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STERILITY DUE TO OVARIAN DYSFUNCTION*

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(With Special Plate)

During the last four years more than 10 per cent. of the women admitted to the Women's and Samaritan Hospitals complained of sterility. As the result of investigation and treatment less than 20 per cent. have become pregnant. These statistics demonstrate the prevalence of the condition, and the poor results attending its treatment confirm those of most authorities and justify my bringing forward a subject which has long been a gynaecological "bone of contention."

TABLE I

Number of admissions (1930 to 1933 inclusive)....	6,773
Number of patients complaining of sterility (excluding those in whom the symptom had been present for less than two years)	654
Primary sterility	532
Secondary sterility	122
Patients traced since leaving hospital (none of these had tubal occlusion)	72*
Patients who have become pregnant	14*

* These statistics were obtained by Dr. J. Polonsky, to whom I am indebted for permission to use them.

Since the rational treatment of any symptom depends on its cause, it is probable that the unsatisfactory results obtained by all workers in this field are due to a defect in our knowledge concerning its aetiology. This communication is therefore based on the causation of sterility in 654 consecutive patients complaining of this trouble. All cases in which the condition had been present for less than two years are excluded. These cases are classified according to their aetiology in Table II (p. 346). In many patients more than one possible causative factor was present, but for the purposes of this table an attempt was made, in every case, to assess the most important abnormality. An obvious defect is the absence of any figures regarding the male partner in sterile marriages. This omission is the result of the difficulty of obtaining such particulars among the hospital class of patient.

In an attempt to nullify this deficiency, figures published by Stein and Leventhal¹ are appended.

The main function of this table is to show that, even

* Paper read at a meeting of the Liverpool Medical Institution, December 6th, 1934.

allowing for male defects, no cause for sterility was found in a large percentage of cases. Moreover, in many of those patients in whom an abnormality was demonstrated, there is no explanation why the particular lesion present precluded conception. There is no doubt as to the cause of sterility in the first five groups of Table II, and there are good grounds for assuming that the pathological conditions found in Groups 6, 7, and 8 were, in some instances, responsible for the complaint. However, it is with Groups 12 to 15 that this paper is mostly concerned. In those either no cause was found or there was present some lesion or symptom the mechanism of which, in preventing conception, is but little understood.

Since Rubin introduced his method for testing the patency of the genital tract very little advance has been made in either diagnosis or therapy, and the existence of so many inexplicable sterile matings is a reflection on the science of gynaecology. I believe with Novak² that "it is possible that our helplessness in this great problem is the outcome of too much attention to anatomical defects and too little to a possibly perverted physiology." Consideration of sterility from this point of view immediately focuses attention on the ovary. If some abnormality in spermatogenesis is present in 10 to 20 per cent. of cases, it is more than likely that an equal, if not greater, number are due to the absence of ovulation. In most English textbooks some interference in the formation and liberation of ova is casually mentioned as a possible factor, but until recently the possibility has never been viewed seriously, nor in this country have there been any attempts to assess its importance. As an introduction to a consideration of ovarian dysfunction it is necessary to review the modern conception of the normal ovarian and uterine cycles.

Normal Physiology

Although great strides have been made during the past few years in the elucidation of female sex physiology many points are still a matter of discussion. For reasons of simplicity the following description omits all mention of alternative views and theories.

FIG. A.—Ovarian and uterine changes during twenty-eight-day (normal) and twenty-one-day (epimenorrhoea) cycles.

TABLE II

Group	Cause	Primary Sterility	Secondary Sterility	Total	Percentage	Additional Lesions and Comments	Cystic Ovary Present
1	Tubal occlusion 89	77	22	99	15.0	Uterine retrodisplacement 22 Fibromyomata uteri 2	14
2	Tuberculous infection 11						
2	Disorders of coitus 2	50	4	54	8.3	Irregular menses 2 Acute antelexion of cervix 11 Prolapse of ovary 2	2
	Semen not retained 52						
3	Dyspareunia						
3	Vaginal discharge due to endocervicitis (15), cervical polyp (5), etc.	15	10	25	3.8	Uterine retrodisplacement 2 Cochleate uterus 1 Prolapse of ovary 1	1
4	Gross malformations of genitalia ...	4	1	5	0.6	—	—
5	Tuberculous endometritis	1	0	1	—	—	—
6	Acute antelexion of cervix (cochleate uterus)	117	3	120	18.4	Hypothyroidism 2 Scanty menses 4 ? Pulmonary tuberculosis 1	6
7	Conical cervix, pinhole os, etc. ...	23	0	23	3.5	Uterine retrodisplacement 2 Cervical polyp (small) 1	—
8	Uterine retrodisplacement with or without ovarian prolapse	47	18	65	10.1	Hypothyroidism 1 Hyperthyroidism 1 ? Pulmonary tuberculosis 2	16
9	Ovarian neoplasms and broad ligament cysts	4	1	5	0.8	—	1
10	Fibromyomata uteri	24	0	24	3.7	Uterine retrodisplacement 6 Endometrioma 1	4
11	Endometrioma	10	2	12	1.8	Uterine retrodisplacement 5	—
	Involvement of uterus 0						
	" one ovary 4						
	" both ovaries 3						
	No ovarian involvement 5						
12	Sterility associated with menstrual upset for which there is no obvious cause	60	21	81	12.3	See Table III	9
13	Uterine under-development	8	0	8	1.2	Uterine retrodisplacement 1 Primary amenorrhoea 2 Scanty, infrequent menses 2	—
14	Cystic ovaries with no associated pathology and no menstrual upset	15	5	20	3.1	Small fibroma of ovary 1	20
15	No abnormality found and no alteration in menses	77	36	113	17.3	See Table IV	—
	Total	532	122	654			73

Male factors in sterility (after Stein and Leventhal)

Male defects acting alone	10.7 per cent.
Male defects in addition to female defects	18.1 "
Female defects acting alone	71.3 "

Figure A is a diagrammatic representation of the monthly cycles which occur in the ovary and in the uterus. The development of the Graafian follicle is brought about by prolan A from the anterior lobe of the pituitary; the formation of the corpus luteum is the result of the action of prolan B, a second pituitary factor. Rupture of the follicle and liberation of the ripe ovum is occasioned by the same gland, but the particular hormone responsible is unknown. It is possibly due to the cessation of prolan A secretion, or more probably the result of the onset of prolan B action, but in the diagram the ovulation factor is denoted separately as X. The ovum is set free between the eighth and the eighteenth day of the menstrual cycle—usually about the twelfth to fourteenth day. After liberation of the ovum the follicle is converted into a corpus luteum, and, in woman, the presence of a functional yellow body usually denotes that ovulation has occurred.

The well-known cyclical changes in the endometrium are the result of two hormones, oestrin and progesterin, which are liberated during the ovarian cycle. Oestrin is secreted by the granulosa cells of the developing Graafian follicle and, after ovulation, by the central portions of the corpus luteum. It induces growth of endometrium from the post-menstrual to the interval phase. Progesterin is the derivative of the corpus luteum, and produces further enlargement of the endometrial glands, but more especially is responsible for the secretory activity of the endometrium: indeed, it produces those changes which have long been recognized as indicative of the premenstrual phase. The corpus luteum begins to degenerate just before the onset of menstruation.

Uterine haemorrhage is an interesting feature of the cycle, and its cause has aroused great discussion during recent years. It is known that a uterus which has been previously subjected to the action of oestrin, or progesterin, or both of these principles, bleeds when it is released from their influence. But the mechanism of menstruation is probably not so simple, and there is evidence to show that removal of these substances from circulation only precipitates haemorrhage indirectly, by stimulating the production of a "bleeding factor" by the anterior lobe of the pituitary. This positive hypophyseal factor, which is responsible for uterine bleeding, is hypothetical, and is denoted in the diagram by Z. There is no doubt that the ovary is not only subjective to the anterior lobe of the pituitary, but its hormones, acting either positively or negatively, in turn affect the motor gland. This conception is denoted in Figure A by the reversed arrows.

From the fourth to the twenty-eighth day the amount of oestrin in the body gradually increases, and reaches its peak immediately prior to the onset of menstruation. It is probable that the liberation of the gonadotropic hormones by the pituitary depends on the amount of follicular hormone (and perhaps progesterin too) in circulation; thus when the quantity of oestrin reaches a certain level the secretion of prolan ceases and the corpus luteum immediately degenerates. The sudden decrease in the oestrin content of the body during menstruation is, however, sufficient to stimulate renewed pituitary activity, and thus ensures the ripening of the Graafian follicle of the next ovarian cycle. There is thus a reversible action, which accounts for the interdependent monthly cycles in the hypophysis and gonad. This mechanism is easily demon-

strated by the appearance of large amounts of prolan A in the blood and urine after bilateral oöphorectomy.

I believe that the same type of reversible control is normally present between the anterior pituitary and the thyroid, and perhaps the suprarenals too. I have previously³ produced evidence of this by demonstrating an increased production of anterior pituitary hormone after surgical removal of the greater part of the thyroid gland.

Sterility Associated with Menstrual Irregularities

Group 12 shows that 12.3 per cent. of the cases of sterility were accompanied by menstrual upset without there being any demonstrable gross lesion to account for either symptom. The menstrual upset varied from amenorrhoea to continued metrostaxis (see Table III). These functional disturbances, especially those characterized by excessive loss, are invariably associated with endometrial changes which were formerly described as "endometritis," but are now recognized as perversions of the normal cycle, many cases presenting the features of "hyperplasia." The endometrial pathology, whether it be described as endometritis or by some term such as hyperplasia, is said to produce sterility since it interferes with implantation of the ovum. This explanation, which has been handed down from one authority to another, is unsupported by any evidence, and is entirely unscientific. Consideration of the causes of menstrual irregularity makes it quite clear that there is a much more convincing reason for sterility.

The type of menstrual cycle does not necessarily indicate the behaviour of the ovary; thus it is possible for conception to occur during a period of amenorrhoea. Nevertheless, in spite of one or two opinions⁴ to the contrary, most observers believe that the uterine cycle is usually some index of ovarian activity. Further, in certain very definite forms of menstrual irregularity, it is possible to deduce the underlying ovarian abnormality. Yet the converse of this is not true, and it is by no means rare to see examples of obvious ovarian dysfunction without there being any change in the normal cyclical loss from the uterus. This is amply proved by the cases in Group 14, for no fewer than twenty patients had cystic ovaries without there being either an associated lesion or any menstrual upset.

The several varieties of menstrual abnormality encountered in Group 12 are shown in Table III, and each variety will be considered in detail.

TABLE III.—Sterility Associated with Menstrual Upset. (No Gross Pathology Present)

Number of Cases ...	81
Primary sterility ...	60
Secondary sterility ...	21
(9 patients had had abortions only.)	

Types of Menstrual Upset:

Secondary amenorrhoea ...	4
Scanty menstruation ...	4
Infrequent menses with periods of amenorrhoea ...	12
Epimenorrhoea ...	5
Epimenorrhagia ...	13
Menorrhagia ...	19
Metrostaxis (preceded by amenorrhoea in 14 cases) ...	24
Cystic ovary was present in 9 patients (all complaining of excessive loss.) Tubal patency determined in 53 cases.	

Additional Lesions which may have had some Bearing on Sterility:

Acute antelexion of cervix ...	15
Uterine retrodisplacement ...	11
Rigid introitus (dyspareunia) ...	4
Conical cervix, pinhole os, etc. ...	3
Erosion of cervix ...	2
Vaginitis ...	1
Small fibromyoma uteri ...	1
Small vaginal septum ...	1
History of syphilis ...	1
Thyroid dysfunction ...	2

SECONDARY AMENORRHOEA AND INFREQUENT MENSES

In these conditions liberation of the bleeding factor of the anterior pituitary is temporarily suppressed. This suppression is invariably associated with, and probably caused by, some disorder in the secretion of the other gonadotropic and the ovarian hormones. If the amenorrhoea is of long standing, the underlying pathology is a deficient stimulation of the Graafian follicle by prolan A. Hence follicular ripening, rupture, and corpus luteum formation do not occur. The endometrium, therefore, lacks the influence of either of the ovarian hormones, and presents atrophic features. But it is quite obvious that the endometrial atrophy is not responsible for sterility; it is the absence of follicular ripening and ovulation.

Amenorrhoea of shorter duration may be brought about by a different mechanism. If prolan A is secreted for a longer period than normal, or if the ovulation factor (X) is absent, then the oestrous phase is prolonged (see Fig. 1 on Plate), and until the oestrin influence is withdrawn no uterine haemorrhage occurs. More commonly, the mechanism is one whereby excessive stimulation of the ovary by prolan B leads to persistence of the corpus luteum, frequently in the form of a cyst. Amenorrhoea due to persistence of the luteal phase is recognized by the continual premenstrual appearance of the endometrium (see Fig. 2 on Plate).

Prolongation of the oestrous, or luteal, phases always induces a temporary cessation of the ovarian cycle, and ovulation does not occur until the persisting endocrine tissue of the ovary ceases to function. Hence, in these cases it is the non-liberation of ova for shorter or longer periods which results in sterility.

METROSTAXIS

The majority of cases included under this heading are examples of the disease, unfortunately named, metropathia haemorrhagica. Figure B represents a diagrammatic conception of this disease. The essential feature is that ovulation does not occur for long periods of time. The Graafian follicle, instead of rupturing, continues to grow; the ovum dies, but the granulosa cells remain active, and a follicular cyst is formed. During this time the endometrium is subjected to prolonged and intensive stimulation by the follicular hormone. It becomes, therefore, unduly thickened, and presents an exaggerated interval picture—the classical appearance of endometrial hyperplasia.

FIG. B.—Metropathia haemorrhagica.

After the elapse of a varying length of time bleeding commences. This is, no doubt, instituted by the pituitary factor (Z), which is affected by a decrease in the amount of oestrin in the body—this decrease resulting from degenerative changes in the granulosa cells lining the follicular cyst. The haemorrhage may persist for weeks or months, and, if it should cease, tends to recur. For diagnostic purposes the main feature of this disease is an endometrium which, although bleeding, has had no previous stimulation by a corpus luteum, and therefore shows no secretory activity, which is so characteristic of the premenstrual or menstrual phase. It is quite obvious that sterility in these patients is not due to endometrial hyperplasia, but to the absence of ovulation. Indeed, if ovulation should occur, then the hyperplasia would inevitably disappear.

MENORRHAGIA

There is evidence to show that menorrhagia is in many instances brought about by the same mechanism as is metrostaxis—that is, it is a form of anovular menstruation (see Fig. 3 on Plate).

EPIMENORRHOEA AND EPIMENORRHAGIA

Fig. A demonstrates the underlying pathology which is present when this symptom is manifest. The cycle is normal in every way, except that it is shortened in length, each phase being diminished proportionately. Ovulation does occur; indeed, two or more follicles may ripen simultaneously. There is therefore no apparent reason why these patients should be sterile, and this argument is substantiated by facts, since it is established that this type of excessive menstrual loss is much less frequently accompanied by sterility than is any other.

SCANTY MENSTRUATION

The significance of this symptom is as yet unknown; a primary under-activity of the hypophysis is probably responsible.

From these remarks it is apparent that, with the exception of epimenorrhoea, infrequent or absent ovulation is a constant feature of most menstrual irregularities. If statistical proof of this be needed it is supplied by Anspach and Hoffman,⁴ who recently reported that of a series of women suffering from various types of excessive menstrual loss two-thirds presented no evidence of ovulation. These observations should dispel any doubts as to the real cause of sterility in Group 12 of the cases under discussion.

Cystic Ovary without any Additional Lesion or Related Symptoms

In twenty women (Group 14) the only abnormality present was a cystic ovary, the cyst(s) in most instances being follicular in type. Such cysts in the absence of local lesions (for example, salpingo-oöphoritis) are almost certainly the result of a primary pituitary derangement. The presence of these cysts frequently, but not necessarily, means that ovulation is suppressed. It is for this reason, and not by way of any anatomical displacement resulting from the presence of the tumour, that sterility results. It is interesting to note that cystic ovaries were found in some of the cases included in other groups (see Table II), and I suggest that, with the exception of Group 1, their presence was of far greater significance than the more obvious lesion under which the cases were classified.

Under-development of the Uterus

A uterus the dimensions of which are smaller than normal has long been held to prevent conception. May I draw attention to views expressed by Bonney⁵ several years ago: since implantation of a fertilized ovum occurs with comparative ease in a narrow Fallopian tube, or in

a rudimentary uterine horn, it is unreasonable to suppose that a uterus, on account of its small size, hinders pregnancy. The true explanation lies in the fact that the uterine under-development is merely a sign of ovarian (and pituitary) under-activity, which, beginning in early life, persists in the adult, and is frequently manifested by the absence of any gonad cycle.

Sterility in the Absence of any Gross Lesion or Associated Menstrual Irregularity

Under this heading come 17.3 per cent. of the cases, and in view of the results of treatment I feel that it would be more correct to transfer to this section many of those patients at present included in Groups 6, 7, and 8. No doubt a considerable number of these sterile matings were the fault of the male partner, but there remain many where no male or female cause was apparent. Incompatibility is an easy but unconvincing escape from defeat. Vitamin deficiency may be the responsible factor on an insignificant number of occasions.

TABLE IV.—*Sterility in the Absence of any Gross Lesion or Associated Menstrual Irregularity*

<i>Number of Cases</i>	113
Primary sterility	77
Secondary sterility	36
(9 patients had had abortions only.)	
<i>Tubal Patency</i>	95
<i>Additional Symptoms:</i>	
Dysmenorrhoea	34
Slight dyspareunia	18
Slight vaginal discharge	7
Obesity (probably of endocrine origin)	3
Previous history of menorrhagia	2

Additional Lesions possibly having some Bearing on Sterility:

Slight delay in passage of air through tubes ...	4
Small cervical erosion	5

In one case there was a familial history of sterility. One patient had had children by her first husband, but not by the second.

It was emphasized earlier in this paper that ovarian dysfunction does not necessarily produce any menstrual change. In view of this I suggest that some fault in, or absence of, ovarian rhythm is the most likely cause of the otherwise inexplicable sterility encountered in this group of the series. The truth or fallacy of this suggestion depends on the existence, or otherwise, of normal menstruation without a corresponding follicular cycle in the gonad. Many surgeons have occasionally noted, during abdominal operations, the absence of any corpus luteum immediately prior to menstruation. There can therefore be no doubt that anovular menstruation can occur, but the question which has recently given rise to much heated discussion is: How prevalent is the phenomenon?

Corner⁶ and Hartman⁷ demonstrated that anovular cyclical bleeding is exceptionally common in some species of monkey, and many American workers, led by Novak,⁸ have continually urged that anovular menstruation may not be rare in the human. In the British Isles very little has been done to solve this problem, although Shaw⁹ has doubted its existence. It is not easy to obtain statistics on this point, since it is rare for the uterus or endometrium to be removed from patients with regular menses. However, I have recently examined slides of endometrium from 150 patients. These were consecutive in so far that only those cases presenting regular twenty-eight-day cycles with normal loss were accepted. Comparison of the histological features with the date of the last menstrual period constituted an essential feature of the investigation. Sixty-three specimens were obtained during the menstrual or premenstrual phase (twenty-first to twenty-eighth days), yet only forty-seven showed any evidence of having been subjected to the influence of a corpus luteum. In other words, the remaining patients

had not ovulated during the cycle preceding operation (see Fig. 4 on Plate). Curettage was performed during the interval phase on sixty-nine occasions, so in these cases a corresponding endometrial picture is of no significance. Nevertheless, nine of these sections revealed hyperplasia.

These findings show that at least 25.4 per cent. (sixteen out of sixty-three) women admitted to a gynaecological ward had anovular menstruation. This figure is very striking, and, although it may not represent the state of affairs found in normal healthy women, it is possible that it under-estimates the frequency of pseudo-menstruation among women complaining of sterility. Evidence in favour of this view is provided by Mazer and Ziserman,¹⁰ who found that 58.5 per cent. of women complaining of functional sterility had anovular cycles. Moreover, Anspach and Hoffman⁴ recently reported anovular menstruation in 21.4 per cent. of women presenting such symptoms as obesity, sterility, etc., but having regular uterine haemorrhage.

The final proof of my contention would be to supply full details as to the frequency of anovular bleeding among the 654 patients investigated. Unfortunately this is impossible, since the endometrium was examined in forty-two instances only. This is no reflection on the staffs of the hospitals concerned, since most of the cases under discussion were examined and treated at a time when the possibility of such ovarian dysfunction was not fully realized. Previously it has been the universal custom to avoid curettage wherever possible in these cases, because it is of no value as a therapeutic measure and it entails the risk of spreading infection to the upper part of the genital tract.

I submit that the risk attending light diagnostic curettage is so slight as to be completely overshadowed by the valuable information derived from the procedure. Twenty-one of the forty-two women whose endometrium was examined were in the premenstrual or menstrual time of the cycle when curetted, and ten of them (50 per cent.) showed no endometrial secretory activity—that is, they had anovular menstruation. Five of these examples of absent ovulation occurred in Group 12, and three in Group 15. In a few cases typical hyperplasia was present.

These statistics suffice to demonstrate the existence of this ovarian disorder in sterile women, but the numbers are too small to give an estimate as to its frequency. It is for this reason that I wish this paper to be regarded, not as absolute proof of a partly theoretical supposition, but as an appeal for an alteration in the present-day methods of investigation of sterility, with a view not only to improving diagnosis and treatment, but to obtaining data which can only be accurate if they deal with a sufficiently large number of cases.

Proposed Method of Investigation

1. *Huhner's Test*.—Examination of the semen should be carried out in all cases, and, in spite of the practical difficulties in a hospital practice, it is possible in most cases if it is performed by the post-coital test introduced by Huhner.¹¹

2. *Tubal insufflation* with air or carbon dioxide.

3. *Curettage*.—The diagnosis of ovulation necessitates examination of premenstrual or menstrual endometrium for evidence of corpus luteum activity. It is therefore essential that curettage should be performed not earlier than the twenty-first day of a twenty-eight-day cycle. The admission of patients to hospital or nursing home must be arranged with this object in view. With the patient anaesthetized, insufflation is performed immediately prior to curettage. Should menstruation have begun when the patient is admitted there is no need to postpone operation, as is so frequently done. Proceed with the curettage, but avoid insufflation; the patency of the tubes

can then be demonstrated by the passage of air or lipiodol, without anaesthesia, before the patient leaves hospital, and as soon as all bleeding ceases.

4. *Dilatation of Cervix*.—After curettage dilatation of the cervix should be performed as a therapeutic measure, since cervical stenosis or distortion is a frequent factor in sterility. Such additional procedures as posterior cervical section may be carried out, but not if insufflation has been postponed. Once posterior cervical section is performed, then insufflation becomes very difficult, since the cannula will not fit the cervix accurately.

In addition to these tests an important feature of the investigation should be a careful inquiry into the menstrual history of the patient. Premenstrual curettage is the simplest and most reliable method of diagnosing anovular menstruation, but another device was described recently by Katzmán and Doisy,¹² and also by Kurzrok and his colleagues.¹³ These workers claim that it is possible by means of a daily examination of blood or urine to demonstrate a rise in the anterior pituitary hormone content about the time of ovulation. Kurzrok and his colleagues showed that anovular menstruation can be diagnosed by noting the absence of this characteristic rise. This work, which still awaits confirmation, entails difficult and repeated biological assays. Nevertheless it may prove of value, since it allows the determination not only of the occurrence of ovulation, but of the exact day on which the ovum is set free.

Treatment of Sterility due to Absence of Ovulation

Faults in the ovulatory mechanism may be spontaneously rectified, or sometimes any local interference, such as dilatation of the cervix, may suffice to correct a temporarily disordered rhythm. However, it is unjustifiable to rely on the occurrence of this happy result. No matter what may be the underlying fault in the mechanism, it is always an anterior pituitary hormone which is lacking. The various factors secreted by this gland have never been isolated one from each other, so that in treating these cases one is at present forced to administer a pituitary preparation* which probably contains all principles. This simplifies treatment, but is hardly satisfactory. It is impossible as yet to assess the value of treatment on these lines, because the existence of this type of sterility has not long been recognized. Nevertheless, I am tempted to quote a recent case about which I was consulted; at the same time I realize that if one accepts the evidence of a single case one can prove the value of any type of therapy.

The patient, aged 34, had been married six years, and during that time had had several typical attacks of metrorrhagia haemorrhagica. Medicinal therapy and curettage had failed to stop the excessive loss, and, finally, in spite of the fact that she complained of sterility, she was given deep x-ray therapy to the ovaries; this she had had on and off for two years. When I first saw her some months ago metrorrhaxis had commenced once more, and she was extremely worried by the fact that she had never become pregnant. The right ovary was palpably cystic. Following the recognized treatment of this ovarian disorder, I prescribed a course of injections of antuitrin "S" (Parke, Davis and Co.). Bleeding not only ceased immediately, but within one month conception occurred. Unfortunately she recently aborted at the sixteenth week of pregnancy.

Another form of attack advocated is the stimulation of the pituitary by small doses of x rays. I have so far hesitated to adopt this procedure, since it is obviously fraught with some risk. If experience shows that it is without the dangers which would appear to be present, it may prove of greater value than the administration of

* Most preparations are obtained from pregnancy urine, but the hormones contained therein, if not identical, have a similar action to those of the anterior pituitary.

prolan preparations. I adhere to the views put forward by Hamburger¹⁴ and Fluhmann¹⁵—namely, that the endocrine principles of the placenta and pregnancy urine differ from those secreted by the anterior pituitary. If the theory advanced by Hamburger is true, then in these cases of ovarian dysfunction the best results are likely to follow the stimulation of the patient's hypophysis, with or without simultaneous parenteral administration of prolan from pregnancy urine.

Ovarian hormones are frequently advised in sterility, especially in those cases associated with some underdevelopment of the uterus. It is quite clear that such measures are valueless in the correction of the main fault in the ovary. Oestrin, of course, may increase the size of the uterus and cause endometrial development; patients with amenorrhoea, if treated with this hormone, may even be induced to bleed, but it is not true menstruation, ovulation is not induced, and sterility persists. Not only is oestrin therapy without value, but I feel certain that it may be harmful in that, if it is continued, it may produce atrophy of the ovary—the least desired result. This view is borne out by animal experiments. Progestin therapy is, for similar reasons, entirely useless as a cure for sterility.

Just as I have quoted a case treated successfully with a prolan preparation, so occasional successes may be ascribed to oestrin or even to progestin. Nevertheless, there is no theoretical basis for such treatment, and very occasional happy results are easily explained by the fact that temporary derangement of ovarian rhythm may be corrected by any form of "shock," or may even correct itself spontaneously.

Any remarks on the subject of the endocrine treatment of ovarian dysfunction would be incomplete without reference to the administration of the active principle of the thyroid gland. This substance has been used extensively in attempts to improve ovarian and uterine development. The foundation of this treatment lies in the well-known clinical fact that scanty menstruation, uterine underdevelopment, etc., are often associated with thyroid underactivity, whereas excessive menstrual loss frequently accompanies thyroid overactivity. It has been assumed that the state of ovarian and uterine activity is directly controlled by that of the thyroid. Recent investigations show, however, that the thyroid gland resembles the ovary in that it is subservient to the anterior lobe of the pituitary. It is therefore probable that underactivity of the thyroid and ovary, when occurring in the same patient, are only related in so far that they are both manifestations of a primary pituitary disorder.

If the conception of pituitary-thyroid relations, outlined earlier in this paper, is true, administration of thyroid is likely to cause further inhibition of hypophyseal activity, with consequent depression, and not stimulation, of ovarian function. It follows therefore, on theoretical grounds, that the administration of thyroid should be reserved for cases of overactivity of the gonads, and should never be used for ovarian and uterine underdevelopment. Personally, I have never seen any good results following thyroid therapy in the latter type of case, and I have discontinued its use in my practice.

I hope I have demonstrated that the non-occurrence of ovulation is, from both theoretical and practical aspects, a factor to be considered seriously as a cause of sterility. It accounts for the majority of those cases in which menstrual upset is an additional symptom, and is probably responsible not only for many of the unexplained sterile marriages, but also for those in which the treatment of some obvious lesion, such as acute anteversion of the cervix, or retroversion, is unsuccessful. I believe, moreover, that suppression of follicular rupture explains the physiological sterility which is admittedly present in early

life and late middle age, for it is at these periods of life that anovular menstruation is most frequently found. Finally, may I mention a view already expressed elsewhere¹⁶—namely, that sterility associated with fibromyomata and endometrioma is not the result of these tumours; nor is the converse true; both the neoplasm and the sterility are manifestations of a primary ovarian disorder.

I should like to express my gratitude to the members of the honorary medical staff of the Women's Hospital for permission to report the details of cases—all of which were under their care. It would be unfair, also, if I did not state that this paper is founded for the most part on the work and writings of the American school, which has done much to forward this branch of medicine.

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SURGICAL TREATMENT OF BRONCHIECTASIS*

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(With Special Plate)

Bronchiectasis is of interest to the surgeon at two stages of its development—when it is incipient and when it is well established. I propose, therefore, to divide my subject into two parts.

Let us first consider the question of prevention, and inquire whether anything can be done in the stage of delayed resolution or early pulmonary fibrosis which follows bronchopneumonia. There is a difference of opinion concerning the mechanics of bronchial dilatation, but its exact pathogenesis does not affect us for the moment. In this pre-dilatation stage anything which diminishes the expanding force, the outward pull, which acts on the weakened bronchial walls will tend to prevent the development of dilatation, whether that force be exerted by contracting fibrous tissue or by the tension of the normal intrapleural negative pressure.

Working on this hypothesis Hedblom used phrenic evulsion extensively in the type of case under discussion. In his hands the operation produced symptomatic cures, which did not relapse and in which lipiodol failed to demonstrate bronchial dilatation. John Alexander¹ has also used temporary paralysis of the phrenic nerve (phrenic crush) in a number of patients, most of them between the ages of 5 and 14, who were suffering from suppurative pneumonitis, before the stage of abscess

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T. N. A. JEFFCOATE: STERILITY DUE TO OVARIAN DYSFUNCTION

FIG. 1.—Photomicrograph showing endometrium from a woman complaining of sterility and of secondary amenorrhoea of seven months' duration. There is no atrophy. The appearances are those of the interval phase, with some hyperplasia. The underlying abnormality is therefore a prolongation of the oestrous phase of the ovarian cycle. ($\times 80$.)

FIG. 2.—Photomicrograph showing endometrium removed from a patient complaining of sterility and having also had four months' amenorrhoea. The glands are in the secretory phase and present typical premenstrual appearances. The underlying abnormality is therefore a persistence of active lutein tissue in the ovary. ($\times 140$.)

FIG. 3.—Anovular menstruation manifested by menorrhagia. This endometrium, which is in the interval phase and shows no evidence of having been subjected to corpus luteum influence, was removed on the 23rd day of a 28-day cycle. The menstrual loss was excessive, and persisted for eight days. ($\times 80$.)

FIG. 4.—Anovular menstruation. This endometrium was removed on the 24th day of a normal 28-day cycle: it presents the typical features of the interval phase and shows no evidence of having been under the influence of the corpus luteum hormone. One of the glands is larger than normal. ($\times 80$.)