases has been impeccable, or that the risks of causing a pelvic inflammation are small if flagrant cases of infection are excluded. In this regard the beneficial results obtained by Van de Velde,³ Polak⁴ and others in the treatment of gonorrhoea in women by means of a temporary radium amenorrhoea are significant. Naujoks⁵ indeed gives tuberculous endometritis as a rare indication. The following case may be cited as an illustration of the problem.

One patient had had one ovary removed for inflammatory disease of the appendages. Menorrhagia and dysmenorrhoea ensued, but when hysterectomy was attempted two years later, it had to be abandoned because of the density of the adhesions present. A castrating dose of radium was then given without any inflammatory reaction ensuing, a complete symptomatic cure being effected.

2. Cases of fibroids in which the uterus is larger than it is at the twelfth week of pregnancy, cases in which the tumours are submucous or pedunculated, and cases in which the fibroids are degenerating and causing pain are excluded. Six of our patients had small fibroids which were regarded as merely incidental factors so far as the treatment was concerned.

The effect of radium on the cells of a fibroid is very small. In a fibroid of the cervix complicating a carcinoma a change was not observed one month after a massive dosage, totalling 6,000 mg.-hours.

3. Thorough curettage to exclude carcinoma.

4. The amount of radium used has varied between 30 and 50 mg. of the element. The hours of exposure have varied between 40 and 60 hours.

For the majority of cases a total dosage of 2,000 mg.-hours has been used, but larger doses, up to a maximum of 2,500 mg.hours, have been adopted for women under 40 years of age.

In many cases, perhaps in a majority of the older women, such doses may have been unnecessarily large. Ill-effects were not found, however, to result from such a dosage, and in view of the occasional failures which do occur with smaller doses, the additional assurance of success obtained makes a dosage of this magnitude desirable.

The consensus of gynaecological opinion shows that these amounts and times lie well within the limits of safety. Within these limits either factor, amount or time, may be varied in arriving at a desired dosage in mg.-hours without modification of the desired biological effect.

5. We have employed a filtration of 0.5 mm. of platinum, 1.2 mm. of silver, and 2 mm. of rubber. The range within which the filtration can be modified without causing alteration of results lies clinically between 0.5 ad 2 mm. of platinum, illustrated in Table II.

The curve²³ obtained by plotting the percentage of erythemaproducing rays emanating from a given amount of radium under varying amounts of platinum screenage, shows a critical point when the thickness of platinum is 0.3 mm.; increase of screenage above this does not significantly modify the percentage of gamma rays emitted, the effect being merely to reduce the gamma-ray intensity out of all proportion to the small increase obtained in the percentage of the highly penetrating rays. For local applications, particularly in benign lesions when the specific cancereffect is not desired, there does not appear to be any strong theoretical evidence for the use of very high filtration. Platinum 0.8 mm. or its equivalent appears to be a suitable thickness, both as regards the degree of filtration obtained and the important factor of the mechanical strength of the radium container.

6. Correlation between the length of the uterus and the length of the radium applicator.

In one of our cases the uterus measured five inches in length and this precaution was not observed. A second irradiation was required. In a personal communication J. B. Dawson^{P.8} of Dunedin records a similar case, one of apparently true subinvolution, in which a secondary hysterectomy was required. The occurrence of such cases is some evidence that in a dosage sufficient to ensure permanent amenorrhoea the endometrial effect is of paramount importance.

7. Retention of the applicator *in situ* by means of thorough vaginal packing, paying special attention to the packing of the posterior fornix.

8. We have seldom found it necessary to employ an indwelling catheter. Despite the firm packing, retention of urine is very rare.

9. Routine periodic warning of the resident and nursing staffs of the precautions to be taken against the loss of radium.

2 (a) The Incidence of Failure to Produce Amenorrhoea.

There were four such cases, a percentage of 2.2. Their details are as follows:—

CASE I, a 3-para, aged 41 years. Continued bleeding for two months. Intra-uterine radium, September 1931; 42 mg. \times 42 hours = 1,764 mg.-hours. Amenorrhoea for six months, then menorrhagia for two months. Subtotal hysterectomy, June 1932.

CASE 2, a multipara, aged 32 years. Menorrhagia for four years. Intra-uterine radium, March 1931; 42 mg. R.E. \times 36 hours = 1,512 mg.hours. Amenorrhoea for five months, then return of menorrhagia. Subtotal hysterectomy, February 1932.

CASE 3, a 4-para, aged 36 years. Menorrhagia for two years. Intra-uterine radium, September 1930, $42 \times 40 = 1,680$ mg.-hours. Amenorrhoea for eight months, followed by return of normal periods.

CASE 4, a 3-para, aged 38 years. Menorrhagia for three years. Intrauterine radium, June 1933, $42 \times 40 = 1,960$ mg.-hours. Amenorrhoea for eight months, then return of normal periods, followed by normal pregnancy February 1935.

In the first case the hysterectomy was, perhaps, premature. The possibility of irregular bleeding continuing up to 10 weeks, after even a massive intra-uterine dose, must always be borne in mind, and it is as well if patients are warned of this.

In our series a relation could not be established between this incidence of immediate bleeding and the time in the menstrual cycle at which the radium was inserted, although Runge⁶ and others consider such a relation can be established in cases in which X-rays are used to produce amenorrhoea. It was noted, however, that the bleeding was commoner in cases in which the uterus was enlarged, or when endometrial hyperplasia had been noted.

The remaining three cases illustrate the need for the use of larger doses in women under 40 in whom permanent amenorrhoea is desired.

A transient late return of bleeding after one or two years of complete amenorrhoea is not a uncommon complication. We have had six such cases. In such an event the presence of a haematometra or a corporeal carcinoma must always be considered, but in each of our cases there has not been any secondary uterine enlargement, and the bleeding has ceased spontaneously. The fact that the bleeding was preceded and followed by a slight purulent discharge in three of the cases is in favour of the view that the cause is not always a recrudescence of ovarian activity but often a mild cervical or endometrial infection, pathologically akin to senile endometritis. In discussing this complication Forsdike⁷ arrives at a similar conclusion.

2 (b). The Incidence of Radium Injuries.

The main step in the elimination of radium injuries was taken when the intra-uterine route of application was generally adopted. The development of a proper technique has further reduced these accidents to a negligible minimum. The absence in our series of any cases of persistent leucorrhoea, indicative of a radium burn of the cavity, may be attributed to the limitations of dosage already indicated, both as regards the amount of radium used and the hours of exposure. As in the case of the vulva, where radium effects can be more readily observed, the duration of tolerance of the connective tissues, and particularly of the bloodvessels, a tolerance which determines the incidence of radium burns appears to be under 70 hours.

2 (c). The Incidence of Menopausal Symptoms.

Only 23 per cent of the patients made a spontaneous complaint of menopausal flushing. This figure is rather lower than that given by Martindale,^{*} who found an incidence of 36 per cent in cases of radio-therapeutic menopause as compared with 42 per cent after surgical castration and 20 per cent in the normal menopause. It is certainly clear that the radium menopause approximates more closely to the normal than that of the surgical.

Symptomatic mimicry of pregnancy, essentially a hormonal phenomenon, is not uncommon in cases of the radium menopause, particularly in younger women, and it may be quite difficult to convince the patients that these symptoms are not due to pregnancy. In one such case the Aschheim-Zondek test was positive three months later, in another the test gave a prolan A effect after two months.

Lassen and Brandstrup⁹ have determined the amounts of urinary prolan after radiological and surgical castration. These authors used a method which showed the presence of prolan only when present in a concentration greater than 400 mouseunits per litre of urine. Their results may be summarized in the following table.

		TABLI	E III.	
			Prolan A present (percentage of cases)	Prolan B present (percentage of cases)
Normal menopause			13	14
X-ray menopause	•••		30	7
Surgical menopause			50	9

The method of hormonal investigation may represent a possible mode of solution of the problem of whether radium acts

primarily on the ovaries or on the endometrium. Seeing that in the radium menopause the effect is usually immediate and these figures indicate a slow atrophy of the ovaries, the primary radium effect would appear to be endometrial.

2 (d). The Incidence of Post-irradiation Carcinoma.

This is perhaps the most important aspect of the subject. In a personal communication Essen-Möller^{P,10} says he had six cases of corporeal carcinoma after radium castration and has accordingly abandoned the method. He considers the carcinoma may have been consequential upon the treatment. The danger is certainly very real. One such case occurs in this series.

A 2-para, aged 49 years, was given an intra-uterine application of 49 mg. R.E. \times 40 hours = 1,960 mg. hours. The uterus was three inches in length; thorough curettage and microscopic examination of the curettings did not reveal any malignant changes. Amenorrhoea ensued for 20 months. She then returned complaining of leucorrhoea which was occasionally blood-stained, and some vague colicky lower abdominal pains. The uterus was enlarged to the size of a 10 weeks' pregnancy. Secondary curettage did not detect any growth, but hysterectomy was performed and showed the uterine wall infiltrated by a columnar-celled carcinoma which the curette must have failed to reach. She died six months later with a rapidly growing recurrence in the iliac fossa and abdominal wall.

Martindale⁸ records a case in which an adenocarcinoma developed one year after radium. Bland¹⁰ records one significant case in which an early endometrial carcinoma was found three years after an intra-uterine dose of 2,400 mg.-hours. Schmitz¹¹ records two cases, occurring one and three years respectively after radium treatment of fibroids. Naujoks, recording one case after three years' amenorrhoea, states that each such case is of great theoretical and practical significance. He quotes three further cases (Koblanck,¹² Philipp,¹³ Werner¹⁴). Leda J. Stacey¹⁵ records two cases, one of fundal carcinoma appearing in a woman aged 55 after an intra-uterine dose of 600 mg.hours, one a corporeal carcinoma appearing two and a half years after an intra-uterine dose of 500 mg.-hours for fibroids.

On the whole it seems likely that in most of these cases the carcinoma was already present at the time of the radium insertion. In the first place curettage, however thoroughly performed, is not infallible. In the second place, even in cases of known carcinoma of the body or of the cervix with corporeal involvement, there is often a free interval of several years before symptoms reappear. Finally, the rarity of post-irradiation carcinoma when curettage has been performed speaks against a causal relation between the two conditions.

If a carcinoma is unrecognized the real danger of radium therapy is that the productive fibrosis induced by the radium rays may so mark the growth that the onset of symptoms is deferred until a late stage of the disease is reached. The recurrence of a watery discharge together with secondary enlargement of the uterus should always be dealt with by immediate hysterectomy. To regard such a case as one of secondary haematometra or pyometra, would be unsafe, even if curettage failed to reveal any growth. In our cases no instance of either condition occurred although many have been recorded, e.g. Bland,¹⁰ Mackay.^{P.24}

B. Cases in which Temporary Amenorrhoea or Control of Bleeding is desired.

The value of radium in the temporary control of bleeding is a much more debatable question than that already considered.

Of the 32 clinics shown in Table II, the chiefs of which use radium to produce the menopause, only 12 favour its use in younger women, and the cases they treat are limited in number (Table IV).

Refer- enceCases per yearDosage (milligram-hours)Subsequent pregnancyP.16Few $P.35$ Maximum 750 $200-400$ No experience, One normal.No experience,P.35I3 $200-400$ One normal.Mal- formations to be ex- pected.P.313 $50 \times 16 = 800$ $1 - 2$ Normal.P.32I-2 $300-400$ Should be avoided.*P.33Rare 800 Normal.P.7Io $300-750$ Three normal, one abortion.P.2Rare 300 m.c.h. 75 to eliminate hyper- sentive cases. LaterNo experience.P.4Rare $50-100$ No experience.P.4Rare $50-100$ No experience.P.4Rare $50-100$ No experience.P.5Io.1400Normal. One case of cleft palate. (Co- incidence?)P.8		,	8 I	•
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P.17 No longer One case.	г. <u>3</u>	Rare	400	One case, normal.
	P.17	No longer		Une case.

 TABLE IV.

 Methods of Clinics Favouring Use of Radium to Control Bleeding.

[Twenty clinics avoid the use of radium for this purpose.]

* Rarely of use in cases of simple bleeding in young women. Occasionally useful in cases of recurrent endometriosis.

Our own cases number only 15. They are shown in Table V. Their small number is due to the fact that recourse has not been made to radium until all other methods have failed. It will be seen that in seven cases the periods returned to a normal amount and frequency, in three cases the loss returned to normal but the interval increased, in two the periods continued heavy with an increased interval, in two an effect was not obtained, and in one the periods became scanty and irregular. While, on the whole, the results are satisfactory enough to justify the statement that there is a place for the use of radium in the control of bleeding, certain difficulties and objections must be considered, some of which certainly preclude the general adoption of the method.

1. Dosage.

This is intimately connected with the incidence of failure to control bleeding. In the Liverpool cases a close correlation could not be established between the results obtained and the dosage employed. This uncertainty of dosage is the main limitation of the method.

Our results would seem to show that radium increases the length of the cycle more readily than it modifies the amount lost at each period. Such a result suggests that the effect of submaximal doses is ovarian.

The only two calculable factors which modify the duration of the amenorrhoea induced are the age of the patient and her general health.

In every labour following the intra-uterine application of radium a dosage of 600 mg.-hours should not be exceeded except when conservation of menstrual function is not of paramount importance. A successful result would appear to depend upon whether the underlying causes of the menorrhagia abate during the period of amenorrhoea which precedes the return of the periods.

2. Post-irradiation Fibrosis.

In every labour following the intra-uterine application of radium the possibility of cervical scarring must be borne in mind. Its rarity, however, is demonstrated by the fact that in very few of the 402 pregnancies collected by Murphy¹⁶ was any dystocia noted.

3. Impairment of the Reproductive Function.

This subject is certainly of outstanding academic interest. Among others Martius,¹⁷ Parkes¹⁸ and Bagg¹⁹ have made notable contributions to the subject.

TREATMENT OF BENIGN UTERINE BLEEDING

TABLE V.

]	Dose			
No.	Age	Mg.	Hrs.	Mg hrs.	Previous history	Results
I	21	4 2	171/2	735	D. and C. failed twice. General treatment failed	Periods normal after five months amenorrhoea.
2	28	42	20	840	D. and C. failed twice. Hormonal treatment failed.	Normal periods after 10 months amenorrhoea.
3	35	46	42	1932		Amenorrhoea for eight months, then normal.
4	38	49	36	1764		Normal periods after 11 months amenorrhoea.
5	38	42	44	1 84 8	D. and C. failed twice.	Normal periods after two months amenorrhoea.
6	35	42	14	58 8		Normal periods after three months amenorrhoea.
7	27	42	12	505		Three months amenorrhoea, then three to four days every 21-25.
8	19	42	8	336	D. and C. failed once. Hormones failed.	Variable but normal.
9	32	42	36	1512		Normal loss but irregular.
10	32	42	40	1960		Normal loss, interval in- creased, dysmenorrhoea not relieved.
II	22	42	15	550		Periods heavy, but in- terval increased.
12	35	40	20	800	D. and C. failed. Partial oöphorec- tomy failed.	Amenorrhoea for seven months, after two heavy periods, then heavy periods interval increased.
13	28	21	30	630	Mayo's operation failed. Ovaries fibrotic.	Amenorrhoea for four months, then heavy periods. Hysterectomy.
14	37	42	30	1260	D. and C. failed once.	Amenorrhoea for nine months, then return of menorrhagia, free in- terval of seven days only; pain not relieved. Hysterectomy.
15	36	42	30	1260		Periods irregular and scanty.

Liverpool Cases in which Control of Bleeding was Desired.

D. and C_{\cdot} = dilatation and curettage.

The fear of injury to the chromosomal constitution of the ovum by the use of radium is based on the known genetic mutations which can be induced in insects and lower animals by the use of very massive doses of pre-conceptional irradiation.

Bagg¹⁹ in his paper published in 1924 makes the following statement, which has formed the basis of much clinical opinion. "In the treatment of menorrhagia in the childbearing age, we believe that complete sterility is preferable to the possibility of a damaged ovum, but such a conclusion is made entirely on the strength of experimental work on lower animals, and I do not feel justified in considering any of the available clinical records as adding conclusive evidence." Martius'⁷ similarly, on the basis mainly of the genetic mutations induced in Drosophila, states that, while the offspring of irradiated parents do not manifest any recognizable anomalies, he considers there may be some profound modification of the genotype which may manifest itself in a later generation.

On the other hand several observers, notably Matthews²⁰ and Murphy,^{16, 21} who record in two papers a total of 600 children born after pre-conceptional maternal irradiation, have not observed any significantly higher incidence of foetal malformations. The total incidence of foetal malformations noted by Murphy was II.6 per I,000. The corresponding incidence of foetal malformations recorded by the author²² in a series of I4,000 normal deliveries in Liverpool was 2I per I,000.

Furthermore, foetal abnormalities and neonatal diseases have a complex aetiology, and to consider them all together is to fall into the error of confusion of categories.

It would appear that in man there is not any risk of foetal lesions following pre-conceptional maternal irradiation within the limits of dosage which we employ. The reaction of the oöcytes to radium is an all or nothing effect.

C. Cases of Postmenopausal Bleeding.

There were three such cases in the series. The need for exclusion of carcinoma is particularly important in this group. In one of the cases non-febrile pyometra was responsible for the bleeding. A dose of 2,000 mg.-hours, while it produced no inflammatory reaction, did not relieve the condition, and hysterectomy was performed later.

D. The Respective Scope of Radium and X-Ray Therapy. In Liverpool we have in the main reserved the use of X-rays

for cases in which for some general reason curettage was impracticable or for patients suffering from cardiac disease or phthisis, when sterilization was desired. In such cases the method of fractional dosage has been adopted, using 220 KV.

The factors which have determined our preference for the use of radium have been that radium affords the opportunity for a confirmatory curettage, the greater assurance of permanent amenorrhoea, and the fact that one treatment only is required. The danger of corporeal carcinoma after the use of X-rays is certainly very much higher, shown for instance by Naujok's series of 58 cases.

E. The Effects of Radium on the Uterus and Ovaries.

Despite much inquiry the problem of whether the effects of intra-uterine radium are to be attributable primarily to its action on the endometrium or the ovaries still remains unsettled. Of 24 replies received in response to a *questionnaire* on the subject, 13 workers considered the ovarian effect to be dominant, four the endometrial, seven that the two effects were combined.

The problem is a typical instance of a common biological dilemma: to which of two reciprocal and simultaneous phenomena shall priority be given when the evidence can be interpreted equally well in either of two opposing ways? Such a consideration prevents any secure conclusions being drawn from the histological changes noted in the ovaries and endometrium after intra-uterine radiation. Animal experiments are unsatisfactory for two reasons, the definite variation in response to radium observed in different species, and the fact that experimental separation of the ovarian and endometrial effects possible in animals is impracticable in women, in whom both are always combined.

The following observations may be germane to the question. By the use of a castrating intra-uterine dose of radium a reasonably complete assurance can be given of a resultant permanent amenorrhoea. When, however, a single massive castrating dose of X-rays, the action of which is admittedly ovarian, is given, there is no such assurance of permanent amenorrhoea, hence the preference of most workers for the method of repeated dosage.

Hormonal studies similarly suggest that in the radium menopause the endometrial effect is predominant. Clinically the fact that menopausal symptoms are mild must be likewise attributed to the maintenance of some ovarian function. Matthews²⁰ specifically attributes this mitigation of symptoms to persistence of the

corpus luteum, the least susceptible to radiation of all the components of the ovary.

On the other hand, in cases in which radium is used merely to control bleeding, there is evidence that the ovarian effect predominates. The response in such cases to a given dose of radium is admittedly inconstant. The amount of radiation received by the endometrium can be measured within fairly precise limits, and the inconstancy of the results must be attributed to the operation of the variable ovarian factors which are present, the size, site and physiological condition of the ovaries.

The explanation of the problem may lie in a consideration of the two types of biological effect exerted by radium, its action on rapidly growing cells such as cancer and germ cells, and the general unspecific action it exerts in larger dosage on adult tissues, an action conditioned largely by their density and vascularity.

In the submaximal doses used when conservation of function is desired we are utilizing the selective effect of radium, mainly on the ripening oöcytes (Matthews) and the dosage is well below the threshold of irreparable reaction of the more resistant endometrium.

A castrating dose of radium on the other hand is over the threshold at which an irreparable endometrial effect is obtained, and what we, as a result of experience, regard as a minimal effective castrating dose, may be regarded as that level of dosage which ensures a permanent endometrial effect no matter what may be the amount of radiation by the ovaries.

CONCLUSIONS.

The present paper is essentially a summary of the results obtained by many workers. The satisfactory and probably permanent place of radium therapy in the treatment of benign bleeding at the menopause is confirmed and its technique discussed. Further consideration is given to the limitations governing the use of radium in women suffering from malfunctional bleeding in whom conservation of function as well as structure is desired.

TREATMENT OF BENIGN UTERINE BLEEDING

Personal Communications (referred to in the text).

Surgeon

Clinic

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Р.1	Adair, F. L			University of Chicago.
P.2	Atlee, H. B			V.G. Hospital, Halifax, Canada.
P.3	Binet, A			University of Nancy.
P.4	Cook, W. R		•••	University of Texas.
P.5	Curtis, A. H			New York.
P.6	Conill, V			Barcelona.
P.7	Dannreuther, W. T			Postgraduate Medical School,
-				Columbia University.
P.8	Dawson, J. B		•••	Dunedin, New Zealand.
P.9	Daels, F			University of Ghent.
P.10	Essen-Möller		•••	Lund.
P.11	Emge, L. A		•••	Stanford University.
P.12	v. Franqué		•••	Bonn.
P.13	Guggisberg		•••	Berne.
P.14	Heynemann		•••	University of Hamburg.
P.15	Henkel, M		•••	Jena.
P.16	Kostmayer, H. W.	••		Charity Hospital,
P.17	Koenig, R		•••	Geneva.
P.18	Kovais, A. F	••	•••	Hungary.
P.19	Litzenberg, J	••	•••	Minnesota.
P.20	McIlroy, L	••	•••	London.
P.21	Miller, N. F	••	•••	Michigan.
P.22	Mylks, G. W	••	•••	Kingston General Hospital.
P.23	Martius, H	••	•••	University of Göttingen.
P.24	Mackay, D. S	••	•••	Winnipeg General Hospital.
P.25	Müller, G		•••	Masaryk's University, Brno.
P.26	Orfila, J. P		•••	Montevideo.
P.27	Plass, E. D		•••	Iowa.
P.28	Phaneuf, L. E.	••		Carney Hospital Clinic.
P.29	Pamboukis, D	••	•••	Athens.
P.30	Stander, H. J	••	•••	Woman's Clinic, N.Y. Hospital.
P.31	de Snoo	•••		Utrecht.
P.32	Scott, W. A		•••	University of Toronto.
P.33	Taylor, H. C			Roosevelt Hospital, New York.
P.34	Tew, W. P	•••		Victoria Hospital, London.
P.35	Villard	•••	•••	Lyon.
P.36	Ward, G. Gray	•••		Woman's Hospital, New York.
P.37	Westmann	•••	•••	Upsala.

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