STUDIES IN HUMAN STERILITY
WITH SPECIAL REFERENCE TO
THE INVESTIGATION OF THE PATENCY AND
FUNCTION OF THE FALLOPIAN TUBES
AND OF THE
CONDITION OF THE ENDOMETRIUM.

PREFACE.

The thesis which is presented here, consists of two parts and an appendix.

Part I concerns the pathogenesis, diagnosis and treatment of Human Sterility and is an endeavour to give a comprehensive account of this subject, incorporating a study of much new knowledge and of recent advances which mainly concern technical refinements in the investigation of tubal patency and function, the endometrial cycle and the "sex hormones." Only slight reference is made to the male aspect of the problem. In effect, this part of the thesis is almost entirely my contribution to the book "Sterility and Impaired Fertility" (1939), Hamish Hamilton Medical Books, London, (jointly with C. Lane-Roberts, K. Walker and B.P. Wiesner). The few pages which are included here and which were not written by me are indicated in the text. The essential features of important researches, published since 1939, have been added.

Part II concerns the results of a detailed study of 500 Cases of "Sterility," with particular reference to (1) the functional condition of the Fallopian/

Fallopian tubes and (2) the uterine endometrium, normal and abnormal. These cases comprise an unselected series of patients who had never conceived and who complained primarily of the infertility of their marriage and who were under my observation in the Royal Samaritan Hospital for Women, Glasgow, within the period - July 1933 until February 1943. I am responsible entirely for Part II, which has not as yet been published, although portions of it formed the substance of a paper read at the Annual Meeting of the British Medical Association in 1938.

The appendix concerns the results of original, unpublished researches in cases other than the series above-mentioned. It involves the most recent work, almost entirely done during the years 1941 and 1942.

I am greatly indebted to Dr. John Hewitt, not only for facilities in his wards since 1933, but also for his co-operation and encouragement; to Dr. E.D. Morton from 1937 to 1939, and to Dr. D. McIntyre, since 1939, for similar facilities; to the Governors of the Royal Samaritan Hospital for Women for providing a Gordon King Kymographic apparatus (the first made in this country); to the British Medical Association for a Research Scholarship at the commencement of this work; and to Dr. I.C. Rubin of New York and Dr. L. Bonnet of Paris for facilities and instruction during visits to their clinics.

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PART I.

GENERAL SURVEY OF THE PROBLEM.

The adult male and adult female are normally fertile - that is to say, he is capable of begetting and she of conceiving and carrying a child. Full reproductive capacity is established during puberty when the infertile state of childhood gives place, not suddenly and dramatically but very gradually, to the fertile state of the normal adult. The physiological and psychological changes of adolescence, although mutually interdependent, do not take place simultaneously or at an equal rate. Menstruation may occur before the first ovulation; adolescent males may experience libido before they produce spermatozoa. Or the order may be reversed.

Sterility. This term denotes complete inability to reproduce. It may be due to failure of the male to produce viable spermatozoa or of the female to produce fertilizable ova. In some cases the fault is not in spermatogenesis or ovulation, but in a failure to bring about the union of the gametes. The male may be incapable of delivering spermatozoa into the vagina; or the spermatozoa may be obstructed or destroyed in their passage through the genital tract. In some cases conception may occur, but the pregnancies regularly end in miscarriage.

Nearly/

Nearly every type of sterility may be temporary or permanent. Temporary sterility is often physiological; e.g.,ovulation appears to be inhibited during lactation. More commonly, however, it is induced by disease or even by slight disorders. Thus women may become temporarily infertile because of inflammation of the ovaries; men may lose potency and fertility during, and for some time after, any severe illness. Permanent sterility may be due to such constitutional disorders as impaired pituitary secretion; more often it results from severe affections of the genital tract. It must be emphasized that the diseases and disorders which in some patients produce permanent sterility produce only temporary sterility in others, and in some no impairment of the reproductive function at all.

Reduced Fertility. Reproductive capacity varies within wide limits, because normal fertility results from the successful operation of a number of independently varying physiological mechanisms. If one or more of these is abnormal, fertility may be diminished to a greater or lesser degree. A simple example of a variable determinant of fertility is frequency of sexual intercourse. Ovulation takes place, as a rule, only once in each menstrual cycle; and neither the ovum nor the/

the spermatozoa can survive in the genital tract for more than about one day without losing the capacity to form a zygote. Hence conception is conditioned by an approximate sychronizing of intercourse and ovulation. Reduction in the frequency of intercourse, except in cases in which it is deliberately reduced to coincide with the fertile period, must correspondingly reduce the chances of conception.

Another important variable is the biological value of semen. The analysis of herd and stud books has shown that the breeding records of sires differ greatly - some bulls and stallions being highly fertile while others are successful in relatively small proportion of matings. Such differential fertility has been shown to be correlated with variations in the viability and constitution of the sperm population. In human subjects, too, a close correspondence between the reproductive history of couples and the quality of the husband's semen has been established in a large and increasing number of cases in which the fertility of the woman could be regarded as a constant.

Similar variations in reproductive capacity occur in the female. Thus ovulation occurs regularly in each menstrual cycle of the average mature woman. But an apparently healthy woman may fail to ovulate in one/

one or two isolated cycles or over a prolonged period, with corresponding reduction in the chances of conception. Or, to take another example, the condition of the genital tract may determine the chances of fertilization. If the tract is unhealthy, the number of spermatozoa which can survive to meet the ovum may be much diminished; indeed, in severe cervicitis the ascent of the spermatozoa may be prevented completely.

Like sterility proper, lowered fertility may result in childlessness for the whole of reproductive life.

Classification of Sterility and Lowered Fertility. The nomenclature adopted in the classification of sterility is highly confusing, such terms as primary, secondary, absolute, relative, physiological, and "one child" being used with different significances by different authors. Meaker defines absolute sterility as "a state in which the initiation of the reproductive process is, at any rate for the time being, definitely impossible," and states that "it may be temporary or permanent." He adds that "relative fertility and relative sterility are the degrees of conceptive capacity intermediate between absolute fertility and absolute sterility."

It has been found useful to differentiate

between/

between sterility, lowered fertility and dyskyesis (namely, incapacity to carry pregnancy to term); and convenience rather than precision has suggested the following classification into three main groups:

(1) Primary sterility or primary low fertility.
(2) Secondary sterility or secondarily lowered fertility.
(3) Dyskyesis.

(1) Primary Sterility or Low Fertility.

In men, primary sterility, a condition in which reproductive capacity has either failed to develop altogether or has not developed fully, is usually caused by constitutional disorders such as pituitary deficiency, but orchitis is responsible for some cases. In women it originates from a number of constitutional disorders, which may result in hypoplasia of the genital organs or abortive menstrual (anovulatory) cycles.

About 20 per cent. of all cases of impaired reproductive capacity in men and women fall within the primary sterility group. This figure must be taken as a rough approximation, for precise confirmatory data are not obtainable and the existing methods of diagnosis fall far short of the accuracy that could be desired. Moreover, many patients are seen at an age when it is difficult or impossible to distinguish primary from secondary sterility.

(2) Secondary Sterility or Secondarily Lowered Fertility.

Absolute loss of fertility or its decrease during the adult phase of life is common to both men and women. To a certain extent it may be regarded as physiological, for in both sexes fertility first diminishes with advancing age, then ceases altogether. The rate of diminution, however, varies greatly from individual to individual. In extreme cases precocious loss of fertility may occur in young men and women, so that sterility is established at ages between twenty-five and thirty. Such premature secondary sterility may occur gradually and without any noticeable symptoms. In women, menstrual periodicity and ovulation may slowly cease without detectable signs of gross disease or constitutional disorder.

"One-child sterility" falls within the secondary group. The term is usually applied to a condition in which the woman has given birth to one child, but fails to become pregnant again, e.g., because of the development of inflammatory processes which cause either blockage of the tubes or disease of the ovaries. Clinical experience shows that "one-child sterility" is often the result of slight lesions which occur after an apparently normal confinement and do not produce symptoms severe enough to make either the patient or her medical attendant aware of their existence. It should/

should be noted that the term is a little misleading, for in some cases the condition occurs after the birth of two or three children.

Constitutional disorders may also cause secondary sterility in women. Thus a condition resembling the menopause characterized by disturbances of menstrual periodicity and accompanied by the excessive excretion of gonadotropic hormone in the urine, may develop early in life. It may clear up, but often ends in persistent ovarian inactivity. Again, specific and non-specific infections - e.g., gonorrhoea and malaria - may completely inhibit fertility.

It is noteworthy that the possibility of secondary impairment of fertility is far less commonly considered in men than women. The reason lies in the fact that the conditions which cause secondary sterility seldom affect potency, for they usually involve the germinal epithelium rather than the endocrine structures responsible for the development and maintenance of libido.

(3) Repeated Abortions.

Many marriages are not sterile in the usual sense of the word, yet remain childless because of repeated abortion. The name dyskyesis was given by Wiesner to the tendency to early abortion which occurs in/

in successive pregnancies without any detectable disease or trauma. Sometimes the existence of the tendency is not suspected, for very early abortion may simulate delayed menstruation. This possibility should always be borne in mind when a childless marriage is investigated.

"Dyskyesis" may be due either to endocrine disturbances or to localized disease of the female genital tract. It may also be due to defective chorionic development, in its turn the result of some constitutional defect of the gametes.

Frequency of Infertility and Lowered Fertility. The proportion of sterile or subfertile adults in our population is not known and could only be determined by an exhaustive inquiry. But data relating to the frequency of sterility and lowered fertility in individuals are perhaps less important than those relating to the frequency of childless marriages. If human beings lived in herds and mated promiscuously, the prevalence of sterility in males would not greatly influence the rate of reproduction of the population as a whole, for any fertile female would still have access to fertile males. Conversely, no infertile female could in effect sterilize a normal male by claiming/

claiming exclusive possession of his reproductive capacity. In human society, however, many healthy persons are effectively sterilized by their marriage ties. An inquiry into the frequency of sterility in males and females would thus not reflect the total effect of sterility on the reproduction rate of the human population; the number of childless marriages is greater than that of either sterile men or women.

The available information on the frequency of sterile marriages is highly unsatisfactory. There are reasons to believe that such marriages are common in all civilized countries, but neither census nor registration returns can provide any information on the subject. On the other hand the incidence of childless marriage, without reference to whether the sterility is voluntary or involuntary, has been determined for many countries with considerable accuracy (Kuczynsky, 1937). It is estimated that in England and Wales, according to the 1911 census 16.6 per cent. of the total number of married couples were childless; in South Africa, according to the 1926 census, the figure among Europeans was 15 per cent.; in Australia according to the 1921 census, it was 15.4 per cent.; and for other countries of roughly the same cultural level the figures are similar.

It is evident, therefore, that incapacity to produce children is not a rare misfortune, but a serious biological defect from which a large proportion of the population suffers.

Patients often ask how long after marriage they should wait before regarding themselves as possibly sterile. This question cannot be answered in precise terms, because observational and experimental data are scarce and the occurrence of conception is always a matter of probability, never of certainty. A rough but useful answer, however, may be derived from a consideration of the relevant biological factors and of some statistical data published by Pearl (1936). It has already been stated that pregnancy depends on the coincidence of intercourse with the fertile phase of the menstrual cycle. The chances of this event depend, therefore, on the frequency of intercourse and the duration of the fertile period. This latter may be assumed to persist for one day and to recur thirteen times in the year, i.e. once in each cycle. If, then, coitus takes place twice every week, except during the menstrual flow, the probability that a single coitus will coincide with ovulation and therefore have a reasonable chance of resulting in fertilization is in the order of one in twenty. If coitus takes place eighty times a year/

year, then the probability of conception in the course of one year is very high (ninety-eight in a hundred). From this study of a group of healthy white women between the ages of twenty and twenty-four, who did not practice contraception, Pearl concluded that about thirty pregnancies occurred in every 200 ovulations. Assuming that his group was a fair sample it may be concluded that the probability of fertilization at any given ovulation is in the order of one in seven.

Allowing for modifying factors in the above data e.g., the possibility that sexual desire in the female may in a proportion of cases coincide with an infertile phase of the cycle with a consequent preponderance of potentially infertile unions - it may be stated in general terms that if one of a possible thirteen ova is not fertilized in any one year there is probably present a condition of sterility or lowered fertility in one or both partners. For these reasons it is suggested that it should be regarded as normal that regularly cohabiting couples should succeed in establishing conception within one year from the date of the first intercourse. This estimate is confirmed by clinical experience, failure to conceive after one year being usually referable to definite causes such as deficient spermatogenesis, disturbances of the ovarian cycle, dysfunction of the/

the Fallopian tubes, and/or infrequent or deficient intercourse.

These facts should be explained to the patient, who should be told further that sterility is not invariably manifested in general ill-health or in impairment of potency, and that potent men and apparently mature women may be infertile because the production and transport of the gametes are highly specialized functions which are easily impaired by local and constitutional abnormalities of which the patient and his doctor may be unaware.

When the sterility or lowered fertility of a marriage is established, any form of treatment should be preceded by an investigation into the fertility of both partners. Only if one partner is found to be wholly and incurably sterile is it permissible to dispense with the examination of the other. Failure to observe this latter rule has resulted in women undergoing major surgical procedures for the cure of sterility even before the semen of their partners has been examined.

The detailed investigation of both partners is particularly valuable when major defects can be ruled out in both the husband and the wife. In such cases investigation often shows that in both the male and/

and the female there are present minor disorders which, though together preventing fertilization, would not result in the complete sterility of either partner. For instance, a combination of lowered viability of spermatozoa with slight cervicitis may result in childless marriage, even when neither could sufficiently account for sterility by itself.

The investigation of sterility often involves two stages: first, an investigation into the absence or presence of some abnormality, and secondly, if such an abnormality is found, the determination of its cause.

Relative Frequency of Male and Female Sterility. The extraordinary divergencies between the various estimates that have been made of the relative responsibility of the male and female in childless marriage call for some explanation. Some authors absolve the male in all except a very small proportion of cases; others find positive evidence of infertility in a majority of the male partners of sterile matings. Meaker (1934) puts the figure as over 30 per cent., but stresses the fact that in most cases, the responsibility must be divided between the two sexes. Two possible sources of error are worth bearing in mind.

(1)/

(1) Many of the available clinical data relate to selected groups, gynaecologists and urologists for instance dealing respectively with female and male patients and tending in some cases to assume that the mere discovery of infertility factors in their own patients suffices to allocate the sole responsibility and renders superfluous an examination of the marital partners. This source of error will progressively diminish with the growing frequency of collaboration between general practitioners, gynaecologists and urologists in the investigation of infertile unions.

(2) The estimates depend very largely on the accuracy and the scope of the diagnostic methods employed. Thus, before the development of present-day methods of semen analysis it was generally assumed that the presence of numerous motile spermatozoa almost certainly implied fertility: this, as is now known is a totally inadequate diagnostic criterion, a high count of motile spermatozoa being consistent with subfertility or even sterility. Another example of the same source of error may be found in the failure to recognise some cases of female infertility before methods had been evolved for the detection of anovulatory cycles.

Until extensive and unselected series of cases of childlessness have been completely investigated by/

by modern diagnostic methods, it is impossible to make an accurate estimate of the relative responsibility of the male and female that would satisfy critical standards.

On the purely biological plane, the male and female sexual functions are so largely equivalent that the same procedures might appear to be suitable for the investigation of sterility in the one sex as in the other. In some respects this is true; but essential differences should be noted at the outset.

In the first place the assay of fertility, which must be attempted in both sexes, is restricted in scope in the female. In the male the assay is positive; it is possible to inspect the gametes and to establish the degree of fertility. There is no equivalent procedure in the female; the gametes cannot be inspected directly, and though, as will be shown presently, some relevant information is obtainable, it is impossible to ascertain, in any individual case, whether or not an ovum has been delivered. Even when all the conditions seem favourable, it is impossible to exclude the chance that the ovum may be genetically defective. In short, the investigation of fertility in women is negative in character, serving at best to eliminate/

eliminate possible causes of infertility, but never offering actual proof of the existence of fertility.

A further difference determining procedure derives from the cyclic and periodic nature of the female reproductive functions. In the male, apart from certain variations and fluctuations, these functions are continuous. In the female the existence of the sexual cycle makes it impossible to determine fertility by examining the subject on any one day. The fact, for instance, that the uterus is normal in the first half of the menstrual cycle does not necessarily prove that it will be in a condition to receive the ovum during the second.

Moreover, even the complete investigation of a given cycle may not give data that would be valid for all other cycles. It is an established fact - to which reference will be made later - that fertile menstrual cycles may be followed by sterile cycles in the same woman. This variation of fertility in time is much more pronounced in the female than in the male and must be considered in every investigation. In short, the assay of fertility in the female cannot be restricted to obtaining a cross-section through the reproductive system at any one point.

To/

To these difficulties must be added those which derive from the complexity of the functions involved. In the male, the production and delivery of the gametes completes the reproductive function. In the female the delivery of the ovum into the tube presents but the first step in a series of functions. Even normal oogenesis and normal delivery of the ovum into the uterus does not ensure fertility, for the preparation of the uterus for pregnancy may be inadequate or may end too soon. The fact must be recognized that the factors which determine female fertility are so many and varied that it is not possible to investigate them all, not even all those that may be regarded as important.

In the account that follows of the investigation of female fertility it will be necessary to indicate the importance of certain procedures such as tubal insufflation, endometrial biopsy and urine analysis. It should, therefore, be stated that though these methods may be necessary they must not be depended upon to the exclusion of evidence from clinical sources. Non-specific factors, such as the general health, psychological condition and age, have far more influence on female fertility than on that of the male. In the investigation of sterility in the female it is thus essential to maintain a balanced outlook, recognizing the value of/

of laboratory methods but not depending on them entirely, and above all, integrating the results of investigations directed specifically to the reproductive system with the information derived from a clinical examination of the patient as a whole.

The difficulties of the assay and the fact that the patient must be subjected to a number of examinations offer sufficient justification for the general rule that the investigation of the husband should precede that of the wife.

STAGES IN INVESTIGATION.

The investigation of female fertility falls into three main stages.

(I) The general clinical examination. This is of much greater importance than in the male. A positive assay being unobtainable, the evidence for certain disturbances, e.g. endocrinopathies, must be sought rather in general symptoms than in the response to specific laboratory investigations.

(II) The Gynaecological Examination. This examination, which should include a study of the sexual and reproductive history, will in many cases yield indications of lowered fertility. It should be borne in mind, however, that, in general, only the major disorders - and not all of these - are detectable by ordinary gynaecological examination.

(III)/

(III) The Functional Examination. Even the most thorough clinical examination cannot yield full information about the functional condition of the reproductive system. It is true that it suffices for the detection of severe structural abnormalities, such as hypoplasia or malpositions; but other features, equally or more important, escape detection by ordinary clinical methods. This applies, for instance, to the condition of the endometrium, which may be inadequately developed or fail to undergo the cyclic changes associated with the nidation of the fertilized ovum; or even to the condition of the tubes, which may not show any gross lesions, yet be occluded and prevent the passage of the ovum. It is necessary, therefore, to amplify the usual gynaecological examination by a series of tests, which aim at the exploration of the functional rather than the anatomical condition of the genital system.

The information sought concerns particularly the tubo-uterine passage, the occurrence of ovulation, and the presence of the endocrine conditions of fertility.

Before these subdivisions of the investigation are described in detail two general observations may be made.

(1) Except in relatively rare and very severe defects and disorders, no single stage suffices to yield an adequate, let alone complete, picture of the anatomical/

anatomical and functional conditions of the reproduc:tive system. Moreover, one and the same objective finding may be produced by different mechanisms which can only be brought to light as the investigation proceeds. Thus, hypoplasia may be caused by hormonal deficiences but may also be due to an inherent incapacity of the genital system to react to stimulation by the ovarian hormones. Complete investigation - even though the very first stage may seem to have revealed the cause of sterility - should therefore be the rule, and an integration of all the findings should, whenever possible, form the basis of diagnosis and treatment.

(2) It has been shown by Meaker and others that sterility or lowered fertility is often due to a multiplicity of minor causes ("infertility factors"), none of which may be sufficient in itself to impair fertility seriously. In such cases only a patient and exhaustive examination will yield the diversity of information on which a satisfactory diagnosis, and thence treatment must be based.

I. General Clinical Examination.

The general condition and the clinical history of a patient are important and should be recorded in full detail. Special attention should be paid to three groups/

groups of data.

(a) Infertility Factors.

Among the conditions which may be associated with a history of female infertility are debilitating diseases, scarlet fever, recurrent tonsillitis, nephritis, foci of infection, venereal diseases, appendicitis and pelvic operations.

(b) Mode of Life.

These include dietetic errors and deficiencies and the use and abuse of drugs (including alcohol).

(c) Constitutional Characteristics.

These merit particular consideration. The American school regards endocrinopathies as responsible for many cases of female infertility, and under Meaker's guidance a fairly complete endocrinological investigation has become a routine procedure in every case under diagnosis. It is indeed a well-established fact that general disturbances, in particular endocrine deficiencies, may be responsible for infertility (Lawrence and Rowe, 1928; Rowe, 1930; Haselhorst, 1933). But severe endocrine disturbances - e.g., thyroid deficiency, diabetes mellitus or even more complex syndromes - are not invariably associated with sterility (Rowe, 1930); nor, on the other hand, is infertility for which a local cause cannot be found, invariably associated with/

with endocrine or constitutional defects, which can be revealed by ordinary clinical methods or indeed by any known procedure.

Since endocrine disorders may - but do not invariably - cause infertility, the attitude that should be adopted towards them may be stated as follows. A careful inquiry should be made into all symptoms which may denote their presence, and, if necessary, confirmatory tests, e.g., determination of the basal metabolic rate or of the sugar tolerance, should be carried out. If such disorders are found they should be noted and dealt with as infertility factors, but it should not be assumed that a satisfactory explanation for infertility has been found, or even that its existence has been proved, simply because a general disorder has been discovered.

II. Gynaecological Examination.

This may be divided into the following stages:

(1) Routine gynaecological examination.
(2) Tests for patency and function of the tubes.
(3) Endometrial biopsy.
(4) Post-coital examination.

Only the first of these stages will be described now; the rest are discussed in the section dealing with the functional examination.

Clinical/

Clinical History.

Before any actual examination is undertaken, the menstrual history should be elicited and a detailed record made of the duration and periodicity of the cycle, the occurrence of menstrual or pre-menstrual discomfort, and any evidence suggesting ovarian disorders. It is particularly important to note the occurrence of aberrations from the menstrual norm (with special reference to their relation to illness contracted in adolescence), of greatly delayed menses (sometimes indicative of dyskyesis) and of very short cycles (often suggestive of anovular menstruation).

Close inquiry should be made into the subject of previous gynaecological illnesses, above all, of pelvic inflammations, whether before or after marriage.

The record of the marital sex life, in its early and later stages, is usually better left to the end. Points to be noted are: the manner and frequency of intercourse (husband and wife do not always tell the same story), the relation of intercourse to the fertile phase of the cycle, the use and methods of contraception, the practice of coitus interruptus (since this may be followed by chronic passive congestion and lowered fertility), and the use of acid lubricating jellies. The significance of some of these data is obvious; to others/

others reference will be made later.

Pelvic Examination.

This examination should be conducted on the usual lines, but with great thoroughness, having in mind the possibility that, in any given case, there may be several factors concerned in the reduction of fertility.

The special points to be noted in the examination may be classified as follows:

(1) Vulval, vaginal, cervical or uterine infection.
(2) Structural abnormalities.
(3) Malformations or malpositions of the uterus and adnexa.
(4) Pelvic inflammatory diseases.

(1) Vulval, Vaginal, Cervical or Uterine Infection.

Such infections do not necessarily cause infertility, but must be included among contributory factors. Special attention should therefore be given to the presence of vulvitis, bartholinitis, skenitis, vaginitis, cervicitis and infection of the body of the uterus. Bartholinitis may be demonstrated by inspection and palpation; chronic infection of Skene's glands by massage; urethritis by inspection and expression of the urethral orifice. The manifestations of uterine infection vary with the nature of the infection and the site, but/

but gross menstrual abnormalities associated with local tenderness point to the need for further investigation. If vaginitis is present a bacteriological examination of the discharge is desirable in order to exclude Trichomonas Vaginalis or Monilia infection.

Chronic cervicitis, though significant, is not necessarily associated with infertility. Thus the condition is often found in fertile multiparae. In some cases, however, conception does not occur until the condition has been effectively treated. A bacteriological examination may be necessary in order to exclude the possibility of gonococcal infection. The discharge which occurs in cases of cervicitis must not be confused with the mucous plug which normally occludes the cervical canal. The consistence of the latter varies with the phases of the cycle and a very tenacious or opaque plug may be regarded as an infertility factor only if it occurs in the mid-menstrual phase or in association with a narrow or pinhole os.

(2) Structural Abnormalities.

These include stenosis of the vagina, tough or unruptured hymen, and varying degrees of arrested development of the vulva, vagina, uterus and adnexa, ranging from uterine hypoplasia to complete absence of one or more genital structures. The hypoplastic uterus is often anteflexed and smaller than a small walnut./

walnut. Meaker, however, has shown that the size of the uterus is a less reliable index of maturity than its proportions. The immature uterus is characterized by the relatively great length of the cervix compared with that of the corpus, and this proportion tends to be reversed as development proceeds to maturity. In the infantile uterus the original proportions tend to be retained. The actual figures are:

<u>Mature Uterus</u>. Corpus about two-thirds, cervix about one-third of total length.

<u>True Hypoplastic Uterus</u>. Corpus about one-third, cervix about two-thirds of total length.

The estimation of the uterine index can be conveniently carried out by an ordinary uterine sound or by Meaker's hysterometer. The method is as follows:

The tip of the sound is gently introduced into the canal up to the internal os. At the point at which resistance is felt, i.e., where the marker is pushed against the internal os, the first reading (length of cervical canal) is taken.

The marker is then retracted and the sound is gently pushed forward until its tip reaches the fundus. The second reading (length of whole uterus) is then taken; the two readings yield the quotient:

$$\frac{\text{length of whole uterus minus length of cervical canal}}{\text{length of cervical canal}}$$

which gives the proportion of corpus to cervix (strictly speaking/

speaking, cavity of uterus to canal of cervix). The uterine index is obtained by dividing this figure by two. This formula was originally devised in the belief that it would give unity as the figure expressing normal development. Its interpretation, according to Meaker's amended account, is as follows:

0.75 or greater indicates a normal adult uterus.
0.60 or less indicates a clinically important hypoplasia.
0.25 or thereabouts indicates a completely infantile uterus.

It should be mentioned that, though it does not invariably signify sterility, hypoplasia is one of the most common signs of this condition and represents one of the more important sterility factors.

Other structural abnormalities to be noted concern the condition of the cervix - e.g., undue anteflexion, elongation, hypertrophy or descent. The long, conical, anteflexed cervix with a tiny external os is characteristic of hypoplasia. A pinhole os may prevent drainage of the cervix and so indirectly impede the passage of spermatozoa; but, as already pointed out, unless the canal is occupied by an excessively tenacious or opaque plug, it is only a minor sterility factor.

(3) Malformations or Malpositions of the Uterus and Adnexa.

The position of the cervix and the direction of/

of the cervical canal are more important than the position of the uterine body in the pathogenesis of lowered fertility. This is a subject on which ideas have changed in recent years, and it is no longer a common practice to correct uterine malpositions as soon as their existence is discovered, on the assumption that this will favourably influence fertility. It is recognised that many young women with wombs in such positions conceive without difficulty.

Although acute anteflexion, retroflexion or retroversion do not themselves cause infertility, their presence is significant in view of the possibility of their being associated with distortion of the tubal lumen. Moreover, such malpositions may sometimes be delaying factors - e.g., in retroflexion and retroversion when the direction of the cervical canal is such that the external os points against the anterior vaginal wall out of immediate reach of the seminal pool deposited in the posterior fornix. The canal may point similarly in cases of acute anteflexion, but in these the associated hypoplasia is the more important infertility factor.

In estimating the significance of the malposition it is necessary to take account of associated signs and symptoms. For instance, a mobile displacement is less likely to be associated with infertility than one which is fixed, for the latter is often caused by

pelvic/

pelvic adhesions or inflammatory diseases. Similarly the presence of tenderness is noteworthy, tender and prolapsed adnexa calling for particular attention in view of their association with dyspareunia. In some cases the tenderness is such that the position and mobility of the uterus can only be clearly defined after the administration of an anaesthetic.

Lateral deviation suggests the presence of adnexal abnormalities - e.g., inflammatory disease on the side of the deviation or ovarian or parovarian tumours on the other. The presence of uterine tumours, e.g., fibromyomata, should also be excluded.

Other conditions noted in this part of the examination have only an indirect or slight bearing on fertility. Uterine descent or prolapse may usually be ignored in this connection; so, too, may so-called angulation of the internal os, for this is no longer regarded as an obstacle to the passage of the spermatozoa.

(4) Pelvic Inflammatory Diseases.

Pelvic inflammation being one of the commonest causes of sterility in women, a thorough examination must be made of the tubes and ovaries. Inflammatory diseases may be manifested by tubo-ovarian masses, tenderness in the lateral fornices, thickening of the bases of the broad ligaments (parametritis), fixed retroflexion of the uterus, or pain elicited on lateral movement of the cervix./

cervix. In cases of doubt, anaesthesia should be employed.

When possible, tubal infection should be differentiated from parametritis and from other pelvic pathological states. The presence of acute or subacute salpingo-oophoritis contraindicates further diagnostic procedures, e.g., tubal insufflation.

Interpretation of Results of Pelvic Examination.

Any definite abnormalities or diseases discovered in the course of the above examination should be regarded as possible causes of infertility and submitted, wherever possible, to the proper treatment. Only the most severe abnormalities and diseases - e.g., extreme hypoplasia or severe infection - may be regarded - and not even these by all authorities - as excluding the possibility of successful pregnancy. Otherwise it should be made clear to the patient that the abnormalities found do not necessarily constitute the cause of sterility and that their cure will not necessarily establish fertility. The decision whether or not to extend the investigation to the further stages now to be described is not always easy. In some cases it is desirable to pass on to the next stage at once before attempting the treatment of local conditions; in others, particularly in cases of acute infection, the further examination must be postponed until treatment has been successfully completed.

III. Functional Examination.

For reasons of clarity the tests that constitute this stage of the investigation will be discussed in relation to the questions they are intended to answer. These may be briefly formulated as follows:

(1) Does ovulation take place?
(2) Can the ovum pass into the uterus?
(3) Does the uterine endometrium undergo normal development?
(4) Are the endocrine conditions of fertility present?
(5) Does insemination take place in an adequate manner and at the appropriate time?
(6) Do the spermatozoa pass into the cervix?
(7) Are the conditions for the development of the ovum maintained at an adequate level?

Some of these questions can be answered by noting the response to simple mechanical tests; this applies particularly to the investigation of the tubes. But others can only be answered - and indeed, can only be formulated - on the basis of the physiological facts reviewed in the following pages: the physiology of the endometrial cycle in particular will be discussed fully here, and this will obviate the necessity for a detailed description of the normal cyclical changes when the results of endometrial biopsy are described in Part II of this work.

The Menstrual Cycle.

The menstrual cycle represents a particular variety of the sex cycle which in one form or another is characteristic of all female mammals. The genital organs of all mammals have to fulfil in succession two groups of functions - the first concerned with fertilization/

tion (namely, with liberation of the ovum, transport of the ovum to the uterus, and transport of the spermatozoa to the tubes), the second with the preparation of the uterus for the reception of the fertilized ovum (progestation changes) and either the continuation of these changes (pregnancy) if the ovum is fertilized or their subsequent neutralization if fertilization does not occur.

Two phases of genital changes must accordingly be distinguished.

(i) The oestrous phase or cycle, so-called because of its association with heat (oestrus). In this phase libido becomes manifest and preparations for insemination are effected. Immediately after insemination and ovulation the changes regress and the completion of the oestrous phase is in many species marked by bleeding from the highly developed endometrium.

(ii) The reproductive phase. The essential feature of this phase is the preparation of the endometrium for the reception of the ovum. If fertilization takes place the prepared endometrium is utilized by the fertilized ovum. But the actual occurrence of the endometrial changes is independent of fertilization. With certain qualifications, it may indeed be stated that the endometrium reorganizes itself after every ovulation and prepares for pregnancy, whether conception, or for that matter coitus, has taken place or not. In other words, unless fertilization occurs ovulation is followed by pseudo-pregnancy even in the virgin animal. In some species pseudo-pregnancy is virtually indistinguishable from true pregnancy so far as the condition of the/

the uterus is concerned; in the bitch, for instance, it lasts for the same period and terminates in a pseudo-parturition, followed by lactation and maternal behaviour. In other species - e.g., the cow - pseudo-pregnancy which follows ovulation is of short duration and vestigial character, but the difference is one of degree only.

The Human Cycle.

The human menstrual cycle corresponds, in all essential characteristics, to that of the lower mammals. As in other mammals, the uterus, the tubes, and the vagina undergo changes corresponding to two phases. The first phase, which begins after the preceding menstruation has completed its course, consists mainly in proliferative processes in the uterine epithelium and, to some extent, in the vaginal wall. These changes correspond to the oestrous phase in lower animals. Unlike the oestrous changes, however, the proliferative processes in the human cycle, do not, in most cases, end abruptly in such a breakdown as might manifest itself in bleeding. Instead there is a smooth transition into the second phase during which the endometrium shows the changes characteristic of incipient pregnancy; that is to say, in the human uterus, too, the proliferative stage is followed, in the absence of conception, by a stage of pseudo-pregnancy. The relation to ovulation is again the same as in lower mammals; for ovulation takes place towards the end of the proliferative phase/

phase and before the preparation of the endometrium for pregnancy (differentiative or secretory or progestational phase) makes its appearance. If fertilization takes place the development of the uterus continues along the same lines; the features of the secretory phase simply develop further. If the ovum remains unfertilized the preparative changes of the endometrium are neutralized by the cataclysmic process manifested in menstruation.

Specific Changes in the Human Cycle.

Only those changes which have an immediate bearing on the study of infertility need be considered in detail.

(a) The Fallopian Tubes.

The changes in the tubes are twofold: (i) in the nature and function of the epithelial lining, and (ii) in the type and frequency of the contraction of the muscular wall.

(i) About the former, it need only be said that during the first phase of the cycle, the epithelium is mainly ciliary in character, whereas after ovulation secretory activity becomes manifest. It is probable that the secretion is necessary for the survival of the ovum, for interference with the development of the secretory phase involves the death of the ovum in the tube.

(ii)/

(ii) The contractility of the tubal musculature is important for the transport of the ova - although there is much evidence that the cilia are also concerned in the removal of the ovum from the ovario-tubal space. This contractility also varies with the phases of the cycle, so that the condition of the tubes cannot invariably be deduced from the findings of a given moment.

Rubin (1939) has investigated, in a series of 513 patients, the tone and activity of the Fallopian tubes by kymographic tubal insufflation in relation to the type of menstrual cycle presented by each patient. In those with normal menstrual cycles contraction and relaxation occurred about three times per minute in the anovular phase, while about the period of ovulation the tone increased and the rate of contraction became about 8 per minute.

(b) <u>The Uterus</u>.

Endometrium: During the first (proliferative) phase of the cycle there are seen numerous mitotic figures, indicative of great cellular proliferation which is most prominent in, but not restricted to, the epithelium. The glands have the appearance of straight tubules; their lumina are round and regular and they are lined by low columnar epithelium (see Fig. 1). Towards the/

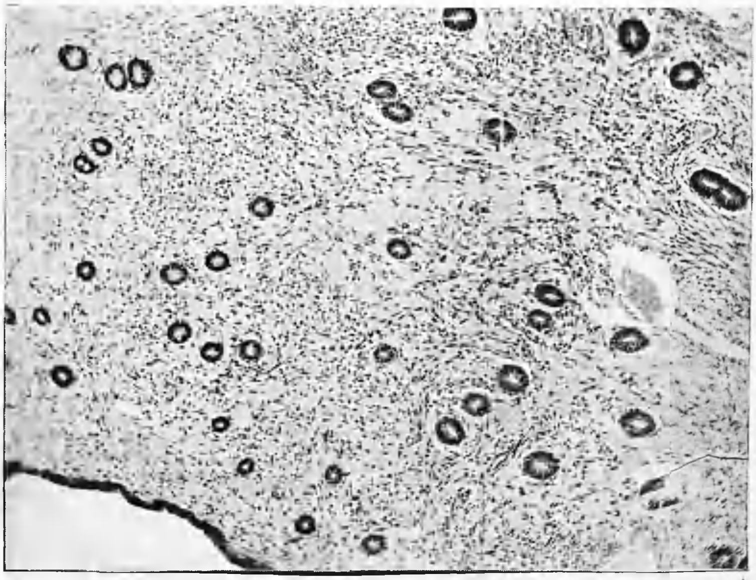


Fig. 1. Endometrium removed three days after conclusion of a period. The appearances are illustrative of the proliferative phase. Note the low columnar epithelium of the glands, whose lumina are round and regular. (x 75)

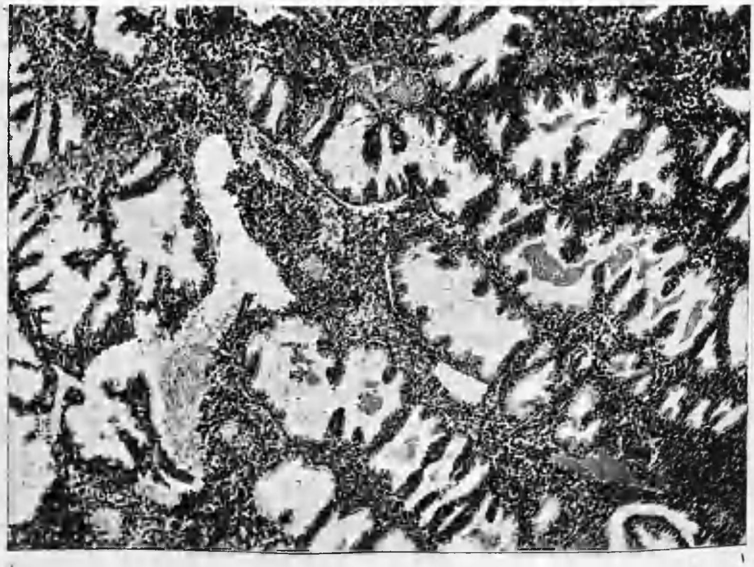


Fig. 2. Endometrium removed two days before menstruation. The appearances are those of the differentiative phase. Note serrated appearance of the glands with tuft-like protrusions into the lumina, in which secretion is present. (x 75)

the end of this phase proliferation becomes less prominent and, on longitudinal section,the glands assume a somewhat wavy outline without actually being coiled.

In the second (progestational) phase, development occurs by a gradual transition from the proliferative processes. The first characteristic is the elevation of the nuclei from the bases of the cells of the glandular epithelium; glycogen appears in the cytoplasm and the outline of the glands changes with the occurrence of a characteristic dilatation and convolution. As the second phase advances these changes become more and more pronounced. The columnar character of the epithelium is intensified; the glands coil round their longitudinal axis so that cross-sections show the well-known serrated appearance; the endometrium thickens; and, corresponding to the enlargement and crowding of the cells, tuft-like protrusions are thrust into the lumina of the glands (see Fig. 2).

Myometrium: The changes of the uterine cycle, though most clearly manifested in the endometrium, also extend to the uterine musculature. Here the changes are twofold: first, the spontaneous motility of the uterus changes in accordance with the endometrial phase, the contractions differing in frequency and character during the two phases; and, secondly, the response to pitocin, which/

which is pronounced during the first phase, tends to disappear in the second. It should be added, however, that some authors have thrown doubt on the regular recurrence of the latter change.

(c) <u>The Vagina</u>.

The corresponding changes in the vaginal epithelium are not equally pronounced and regular in all women. In many cases they can be followed by studying the cell content on vaginal lavage (Papanicolaou, 1933). The findings are as follows:

(1) Early proliferative stage. Numerous leucocytes and large epithelial cells.

(2) Late proliferative stage. Considerable diminution in the number of leucocytes or practically their total absence; increase in mucus; increase in the number of epithelial cells with increasing tendency to cornification, and often with increase in the glycogen content.

(3) End of proliferative stage. Epithelial cells of more scaly type; reappearance of leucocytes. Erythrocytes may appear at the same time and the proportion of mucus may again decrease.

(4) Late secretory phase. Increase in leucocytes continues, sometimes after an intervening phase of leucopenia; the aggregation of epithelial elements is more definite.

These changes may be obscured in normal women, but where they can be demonstrated their relation to the other/

other changes of the menstrual cycle is clear. Their demonstration may be of considerable assistance in the control of treatment by oestrogenic hormones and in the determination of ovulation time.

(d) The Ovaries.

As already pointed out, the successive changes in the uterus and vagina occur in co-ordination with ovulation. It is generally known that a follicle begins to develop soon after completion of a menstrual period, that it attains maturity and expels an ovum during the interval (i.e., between two successive menstruations), and that the delivery of the ovum is followed by luteinization of the follicular cavity.

The actual process of ovulation has now been observed in several species. It is preceded by enlargement of the follicle and increase of intrafollicular pressure. But ovulation depends not only on these processes, but also on specific cellular changes: (a) the formation of a cell cone (Strassmann's cone), which, as it were, prepares the ascent of the follicle to the surface of the ovary; and (b) the development on the surface of an area in which the cell layer becomes thin and so offers little resistance to the pressure of the follicle. Even large follicles do not ovulate unless these conditions are fulfilled. In some abnormal states a number of follicles undergo enlargement without subsequent/

DAY OF CYCLE.

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Schroeder,														X	X	X													
Fraenkel,																		X	X										
Ancel,																X	X	X	X	X	X								
Schickele,												X	X	X															
Meyer & Ruge,				X	X		X	X	X	X	X	X	X	X															
Halban & Koahler,																	X	X	X	X									
Marcotty,																X	X												
Seitz & Wintz,											X	X																	
Villemin,													X	X															
Shaw,														X	X	X	X												
Tschirdewahn,															X	X	X												

Fig.3. Occurrence of ovulation in menstrual cycle.
The horizontal lines indicate the days of the cycle on which a number of independent authors have observed ovulation (also marked by x). All observations were made on opening the abdomen. Note prevalence of mid-menstrual dates. (After Dickinson, 1938; modified and abridged).

subsequent ovulation.

Although characteristically a mid-menstrual phenomenon, ovulation does not occur on the same day of the cycle in all cycles or in all women. As with all other biological phenomena, considerable variations occur, and there is reason to believe, in view of the direct evidence supplied by variations in pregnandiol excretion during successive cycles, that ovulation may occur on widely different days in different cycles, and that even in the same woman ovulation may occur before the fourteenth day in one and later than the seventeenth day in the next cycle. Hartmann's (1936) observations on monkeys bear out this conclusion.

The range of variation may be judged from the data in Fig. 3 based on the researches of a number of independent investigators. It will be seen that, with two exceptions, the authors place ovulation between the ninth and the twentieth day of the cycle. It is possible that abnormal endocrine conditions may either advance or delay the date beyond the limits shown; but there is no doubt that mid-menstrual ovulation is the rule.

Luteinization.

The corpus luteum (whose cells are derived mainly from the membrana granulosa) is normally formed after ovulation. Experimental evidence, however, shows/

shows that luteinization may take place without preceding ovulation and that it may even occur in follicles which have not developed fully or undergone pre-ovulatory enlargement. Normal luteinization is a rapid process which, in the human subject, is completed within three to five days after ovulation. In the absence of fertilization, degenerative processes begin within six to nine days after the formation of the corpus luteum, though the final degeneration of the corpus luteum occupies a long space of time. But if fertilization takes place, the corpus luteum persists for a period corresponding to that of pregnancy. Even without the intervention of pregnancy the corpus luteum may, in pathological cases, persist for prolonged periods and interfere not only with the ovarian cycle of ovulation and luteinization, but also indirectly with the uterine cycle.

<u>Co-ordination of the Ovarian and Uterine Cycle</u>.

The outstanding biological characteristic of the sex cycle - whether it be the oestrous cycle of lower mammals or the menstrual cycle of Primates - is the co-ordination of the ovarian cycle with the changes in the endometrium and the other genital organs. It is obvious that the reproductive processes can run their normal course only if the tube is in the appropriate condition required for the transport of the ovum at the/

the time of ovulation; if the endometrium is prepared for the reception of the fertilized ovum at the moment of its arrival; and if all other changes are similarly integrated into the orderly whole of the sex cycle.

This co-ordination is brought about mainly by the operation of endocrine factors; and of these the endocrine secretions of the ovary are of prime importance. In this context two fundamental aspects of ovarian secretion must be considered.

It will be recalled that complete oophorectomy causes cessation of the cyclical changes, followed by genital involution. Ovarian grafts repair this involution and may maintain the cyclical changes. The effect of ovarian grafts can be largely imitated by ovarian extracts prepared by extraction with volatile media, such as alcohol. The active substance involved has been identified as a sterol to which has been given the name oestradiol. Like other oestrogens, it is characterized by its capacity to invoke the changes of the oestrous cycle in castrated or immature mice or rats.

When oestrogenic extracts were first prepared, and when it was demonstrated that they could repair the involution caused by castration and, in immature animals, invoke precocious development of the uterus and the other genital organs, it was assumed that oestrogenic hormone represented/

represented the ovarian hormone. But it was soon shown that even very large doses of oestrogenic extracts, whether purified or in their original form, could not invoke the full complex of uterine changes. It was demonstrated in particular that the changes of the secretory phase would only develop, in the absence of an ovary, if the administration of oestrogenic extracts was followed by the use of corpus luteum extracts of a particular type. Further research showed that the corpus luteum elaborates a substance not dissimilar to the oestrogenic compounds, which has been termed progesterone. This substance is excreted in the form of a derivative (pregnandiol), the output in normal women showing characteristic fluctuations, which corresponds to the rise and fall of luteal development.

Progesterone incites the specific development of the secretory phase in animal and human females. It can only act in this manner, however, if the uterus has been, or is, under the influence of a sufficient amount of oestrogenic hormone. This priming effect of oestrogenic substances is of considerable practical importance.

The extensive researches of the last decade have thus confirmed and extended the hypotheses suggested by/

by many earlier clinical observations on the co-ordination of ovarian and genital changes. The essential conclusions may be summarized as follows:

(i) Before the occurrence of ovulation, the ovary secretes an oestrogenic compound. This substance affects the tubes, determining their motility and evoking the specific epithelial development. It also affects the uterus in two ways, causing the endometrial development seen during the early (proliferative) stage of the cycle and invoking characteristic motility of the musculature. It affects the vagina, where it causes the epithelial development which can in many cases be studied by the smear method. Finally, but not least important, it imparts to the endometrium the capacity to react to progesterone.

(ii) The developing corpus luteum secretes progesterone. This hormone rapidly brings about the differentiation of the endometrium so that, within a few days, the typical picture of the secretory phase develops. It also appears to invoke the secretory phase in the tubal epithelium; and it affects the character of uterine contractility.

It is probably incorrect to assume that the two phases of ovarian secretion - the oestrogenic and the kyogenic (i.e., pregnancy-producing) are sharply divided from each other. The recent work of Zuckerman (1937/

(1937, 1938) and others indicates that secretion of oestrogenic hormone continues throughout the lutein phase and that oestrin is not solely a precursor and pathmaker of progesterone.

The Role of the Pituitary.

The ovarian function which governs the uterine and vaginal cycle is in its turn regulated by secretions originating in the anterior lobe of the pituitary gland. Extirpation of this lobe prevents genital maturation and causes permanent infantilism. On the other hand, anterior lobe grafts placed in immature female animals invoke precocious development of the genital system. When administered to mature animals, grafts or suitable extracts from the anterior lobe intensify the normal function of the ovary and in certain circumstances may produce excessive ovulation. Thus, as many as fifty ova may be released from the ovary of the rat under artificial stimulation from anterior lobe substance.

The Pituitary-gonadal Mechanism.

The main features of the pituitary mechanism in the female may be summarized as follows. At the beginning of every sex cycle the anterior lobe of the pituitary secretes a gonad-stimulating hormone, which has a twofold effect: (a) it incites the secretion of oestrogenic/

oestrogenic hormone and thus indirectly promotes the development of the uterus and other genital organs: and (b) it stimulates follicular growth.

The second phase of ovarian secretion, during which progesterone is liberated, also depends on pituitary control. Removal of the pituitary gland interferes with the secretion of progesterone, though it does not necessarily lead to precocious involution of the corpus luteum; on the other hand, administration of pituitary extracts may prolong the active life of the corpus luteum in experimental animals. Whether the ultimate degeneration and inactivation of the corpus luteum which occurs at the end of the cycle expresses an active participation of the pituitary or simply a cessation of pituitary secretion is as yet uncertain.

The "gonadotropic" or "gonadotrophic" secretion of the anterior lobe, which is responsible for the effects described upon the ovary, and thus for genital development and the genital cycle in general, can be extracted by various aqueous media and purified by a number of methods, which aim at separating fatty and protein-like substances from the active factor. This factor has not yet been obtained in chemically pure/

pure form, but the active molecule seems to be characterized by the presence of certain sugars attached to a protein-like group.

While it is certain that the ovarian cycle is controlled by a pituitary cycle, that is to say, by variations in the activity of the anterior lobe, many important questions arising from this fundamental fact are still obscure. Research in this field is impeded by a twofold difficulty. First, the gonadotropic hormones are very labile substances, and thus chemical investigation and purification is exceedingly difficult. Secondly - an even greater difficulty - physiological conditions in the various species are very different. Thus, the mouse, the rabbit, and the monkey, to name only the more important animals used in research work, react very differently to the same experimental conditions - e.g., to the administration of exactly the same pituitary extract. Ovulation may be incited in one species by an extract which fails to produce it in another, and the same is true of luteinization.

INVESTIGATION/

INVESTIGATION OF SPECIFIC FUNCTIONS.

The more important characteristics of the sex cycle (menstrual cycle) and the principles which must be considered in the analysis of its disturbances have now been discussed. It has been pointed out that apparently normal manifestations of genital function (e.g., bleeding) may mask severe deficiences (e.g., absence of ovulation), and that any given anatomical or functional defect may be caused by widely divergent physiological conditions (e.g., either irreactivity or lack of endocrine stimulation). The specific questions which have to be answered in the course of the investigation may now be examined in detail.

(1) Does Ovulation Take Place?

The only certain method of diagnosing ovulation is by flushing out the Fallopian tubes in situ, and this is rarely available clinically. Indirect methods therefore must be employed.

The question whether or not ovulation occurs must be carefully considered in each case. The occurrence of bleeding does not necessarily signify the termination of a complete menstrual cycle involving both phases of ovarian function (follicular maturation and luteinization). Bleeding, simulating true menstruation, may simply represent the termination of a cycle in which secretion of oestrogenic hormone has taken place

without/

without follicular maturation. In such circumstances the endometrium degenerates when the secretion of oestrogenic hormones ceases and as a result extravasated blood ultimately passes into the vagina. The fact that this condition is met with in actual practice emphasizes the need for investigating the occurrence of ovulation even when regular bleeding occurs.

On the other hand, the absence of menstrual periodicity does not necessarily prove the absence of ovulation; indeed, cases are on record in which even primary amenorrhoea has not proved incompatible with fertility. Nor does the fact that the patient's general health is good prove the occurrence of ovulation. In certain physiological conditions - e.g., pregnancy and lactation - ovulation does not as a rule take place although all general functions remain unimpaired.

The conditions which may be associated with absence or abeyance of ovulation may be classified as follows:

(a) Structural Abnormalities of the Ovaries.

In cases of juvenilism or infantilism the ovaries are incompletely developed and retain their prepubertal appearance throughout life. In milder cases of this description follicular enlargement may take/

take place but it never terminates in full maturation and rupture. This condition of the ovary cannot be detected by examination of the uterus. On the one hand, an infantile uterus is not necessarily associated with an infantile ovary: on the other, juvenilism of the ovary does not necessarily imply hypoplasia of the uterus, for oestrogenic secretion may take place and invoke uterine development. Secondary involution of the ovary occurring after pregnancy may involve a disturbance or complete cessation of ovulation without impairment of the secretion of oestrogenic hormone. This, too, is a condition which cannot be recognized by inspection of the uterus. The ovary may be fairly large, and only its smooth surface, as revealed on laparotomy, may provide a clue to its real condition.

(b) Pathological Changes in the Ovaries.

The most important are retention cysts. It is uncertain whether these inhibit ovulation by a direct mechanical action upon the follicular apparatus or by interfering with the follicle-stimulating action of the pituitary.

Focal haemorrhages, endometriomata, and true neoplasms, either cystic or solid, may have an inhibitory effect on ovulation. X-rays may destroy the follicles of the gonad without interfering with its secretion. It is well known, however, that remnants of the follicular apparatus may remain undisturbed by radiation and lead to restoration of fertility.

Inflammatory/

Inflammatory changes of the ovaries may gravely interfere with both oogenesis and the development of the follicles. Such interference with follicular dehiscence, or even with the maturation of the follicles, is frequently observed in the presence of salpingo-oophoritis or of actual abscess formation or of peri-ovarial adhesions. General fibrosis of the ovarian stroma has a similar effect.

(c) Excessive Gonadotropic Stimulation.

Just as lack of pituitary gonadotropic secretion spells infantilism of the ovary and cessation of ovulation, so may excessive gonadotropic stimulation have the same effect. It may cause the formation of numerous abnormal follicles which fail to ovulate; or it may lead to the persistence of an active corpus luteum which prevents further ovulation. The latter condition seems to occur not only in cases of chorionepithelioma, but also in disturbances of the pituitary-gonadal mechanism such as sometimes occur after pregnancy, whether normal or ending in miscarriage.

Diagnostic Significance of Pathological Ovarian Conditions.

The existence of pathological conditions in the ovary associated with disturbances or complete absence of ovulation has, of course, been recognised for a long time. But the practical significance of such/

such changes both for diagnosis and prognosis must not be overrated. Two facts are important in this connection.

(i) Even severe changes may take place without preventing ovulation, conception occurring in the presence of neoplasms, cysts and other structural abnormalities. Hence the demonstration of gross lesions of the ovary does not prove anovulation.

(ii) Conversely, the absence of such gross lesions as can be demonstrated clinically and without laparotomy does not prove that the ovarian cycle is normal. Even a normal ovary may persist in an anovulatory condition for months at a time (e.g., during lactation); and the incomplete cycle (follicular phase without ovulation) is not detectable anatomically.

Diagnostic Significance of Biopsy.

It used to be believed that menstruation was conditioned by the previous occurrence of ovulation. The theory (Meyer, 1913; Schroeder, 1928) which culminated in this conclusion has, however, been disproven, if by menstruation is understood the occurrence of more or less regular bleeding. Experiments have been done in which monkeys were made to reproduce externally all signs of menstruation although they had received injections of oestrogenic hormone only. Again,/

Again, stimulation of the ovaries of monkeys by gonadotropic hormones results in rapid proliferation of the uterine endometrium with subsequent bleeding although ovulation has not taken place. This external bleeding which, though it simulates menstruation, corresponds to the oestrous bleeding of lower mammals may also take place in healthy monkeys. In such animals all external signs point to normal ovarian function, e.g., the external genitalia undergo the swelling and reddening which is peculiar to Rhesus and other monkeys, the uterus is well developed and bleeding occurs at the expected time. Yet sections through the uterus taken shortly before the date of the expected menstruation show that the endometrium has failed to undergo the pre-menstrual changes and has retained the appearance of the proliferative phase. The ovarian condition in such cases corroborates the conclusion that the uterus has been exposed to the action of oestrogenic but not of luteal hormone, there being no sign of ovulation.

These observations (for bibliography see Hartman, 1936) suggested that in women, too, periodic bleeding, however regular, may simulate rather than represent the end of a complete menstrual cycle.

Novak/

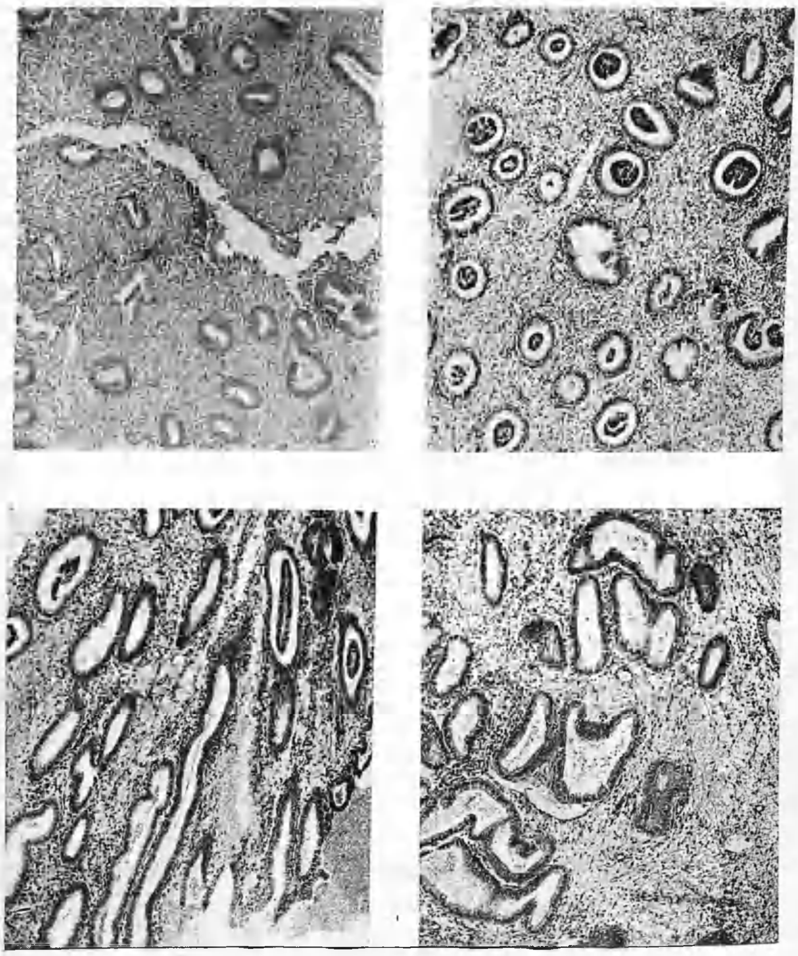


Fig. 4. Endometrium in three cases of sterility showing characteristics of anovulation. A. The patient had been married two years without pregnancy. This specimen was taken on the twenty-sixth day of the cycle and the period began three days later. B. The essential features corresponded to those in A. C and D. The patient had been married for four years without pregnancy. Specimen C was taken on the twenty-second day of the cycle, and the period began five days later. Specimen D. was taken three months after C on the twenty-fourth day and the period began six days later. The absence of differentiation in both specimens suggests a tendency to repeated anovulatory cycles.

Novak (1934, 1935), Tietze (1933) and others have confirmed this hypothesis; Tietze, indeed, found examples of anovulatory cycles in the very material on which Schroeder based his view that such cycles did not occur. Some of my own findings are shown in Fig. 4.

On the basis of present views - namely, that in the great majority of cases ovulation is followed by the formation of a corpus luteum, the secretion of progesterone, and the development of an endometrial condition characteristic of the secretory phase of the endometrial cycle - a method has been evolved ("endometrial biopsy") whereby the occurrence or absence of ovulation is ascertained by an examination of a portion of endometrium removed during the presumptive secretory phase of the menstrual cycle. If the endometrium is normal - that is to say, if the endometrium is differentiated - the occurrence of luteinization is proved and by inference the occurrence of ovulation may be accepted. Absence of differentiation - with qualifications to be discussed later - indicates that ovulation has not occurred.

Technique/

Technique of Biopsy.

Time of Operation.

It is important that the biopsy should be carried out at a suitable stage of the menstrual cycle. In cases in which sterility is associated with amenorrhoea,or with menstrual irregularity,or with excessive menstruation, the endometrium may, of course, be examined at any time of the cycle, but examination may then have to be repeated at intervals. In cases of regular menstruation the endometrium should be removed within a few days of the expected menstruation.

A further warning is necessary. The choice of date is based on the fact that ovulation normally takes place about the middle of the cycle and that the endometrium will have undergone its typical changes a few days before menstruation. In fact, the secretory phase should begin to appear any time after the thirteenth day of the cycle and should not be delayed normally much beyond the nineteenth. Biopsy on the twenty-fourth day of a twenty-eight day cycle should invariably yield premenstrual endometrium in ovulating women. But since it cannot be known, until the occurrence of the next menstruation, whether the menstrual cycle in which the biopsy has/

has been made is of normal duration, the possibility of the cycle being prolonged, with concomitant delay in ovulation, must be considered. It is therefore necessary to ascertain the date of the menstruation following upon biopsy and to regard a negative finding as significant only if this menstruation has not been delayed; the date of the preceding menstruation must never be taken as the sole guide. If menstruation is delayed after a biopsy which has given a negative finding, the investigation must be repeated until a sample has been obtained a few days previous to menstruation.

Method.

The earliest attempts to obtain a portion of endometrium for biopsy, apart from the customary dilatation of the cervical canal and diagnostic curettage under anaesthesia, were made by the use of a very narrow curette. The piece of mucosa removed was often of insufficient size and in many cases it was lost in the uterine cavity. The stem of the curette was then made hollow in order that suction might be applied through it with the object of holding the scraping. Suction methods used by Klinger and Burch (1932), Lörincz (1934), Novak (1935), and Tamis (1936) gave better/

better results. Lörincz used electric motor suction only, but Novak combined this with simultaneous curettage. In 1936 Randall of the Mayo Clinic described his modified cannula curette. In 1937 Sharman and Sheehan introduced a biopsy curette (see Fig. 5) which was simple in construction and effective without suction. It has a shaft and handle of the same size and shape as those of an ordinary uterine sound, but is furnished with a tubular terminal portion 1.8 cm. beyond the cutting edge, into which the portion of curetted endometrium slides.

To obtain the specimen, the patient is placed in the lithotomy position and the usual antiseptic precautions are taken. The cervix is then pulled down with a vulsellum forceps and the biopsy instrument is passed into the uterine cavity exactly as a uterine sound, no previous dilatation being necessary. The curette is placed against the mucosa of either the anterior or posterior wall, drawn downwards for about an inch, and then withdrawn through the cervical canal, avoiding any pressure of the cutting edge against the cervical wall. An attempt should be made to obtain the specimen from a region as near as possible to the middle of the anterior or of the posterior wall of the uterus

towards/

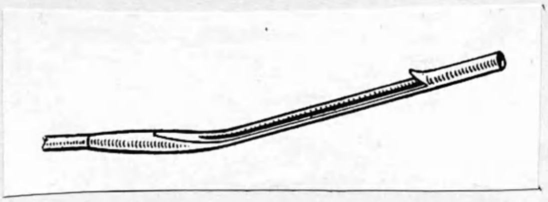


Fig. 5. Sharman and Sheehan's biopsy curette (approximately four-fifths actual size). Only the head of the instrument is reproduced; it shows the tubular terminal portion (1.8 cm. long) extending beyond the cutting edge. As the piece of endometrium is cut it slides into this chamber. The shaft and handle are of the same size and shape as those of an ordinary uterine sound and are not shown

towards the fundus, for the changes are most conspicuous in these areas. After removal of the specimen, any further specimens of mucosa required can be obtained by reinserting the instrument.

Some discomfort is usually felt at the moment when the instrument first passes the internal os, but this passes off at once. There is also some discomfort, in some cases, when the tip of the instrument touches the fundus, and in varying degree during the actual curettage. Neither at the time of the biopsy or later is the average patient much more disturbed than by bimanual examination of the pelvis. No after-treatment or care of any sort is required. The absence of any real pain is very important from the point of view of obtaining the patient's co-operation, should a subsequent biopsy or a series of them be desired.

The specimen is found lying flat, with its mucous surface downwards, in the tube at the tip of the curette. In most cases a solid piece of endometrium, nearly 2 cm. long and 3 mm. in diameter, is obtained, and is easily removed from the tube by pulling its lower end gently with a needle. It may then be simply dropped into the fixative, or, preferably, laid mucous surface upwards on a piece of thin card/

card and then placed in the fixative. By adopting the latter procedure, it is possible later so to orientate the block as to obtain longitudinal sections vertical to the mucous surface. Endometrial biopsy, therefore, takes only a few moments, rarely requires an anaesthetic, causes little or no pain and does not necessitate keeping the patient in a hospital or nursing home. Its value is unquestioned, Novak indeed going so far as to state that the microscopic study of the endometrium often yields much more useful information than even blood or urine hormone studies.

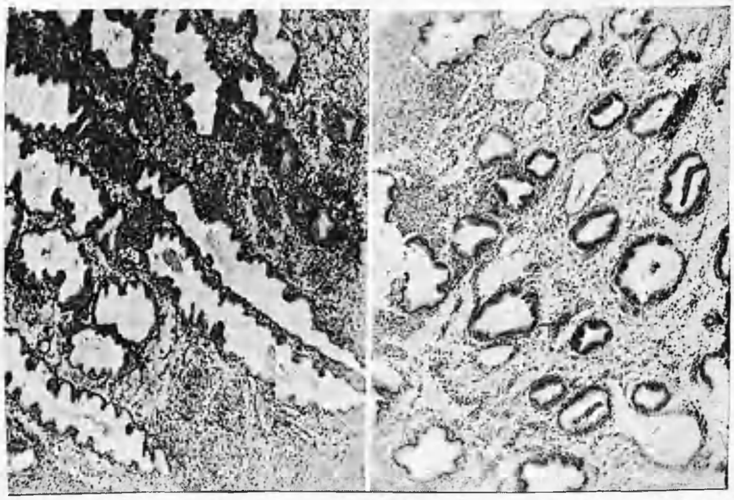
Interpretation of Results.

In most cases it is easy to decide whether a given specimen corresponds to the follicular (proliferative) or to the luteal (secretory) phase of the uterus. The degree in which the changes in the secretory phase have developed depends largely on the interval that has elapsed between ovulation and the collection of the specimen. In examining the sections particular attention should be paid to the glands, which in the late proliferative phase may show a somewhat wavy form upon longitudinal section, but are never definitely coiled (see Fig. 1).

As/

As the secretory phase progresses, the glands coil into a screw-shape on their longitudinal axis, the sections assuming a characteristic serrated appearance. At the same time the glandular epithelium tends to become more columnar in structure and the relative volume of the cytoplasm is increased. The presence or absence of glycogen is of diagnostic importance, but cannot be judged from the sections made in routine laboratory practice. A further characteristic of the secretory phase to which attention should be paid is the enlargement of the secretory cells and the tuft-like protrusion of these cells into the lumina of the glands. In the middle layer of the endometrium, the dilatation may become sufficiently pronounced to crowd the stroma cells out and force them towards the surface. (See Figs. 2 and 6).

During the secretory phase differentiation of the endometrium is generally at its height, whereas during the follicular phase proliferative changes predominate. Since the premenstrual or secretory phase represents merely the early stages of pregnancy changes, there is no sharp distinction between the fully developed endometrium and the changes found in the earliest stages of pregnancy. Certain authors have classified/



A B

Fig. 6. Differing appearances of the same endometrium removed a few hours before menstruation A. This shows characteristic appearances of the pre-menstrual or late differentiative phase. The glands seen in longitudinal section show "saw-tooth" outline. Secretion is present in the lumina and the stroma is loose. B. The glands are seen here in cross-section. Dilatation and tortuosity is not so apparent as in A. The stroma, however, is much looser and more "spongy." The section is more superficial (nearer uterine cavity than A)

classified the changes of the menstrual cycle into four phases, early proliferative, late proliferative, early differentiative and late differentiative. For practical purposes this fine distinction is not required, and it is only necessary to ascertain whether the main characteristics of the secretory phase have developed.

The abnormal endometrium which is found in anovulatory cycles does not require specific description, since its appearance corresponds to the proliferative epithelium of the follicular phase. This is illustrated in Fig. 4 which shows sections of endometrium taken from three different cases of sterility during the presumptive secretory phase. But it should be noted that the endometrial picture may vary in anovulatory cycles - e.g., that cystic glandular changes and inflammatory reactions in the stroma may be present. These must be considered in judging the patient's condition, but the essential question is whether or not the characteristic features of the secretory phase are present.

Fig. 4 and the case histories summarized in the legend illustrate both the existence of anovulatory cycles and the fact that they may occur without external signs of disturbed periodicity. But the frequency of anovulatory cycles in general and of follicular/

follicular menstruation in particular is still doubtful. Mazer and Ziserman (1932) report that the secretory phase was in abeyance in twenty-four of forty-one women who, though menstruating regularly, were childless, whereas a much lower percentage (just under 7 per cent.) was reported by Tietze (1933). At the present time it is still a matter of individual experience and opinion whether the anovulatory cycle is regarded as associated frequently or infrequently with sterility.

The application of the method is not restricted to cases in which some type of menstrual cycle occurs. Some reference has already been made to the fact that conception may take place even in amenorrhoea. Since, however, amenorrhoea is in many cases symptomatic of a general disturbance, biopsy forms a valuable diagnostic procedure for determining whether or not luteal function has developed. It may usefully be preceded in such cases by a determination of the pregnandiol output.

One other point should not be overlooked. Endometrial tuberculosis is much more common than is generally thought and should be borne in mind even if not suggested by anything in the clinical history or signs./

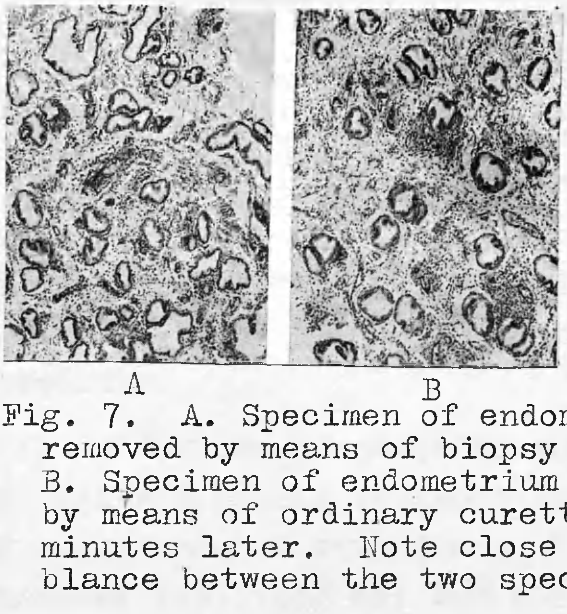


Fig. 7. A. Specimen of endometrium removed by means of biopsy curette. B. Specimen of endometrium removed by means of ordinary curette a few minutes later. Note close resemblance between the two specimens.

signs. Schockhaert and Ferin (1939) have reported twelve cases which were unsuspected and owed their discovery to endometrial biopsy. Sterility was the main complaint in eight of the cases, five of which showed tubal permeability.

Criticism of Method.

(1) It may be asked whether a single biopsy can yield a representative picture of the whole endometrium such as might be obtained by means of diagnostic curettage under anaesthesia. This question is answered by Fig. 7, wherein may be seen how close is the resemblance between a specimen of endometrium removed by a biopsy curette and one removed by an ordinary curette a few minutes later. My own experience has abundantly confirmed the fact that biopsy provides histological material representative of the entire endometrium.

(2) A further question is whether positive or negative findings afford reliable proof for or against the occurrence of ovulation. In practice it may be assumed that they do, but the general qualifications imposed upon any diagnostic method for the determination of ovulation are valid for this one also. Animal experiments have shown that complete luteinization may occur without actual release of the ovum, so that endometrial development may occur in the absence of ovulation. Again, it may be recalled that disturbances of oestrogenic secretion may inhibit the differentiation of the endometrium, the endometrium responding to progesterone only when it has been adequately/

Fig. 8. Endometrium removed in the premenstrual phase (twentieth day of an apparently anovular cycle), showing no evidence of differentiation. Menstruation began three days later. (x 75) Compare with Fig. 9.

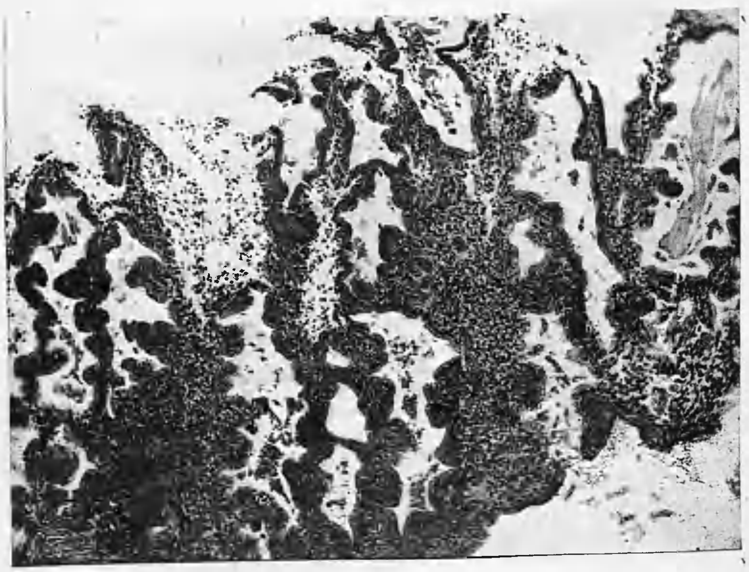


Fig. 9. Same case as in Fig. 8. Endometrium removed one month later in the premenstrual phase. Normal differentiative features are seen. Menstruation began one day later. (x 75)

adequately stimulated by oestrin. Lastly, it has not been proved with respect to the human subject that ovulation is invariably followed by luteinization. It is doubtful whether these qualifications greatly reduce the value of endometrial biopsy for practical purposes. Negative findings instantly indicate a grave disturbance of the cycle and favour the conclusion that ovulation is in abeyance, whereas positive findings make it likely that ovulation has occurred. Whatever the results, however, they refer only to the cycle in which the biopsy is made. In any normal woman a given cycle may be anovulatory; conversely, even a sequence of anovulatory cycles does not justify the diagnosis of permanent sterility (see Figs. 8 and 9).

Determination of Lutein Function by Urine Analysis.

Determination of the urinary output of sodium pregnandiol glucoronidate also yields information about the occurrence of ovulation. The principle on which this method is based has already been mentioned. Since considerable quantities of pregnandiol begin to be excreted soon after ovulation and continue to be present in the urine until just before menstruation, urine analysis may provide an index of luteal function, and thence of ovulation.

Venning and Browne (1937), who introduced the method, realized that it might provide a means for the recognition of anovular cycles. They reported on three doubtful/

doubtful cases and seven positive cases in which they followed the pregnandiol cycle. Theoretically a single positive result, i.e., one in which the presence of pregnandiol has been demonstrated, should be regarded as proof of ovulation. In practice it is desirable to make more than one test.

The urine must be collected during the presumptive luteal phase of the cycle. Since in any given cycle ovulation may be delayed, it is not sufficient to rely on the date of the preceding menstrual period. It is necessary - as explained in connection with endometrial biopsy - to ascertain after the test whether the next period arrived on the expected date. If the period is delayed after a negative result the test must be repeated. Experience has shown that the urine should be collected between the twentieth and the twenty-fifth day of the cycle. A twenty-four-hour sample gives more accurate results than a combined morning and evening sample, but for reasons of convenience the latter is usually favoured, particularly when the test has to be repeated several times.

Present Value of the Method. The Venning-Browne test is of recent origin and it is too early yet to make a definite estimate of its clinical value. Four/

Four criticisms may be directed against its sole use.

(a) It is not certain whether the correspondence between the production and excretion of progesterone is constant. Losses in the process of excretion may simulate absence of luteinization.

(b) The Venning-Browne test demonstrates the occurrence not of ovulation, but of a process - luteinization - which, though normally associated with it, is not entirely dependent on its occurrence.

(c) Luteinization is not necessarily followed by uterine development. Wiesner has recorded two cases in which the Venning-Browne test yielded a strongly positive result, but simultaneous biopsy proved that the endometrium was almost atrophic. In one case the lack of endometrial development was probably caused by preceding treatment with X-rays.

By way of summary it may be tentatively stated that the presence of large amounts of pregnandiol in the urine suggests the occurrence of ovulation irrespective of the condition of the endometrium. As in other biological tests, such positive results are of greater significance than negative ones. Biopsy and the Venning-Browne test are therefore supplementary to each other; where the former is "negative" the latter may yet reveal the occurrence of ovulation; where the Venning-Browne test is doubtful, the biopsy may decide the issue, and vice versa.

Other Tests for Ovulation.

Several other tests for the detection of ovulation have been proposed. Their value is limited but/

but not negligible; some of them afford considerable assistance in the approximate determination of ovulation time - a matter of importance in adjusting intercourse to the fertile period and in choosing the days on which to carry out artificial insemination.

The following methods will be discussed:

(1) Potentiometric methods.
(2) Samuel's spectroscopic method.
(3) Examination of vaginal smears.
(4) Inspection of cervical mucus.
(5) Determination of variations in excretion of hormones.
(6) Recording of the temperature curve.
(7) Observation of general signs.

(1) Potentiometric Methods. Changes in electric potential are associated with ovulation, not only in the rabbit, in which they were first discovered, but also in women. The difference in electric potential between the abdominal skin and vagina increases greatly and rapidly at the time of ovulation. The method, however, demands not only the use of complicated apparatus, but also continuous observation of the patient for fairly long periods (at least two days).

Notwithstanding these and other disadvantages it is believed to hold great promise for the investigation and treatment of sterility (Musselman and Burr, 1938; Rock et al., 1937; Reboul et al., 1937).

(2) Samuels' Spectroscopic Method. Samuels (1937, 1938) has devised a spectroscopic method whereby changes in the period required for the formation of methaemoglobin after interruption of the circulation in/

in a skin area have been related to the occurrence of ovulation. His conclusions, however, await verification, and his claim to have demonstrated more than one ovulatory phase per cycle is certainly not in accordance with well-established data.

(3) Examination of Vaginal Smears. It has already been mentioned that the vaginal cycle which is synchronized with the ovarian cycle is manifested in the changing composition of vaginal smears. This fact can be utilized by determining the day at which the ovulative smear first occurs, but it must be borne in mind that in many women the vaginal cycle does not show very clearly. The method, though often useful in individual cases, is by no means universally applicable.

Intelligent patients can be taught to take vaginal smears, so that continuous records are obtainable without repeated visits to the practitioner.

(4) Inspection of Cervical Mucus. As mentioned previously, the cervical secretion changes with the phases of the cycle. During the ovulatory period the cervical mucus is glairy and transparent. Seguy and Vimeux (1933) have utilized this cervical sign, which they discovered, for the purpose of determining ovulation time.

(5) Determination of Variations in Excretion of Hormones. Some authors have stated that the excretion of gonadotropic hormone is either confined exclusively to the phase of ovulation or else that it reaches a peak during that phase. Oestrogenic hormone is also said to be excreted in particularly large amounts at the time of follicular maturation. These observations/

observations have an obvious bearing on the question of determining ovulation time, but their practical significance is slight because of the difficulty of carrying out quantitative assays in clinical practice.

(6) Recording of the Temperature Curve. The researches of Rubenstein (1938) and Zuck (1938) indicate that the temperature curve varies in relation to the ovarian cycle. The procedure consists in the woman taking her rectal temperature in the early morning before rising, the temperature being read to one-tenth of a degree. During the mid-menstrual phase the curve reaches a low level, rising again immediately afterwards and remaining almost horizontal until the onset of the next menstrual flow. This variation was demonstrated in more than 80 per cent. of the menstrual cycles so far studied. A number of women who assisted in these studies planned the date of conception on the basis of temperature graphs. In this group pregnancy did not occur more than three days before or one day after the initial rise of temperature from its mid-menstrual low level. Moreoever, the temperature cycle ceased once conception had occurred, the temperature remaining at a level of 98.5° to 99.5°.

(7) Observation of General Signs. 'Mittelschmerz' and intermenstrual spotting are of particular interest, not only because they occur rather more frequently than other symptoms and signs, but also because their association with ovulation, though not established beyond doubt, is fairly definite. Neither 'Mittelschmerz' nor the occurrence of intermenstrual spotting - which can only be discovered/

covered by vaginal lavage - may be taken as reliable indices of ovulation, but they offer valuable corroborative evidence of this event. The same applies to other subjective symptoms often recorded during the mid-menstrual phase (e.g., unilateral pain, increased vaginal secretion, flatulence). Several authors have suggested that women can be trained to pay attention to these symptoms and to assist the practitioner by recording them carefully.

(2) Can the Ovum pass into the Uterus?

Tests for Patency of Fallopian Tubes.

The tubo-ovarial apparatus is not a static entity, but is subject to continuous changes in the interrelationship of its parts. In all animals (including the monkey) which have been investigated, it has been found that the various muscles of the adnexa effect periodic changes in the relative position of the fimbriae and the ovary. In some animals the ovary appears to be cupped by the tube at certain stages of the cycle and this approximation, which seems to facilitate the reception of the ovum by the tube, coincides with the ovulatory phase. When, as in the monkey, the infundibulum reaches and embraces the ovary, the latter does not play a purely passive part. Shortening and elongation of the ovarian ligaments occur/

occur, and Hartman (1936) concludes that, as a result of the observed movements, the fimbriae come into contact with the whole surface of the ovary at short intervals.

The tube itself is subject to cyclical changes, the fibres of the muscular coat of the tube increasing and decreasing in length with the phases of the cycle (Anapolsky, 1928). The changes in the epithelium were referred to earlier.

These facts - which have been the subject of much research - have to be considered in the present context for two reasons. It should be remembered, in the first place, that the tube is not simply a canal which is either open or closed but otherwise subject to few variations. The tube is a highly variable and complex organ. The condition of its epithelium may affect the transport of the ova, either by abnormalities of tubal secretion or by incomplete ciliary function. The development of its muscular coat may alter the mode of contraction and thus again affect the passage of the ova. Secondly, the deviations from the norm may be graded. It has been shown that the developmental condition of the muscular apparatus of the ovario-tubal region depends on the supply of ovarian hormones. Disturbances/

Disturbances of the endocrine function of the ovary may, it seems, interfere with tubal contractions and with the finer adjustments between the ovary and tubes. Such interference (which can be imitated, in a crude fashion, by surgical methods) does not entirely abolish fertility, but it reduces the chances of the ovum finding its way into the tube, and possibly equally similarly affects the other characteristics of the tube; this influence manifests itself after oophorectomy (through atrophy of the tubes) and after injection of oestrogenic substances (which results in development of the tube). Rubin (1938) states that in patients with a long menstrual cycle and with amenorrhoea, the tone and the frequency of contractions are both diminished. In cases with prolonged menstruation the utero-tubal tone and the contraction rate are less than normal but greater than in the above group.

Since the functional condition of the tube and the associated muscular apparatus determine to a considerable extent the chances of fertilization, it would seem desirable to carry out a complete investigation of this aspect of the reproductive mechanism. The available methods do not permit very fine distinctions. In fact, they are relatively crude.

True,/

True, beginnings of more delicate methods have appeared in the work of van Ott (1925) and others, who studied the transport through the tubes of small particles injected into the peritoneal cavity. But the relatively unphysiological procedures used in practice have the advantages of being easy to apply and of yielding sufficiently accurate information for clinical purposes. They should be adopted as part of the routine examination of the wife, for impairment of tubal function cannot be excluded by the ordinary gynaecological examination, however carefully conducted.

The methods in general use fall into two main groups - those designed to investigate the passage of a gas through the genital tract and those in which the condition of the tubes is revealed by their radiographic appearances after the injection of a suitable opaque substance. Both types of method are unphysiological, for they yield information about the passage of a fluid or a gas under pressure from the uterine end of the tube, not about the passage of a small formed body like the ovum from the fimbrial end. This difference is of little practical importance in many, if not most cases, for the normal tube permits, but most severe abnormalities inhibit, the passage of gas/

gas or liquid. The nature of the available methods does, however, impose certain limitations upon the interpretation of results.

Utero-tubal Insufflation.

In 1920 Rubin first described his method of investigating tubal patency by means of intra-uterine inflation with oxygen and the production of artificial pneumoperitoneum. Since that date, the principle of Rubin's method has been universally adopted and variations and modifications of apparatus and technique have been developed. It is now well established that the tubes may be occluded and the patient rendered sterile without physical signs or symptoms.

The many types of apparatus for testing tubal patency may be classified in the following three groups (King 1936).

(a) Apparatus consisting of a rubber bulb or glass syringe, a manometer, and a uterine cannula with the necessary connections. In this type of apparatus, examples of which are the instruments of Furniss, Jacobs and V. Bonney, atmospheric air is used and the pressure developed is indicated on a manometer. Douay's apparatus is similar, but is also supplied with an air reservoir to enable the pressure to be increased more evenly and slowly.

(b)/

(b) Apparatus similar to the above, but in which the source of gas supply is a cylinder of carbon dioxide or oxygen. Carbon dioxide has now almost entirely replaced oxygen for tubal insufflation, for it is more rapidly absorbed and as a result causes less discomfort. Currier's instrument, described by him in 1923, is of this type. Provis's modification of Currier's apparatus contains a volumometer which indicates not only the pressure of gas, but also the volume injected.

The essential parts of Provis's apparatus are (1) a sparklet of carbon dioxide gas, (2) a manometer, (3) a wide-mouthed jar for water in which is placed the volumometer, and (4) a uterine cannula. The sparklet is fixed in a holder which, when tightened, drives a pin through the end of the sparklet; the carbon dioxide thus liberated is controlled by a stopcock. When the stopcock is opened, the gas pours through the rubber tubing into the volumometer and thence into the jar. The latter is connected by two tubes, one to the manometer, which registers the pressure, and the other to the uterine cannula. The stopcock is used to control the flow of the gas. The apparatus should first be tested to ensure that all joints are sound and that there is no gas leakage. This may be done by compressing the tubing leading to the cannula and turning on the gas, when the manometer needle should mount steadily.

The outstanding advantage of this type of apparatus is that the injection of the gas is more finely controlled than is possible with hand-worked bulbs or syringes. Undue rapidity and irregularity in the rise of pressure is very liable to induce irregular/

irregular and spasmodic tubal contractions and to give erroneous results.

(c) Apparatus involving the use of a mercurial manometer and kymograph. Whereas most methods serve only to distinguish between the "blocked" and the "open" tube, the use of the kymograph makes possible the registration of tubal contractions and thus takes into consideration the actual behaviour of the tubes during the test.

The Kymographic Method of Tubal Insufflation.

This method had its origin in 1925, when Rubin began the study of human tubal peristalsis by recording on a revolving drum the variations in pressure which synchronize with the passage of gas through the uterus and tubes. At first, Rubin used a "smoked" drum, but this was soon replaced by a drum provided with interchangeable sheets of paper on which pressure variations could be shown in ink. His modifications since then have been mainly in the direction of reducing the bulk of the carbon-dioxide supply and of the mercurial manometric attachment and of rendering the whole apparatus less cumbersome. The present portable apparatus has now been used by him for several years and has been adopted by most investigators in America. It was little known or used in Europe until its existence was brought to the attention of the Paris Obstetrical and Gynaecological Society in 1930/

1930 in a short note from Rubin; nor was it much used in Great Britain until a somewhat simpler apparatus was devised and described by Gordon King in 1936. In December, 1937, Bonnet presented to the Paris Obstetrical and Gynaecological Society a new apparatus in which an ingenious regulating and measuring system replaced the volumetric water-system of Rubin and in which a metal manometer replaced the mercurial one. Bonnet's apparatus is compact and portable, all its elements, apart from the registering manometer, being grouped within a metal container (see Fig. 10).

Principles of the Kymographic Method.

It is well known that the human tube shows rhythmic contractions whether studied in vitro or in vivo. In this respect it resembles the tubes of other mammals which have been the subject of much research concerned with such matters as the nature of the contraction and the relation between ovarian secretion and muscular activity. It was thus easy to see that the investigation of the activity of the tubes might be of significance in the examination of the female. But it seemed doubtful whether this would be possible, since the motility of the tube is slight even in conditions of health while the diseased organ may be completely immobilized: moreover, anaesthesia affects the tubal motility. The possibility that uterine motility might obscure/

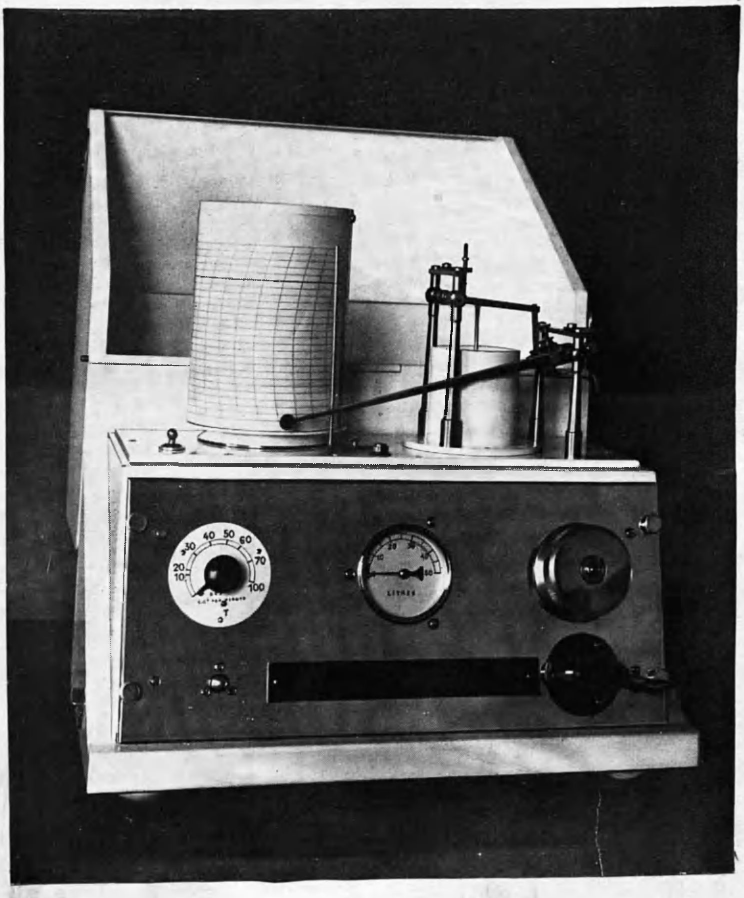


Fig. 10. Bonnet's apparatus for kymographic insufflation. Carbon dioxide is supplied by a cylinder enclosed in the metal container on top of which is a metal registering manometer. The revolving drum is operated by an electric motor. The dials on the front panel are connected with the mechanism regulating the supply and flow of gas.

obscure the tubal contraction seemed to offer greater obstacles to the use of the method. But it was shown by Guthman (1922) that these difficulties were theoretical rather than practical. By the use of a writing lever he demonstrated that the oscillations seen on the mercury manometer originated in the tubal contractions themselves.

Rubin, in his early experimental work in 1919-20, had noted fluctuations in pressure during insufflation, but it was not until 1925, as a result of his kymographic studies, that their interpretation was established. He undertook a series of tests to prove that the pressure fluctuations were determined by tubal contractions and by these alone. The more important results may be summarised as follows:

(1) Immediately after removal, the uterus with at least one permeable tube was placed in Locke's solution at a temperature of about 38°C. and insufflated with oxygen; naked-eye observation showed rhythmical segmental contractions in the tube during the entire passage of the gas. These contractions almost invariably began at the fimbriated end and progressed towards, but did not always reach, the uterus. If a tracing on the drum was made simultaneously, it could be seen that, representing the rise in pressure, an oblique line ascended until the resistance due to muscular tone at the uterine orifice of the tube was overcome, when the line descended to a varying degree and began to show a series of vacillations. Though irregular, these synchronized with the observed tubal contractions.

(2)/

(2) If both tubes were patent and one of them was tied, contractions ceased in the tied tube but continued in the other without alteration in the tracing. If the second tube was also tied, the fluctuations ceased completely. The completely impermeable tubes ceased to show contractions when they were distended by gas.

(3) The results obtained by bilateral ligation of the tubes in the extirpated uterus and tubes were confirmed clinically in cases showing normal tubal patency. First, it was shown that to demonstrate uterine contractions by the manometer or to record them on the kymograph it was necessary to use, as a detector of the contractions, a rubber balloon inserted in the uterus and connected with the apparatus. Secondly, the tracings thus obtained were clearly distinct from those seen in utero-tubal insufflation. It thus followed: (a) That the mode of contraction of the uterus and tubes differed, and (b) that the procedure of utero-tubal insufflation did not record contractions of the uterus.

(4) Tubal peristalsis was demonstrated with the aid of the fluoroscope after the injection of a small quantity of lipiodol into the uterus and tubes.

<u>Equipment for the Kymographic Method.</u>

(1) <u>Rubin's Apparatus.</u>

The Rubin apparatus is composed essentially of a cylinder of carbon dioxide under pressure, from which the gas, after passing into a pressure-reducer, is carried into a bottle containing a volumometer to measure/

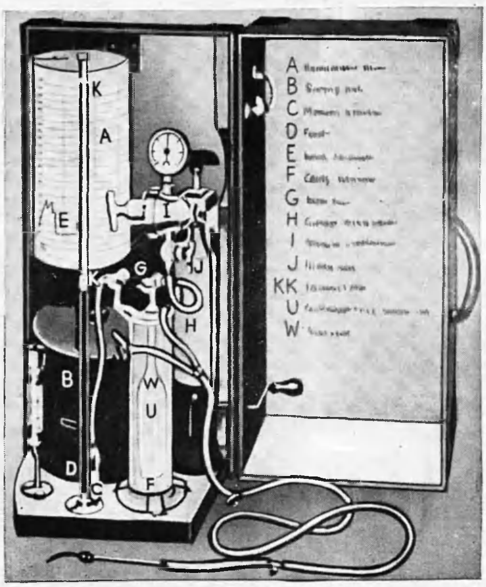


Fig. 11. Rubin's apparatus for utero-tubal insufflation.
A, kymographic drum; B, spring motor; C, mercury manometer; D, final; E, ink-writing pen; F, glass syphon-meter; G, stop cocks; H, carbon dioxide cylinder; I, reducing valve pressure gauge; J, needle valve; KK, blow-off valve; U, U-shaped tubes for syphon-meter; W, water level. (From Curtis's "Obstetrics and Gynaecology.")

measure the speed of gas-flow and its quantity. From the bottle the gas, its destination regulated by a three-way tap, has two connections: (i) By means of a cannula with the uterine cavity, and (ii) with a mercury manometer, the pressure variations of which are recorded by means of an ink-writing pen on a metal recording drum, 22 cm. in diameter. The drum surface is covered by a sheet of white paper. After each insufflation the sheet is removed, forming a permanent record on which the time is shown on the abscissa and the pressure on the ordinate. The drum, operated by a spring motor the speed of which is practically constant, makes a complete revolution in about five minutes. The Rubin cannula is made of metal with a cone-shaped removable rubber nozzle, which is so placed that the end of the cannula extends above the internal cervical os and the rubber nozzle presses firmly against the external os to form a gas-tight joint. The improved apparatus is illustrated in Fig. 11.

(2) Gordon King's Apparatus.

The principle is the same as in Rubin's apparatus described above. The source of supply of the carbon dioxide is a size "J" sparklet container, the/

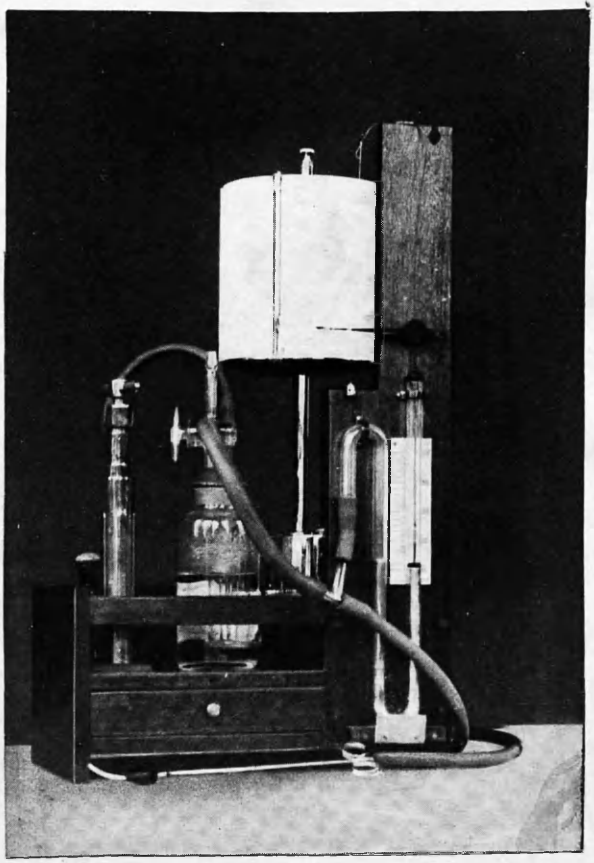


Fig. 12. Gordon King's apparatus
for utero-tubal insufflation.

the efficient needle-valve of which provides a finely adjustable control over the rate of flow of the gas. The tubing from the carbon dioxide container is connected with a volumometer contained in a bottle half-filled with 2 per cent. phenol solution. The efferent tube from this bottle leads to a three-way valve which can be adjusted to any one of three positions. In the first position the gas is allowed to escape directly into the atmosphere; in the second the flow of carbon dioxide is directed towards the patient and the manometer; and in the third, or open, position the pressure everywhere in the apparatus is allowed to fall to atmospheric level. From the three-way valve a short piece of tubing leads to a T-piece which is connected in turn to the uterine cannula and to the mercury-filled U-tube. By means of a float and needle, with ink-writing pen, pressure changes are recorded on the kymographic drum. The components of the apparatus are secured on a wooden stand, which with the carrying case completes this portable form of apparatus (see Fig. 12).

(3) Bonnet's Apparatus.

This apparatus, the most recent in the kymographic class, has given me excellent results. By/

By an ingenious system, the pressure of gas is kept constant, and its rate of flow can be accurately regulated by moving a tap indicator on a dial till it faces the figure corresponding to the desired rate (anything up to 100 cc. per minute). A knob on the front panel of the instrument, moved to the left or right, turns the gas supply on or off and acts independently of their regulating system. The mercury manometer is replaced by a more compact metal one. The pressure limit obtainable is 250 mm. The revolving drum, 9 cm. in diameter and 13 cm. in height, is operated by an electric motor. Bonnet uses the Rubin uterine cannula with a tap for rapid evacuation of gas, but he has added a device for altering the level of the rubber nozzle, whereby the pressure of the latter against the external cervical os may be increased as desired (see Fig. 10).

Technique of Insufflation.

The safest and most favourable time in the cycle to perform the test, is from the fourth to the seventh day after the cessation of the menstrual flow, i.e., from the seventh to the eleventh day of the cycle. During this postmenstrual phase, the endometrium is in a relatively quiet stage and is least liable to infection,/

infection, although the risk of this event is in any phase negligible if adequate precautions are taken. During the postmenstrual phase, too, there is little tendency to haemorrhage and the swollen premenstrual type of mucosa, such as might obstruct the uterine orifices of the tubes, is absent (see Fig. 24). Moreover, interference with early pregnancy is avoided, for ovulation does not occur until some days later.

In the great majority of cases, insufflation of the tubes may be carried out in the consulting room or as a hospital out-patient procedure. Anaesthesia is not only rarely necessary, the procedure being less disturbing to the average patient than cystoscopy, but is inadvisable since it interferes with tubal motility and with the patient's subjective response. Occasionally, however, it is called for in highly nervous patients or in those who suffer from introital dyspareunia. In these cases very light anaesthesia should be used for the introduction of the cannula, and insufflation can be undertaken when the patient has regained consciousness.

The patient is placed in the lithotomy position and examined to determine the position of the uterus and to ensure that no acute or subacute inflammatory condition of the genital tract is present. The usual aseptic and antiseptic precautions must be taken and all instruments coming/

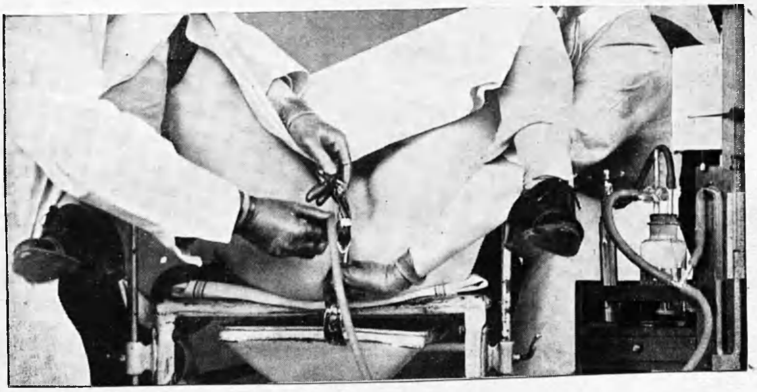


Fig. 13. Gordon King's apparatus in use. The cannula is being held in place within the cervical canal. The position of the apparatus and of the operator is clearly shown. No special preparation of the patient is necessary, and the procedure is thus suitable for out-patient use.

coming in contact with the genital organs must be sterilized. A vaginal speculum is used in order to obtain better exposure of the cervix, which is seized with light vulsellum forceps and swabbed with iodine or dettol. If the cervical canal is too narrow to admit the cannula, it may be necessary first to pass a dilator.

From this point the technique varies a little with the type of apparatus employed, but whichever it is, the basic principles are the same. The following account refers to Gordon King's apparatus.

The apparatus is conveniently situated on a table at the right of the examiner and near to the patient's left foot (see Fig. 13). The three-way valve is set in the first position, which allows all the gas to escape into the atmosphere. The needle valve is opened gently so that gas slowly begins to fill the volumometer. The flow of gas is so regulated that a volumometer of, say, 15 cc. capacity will empty three or four times a minute - in other words, so that the rate of flow of the carbon dioxide at atmospheric pressure is between 45 and 60 cc. per minute. The three-way valve is then turned into the second position, thus allowing the carbon dioxide to enter the remainder of the system and to displace all the air from it, including that contained in the sterilized tubing attached to the cannula. The/

The gas is allowed to pass for a few moments and the valve is then turned into the third or open position, whereupon the uterine cannula is introduced into the cervical canal. The rubber nozzle is pressed firmly against the external os to form a gas-tight joint.

The assistant (or nurse) now starts the kymograph rotating and turns the three-way valve back to the second position, synchronizing this movement with the beginning of one of the strokes of the volumometer. The slowly mounting intra-uterine pressure is recorded on the drum, which should be set to rotate at the speed of between 1 and $1\frac{1}{2}$ inches per minute. The chief function of the examiner during the performance of the test is to maintain a gas-tight joint at the external os. This is best done by making a steady upward pressure. In cases where cervical leakage occurs, traction on the vulsellum or even a slight alteration in the direction of the pressure, will usually rectify matters. An assistant, meanwhile, may be usefully employed auscultating (preferably with the double stethoscope described by Gordon King) on both sides of the abdomen.

During the test a close watch is kept upon the volume of gas injected and upon the behaviour of the manometer as shown on the drum. Any auscultatory signs,/

signs, the presence or absence of cervical leakage of gas, and any subjective symptoms experienced by the patient, are also carefully noted. Except for some special reason, the amount of gas injected is not allowed to exceed 200 cc., for a diagnosis of normal patency can be made with amounts as small as 30 to 50 cc. The pressure is rarely allowed to rise above 200 mm.Hg., at which point the three-way valve is turned back into the first position, thus completely cutting off the further supply of gas. If the pressure then remains stationary at this level, a complete blockage is indicated (see Fig. 14). If it falls slowly, there is either a leak in the apparatus, which should have been excluded, or gas is slowly passing into the peritoneal cavity (see Figs. 15, 16 and 17).

In either case, after a pause of some moments, the pressure is allowed to return to the atmospheric level by slowly turning the valve through the fourth possible position into the third, or open, position. The pressure against the cervix is now relaxed and the cannula gently withdrawn. The vulsellum is removed, the cervix again swabbed with iodine or dettol, and the speculum withdrawn. The patient is then asked to rise slowly from the table and to report any further symptoms which she may experience. It should be realized/

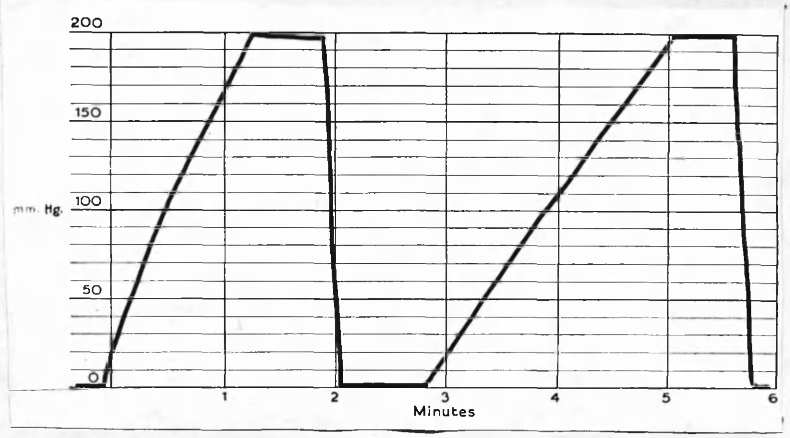


Fig. 14. Kymographic tracing in tubal occlusion. Test performed on sixteenth day of cycle. Pressure rises to 200 mm. Hg. and is maintained at this level by the operator preventing further flow of gas. Pressure falls when gas escapes.

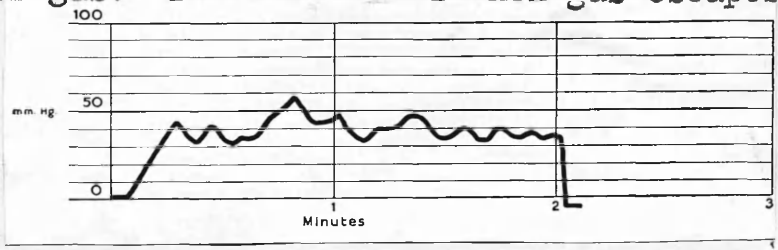


Fig. 15. Kymographic tracing in normal tubal patency. Gas passes at a pressure below 50 mm. Hg. Test performed on sixteenth day of cycle. Well-marked tubal contractions are seen.

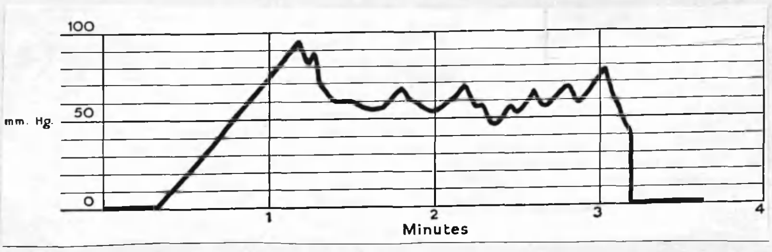


Fig. 16. Kymographic tracing in normal tubal patency. Gas passes at a pressure between 50 and 100 mm. Hg. Test performed on tenth day of cycle. Tubal contractions of great amplitude.

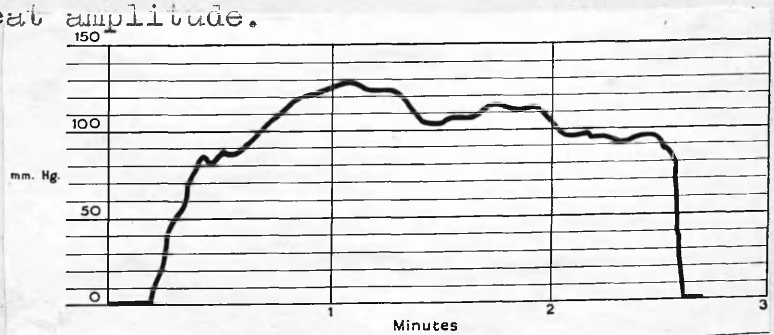


Fig. 17. Kymographic tracing in tubal patency. Contractions are of low frequency and amplitude and suggest deficient ovarian activity. The patient was abnormally stout.

realized that, once the rate of flow of the gas has been adjusted, all further regulation of pressure-changes is completely under the control of the three-way valve, and it is impossible for any unexpected or sudden rises of pressure to take place to the detriment of the patient.

When one or both tubes are patent, insufflation is almost invariably accompanied or followed by shoulder pain. It is due to gas rising within the abdominal cavity to the diaphragm, whence impulses are conveyed, by way of the phrenic nerves, to the third, fourth and fifth cervical cord segments, from which arise the nerves supplying the shoulder girdle. The pain varies in intensity and duration, being most marked and prolonged (occasionally for two or three days) in thin subjects or in cases in which a large amount of gas has been used or in those which show bilateral patency at low gas pressure. It is occasionally felt while the patient is recumbent, but it is best elicited when she sits up immediately after insufflation. In the rare cases in which, despite undoubted tubal patency, this characteristic pain is not felt, the explanation appears to be that the gas is "caught" by pelvic and sub-phrenic adhesions. The occurrence of shoulder pain after insufflation may be/

be regarded as pathognomonic of some degree of tubal patency. It is sometimes felt at the right shoulder, less commonly at the left, and occasionally at both, but this distribution has no diagnostic significance. Usually it is not severe and is gone in one or two hours, but when desired, e.g., in highly strung subjects or when much discomfort is complained of, relief can be obtained almost instantly when the recumbent posture is adopted or when the patient sits with her head to her knees for a few minutes.

When the test is completed, the paper is removed from the drum and may be incorporated in the patient's record, or a tracing of it may be made over an illuminated glass on to a special form which shows the pressure and time relation of the graph.

After insufflation, slight bleeding is not uncommon and may appear through the cervical canal or from the site of the teeth of the vulsellum forceps. Occasionally it may persist for a day or two, but the insertion of a vaginal dressing almost invariably stops it in a short time. The next menstrual period is sometimes advanced by a few days.

Kymographic insufflation is readily performed in a few minutes and in most cases the patient is able to dress herself and go home immediately. Occasionally, faintness/

faintness may necessitate a short rest in the recumbent position.

Results of Kymographic Insufflation.

The graph or record obtained at each insufflation demonstrates the pressure of gas in the Fallopian tubes and the behaviour and response of the latter to the gas. Four types of record are obtained, corresponding to the following conditions:-

(1) Normal tubal patency.
(2) Non-patency.
(3) Tubal spasm.
(4) Tubal stenosis, i.e., complete or partial stricture of the canals either by an internal cause (e.g., mucosal lesions) or by an external one (e.g., peritubal adhesions or kinks). Thickening or disease of the wall or its involvement in adhesions may seriously interfere with its contractile power.

(1) Normal Patency.

After the pressure reaches a variable height, most commonly between 60 and 120 mm.Hg., gas begins to pass through the tubes into the peritoneal cavity, the pressure thereafter showing definite oscillations, usually between five and ten per minute, due to the presence of normal peristaltic contractions of the tubes. The/

The amplitude of the oscillations varies, but ranges usually from 10 to 30 mm.Hg. These features are clearly shown in the kymographic tracing. The occurrence of the shoulder pain and the fluoroscopic demonstration of sub-diaphragmatic pneumoperitoneum are also features of tubal patency, but, as they are just as likely to be present in cases of tubal stenosis, their presence does not prove normality. Graphs illustrating tubal patency are shown in Figs. 15, 16 and 17.

(2) Non-patency.

In these cases the characteristic graph rises steadily in a straight line which ascends obliquely until a pressure of 200 mm.Hg. is reached, when it is usual to cut off any further supply of gas. The tracing then follows a horizontal line until the pressure of gas is released (see Fig. 14). Auscultation and fluoroscopy yield negative results. During the test, when the pressure exceeds 100 mm.Hg., the patient often notices central pain due to distension. When the blockage is at or near the fimbriated ends, some lateral pain may be experienced as the gas pressure within the tubes increases. In cases in which one tube is obstructed at the uterine end and the other at the fimbriated end, unilateral pain is often felt on the side of the latter tube. Shoulder pain is absent.

(3)/

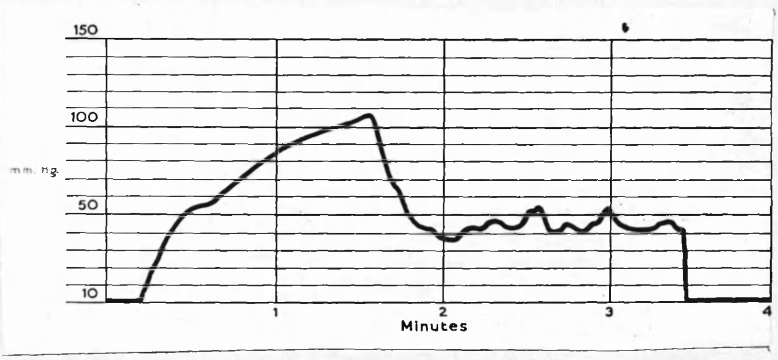


Fig. 18. Kymographic tracing in tubal spasm. Test performed on twenty-first day of cycle. There is a sudden drop in pressure at 110 mm. with subsequent rapid descent to 40 mm., after which the oscillations are of the type seen in normal patency.

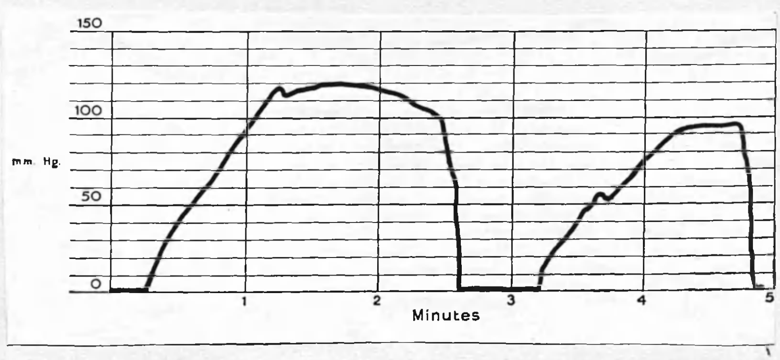


Fig. 19. Kymographic tracing in tubal stenosis. Test performed on nineteenth day of cycle. No gas passed until a pressure of over 100 mm. was reached. Note absence of tubal contractions.

(3) Tubal Spasm.

When tubal spasm exists, a high initial pressure is required to overcome the resistance of the tubal musculature; but, when this is achieved, there follows a rapid fall of pressure, after which normal tubal contractions are recorded at the normal level (see Fig. 18). The initial pressure required may be anything from 100 to 200 mm.Hg. If the test is repeated in a few moments, it is often found that the spasm has disappeared and that a graph of normal patency is obtained. Meaker (1934) claims that anti-spasmodic drugs, such as atropine, can abolish spasm with the production of a curve indistinguishable from the normal.

(4) Tubal Stenosis.

In a case of tubal stenosis, the pressure rises above 100 mm., but before reaching 200 mm. begins to fall steadily. There is complete absence or marked impairment of tubal contractions, as shown by the fact that oscillations are absent or very feeble. Repetition of the test, a few moments later, gives a very similar picture - a finding which serves to differentiate the condition from spasm. A good guide to the severity of the stricture may be obtained by noting whether the fall of pressure occurs above or below 150 mm. (see Fig. 19).

Tubal/

Tubal stenosis may be unilateral or bilateral and the stethoscope may give valuable evidence on this point. When one tube is stenosed and the other completely occluded, the curve produced corresponds to stenosis; when one is stenosed and the other patent it corresponds to normal patency.

Respiration and conversation do not affect the type of graph obtained. Marked increase of intra-abdominal pressure, however, such as may result if the patient bears down forcibly, is registered on the kymograph, but only if the tubes are patent.

Advantages of Kymographic Methods.

It may be asked whether the extra information gained by the use of kymographic methods is commensurate with the inevitable elaboration of the apparatus and the increased trouble to the investigator. The special value of the kymograph, as Rubin was the first to point out, is that it serves to distinguish not only between patent and non-patent tubes, but between tubes which are normally patent and those, which, though patent, are the site of spasm, stenosis or peritubal adhesions. The kymograph is thus an indicator not only of disordered tubal anatomy but of disordered function. It is more accurate than/

than the older types of insufflation apparatus; it gives a permanent record of the tests and their results (thus facilitating comparisons between the results of tests on different dates); and it gives graphic information about physiological and pathological tubal processes.

As a mere vehicle for passing gas into the tubes - in other words, as a therapeutic instrument - it has little, if any, advantages over the older types of apparatus; but in so far as it facilitates more accurate diagnosis it promotes more precise treatment. In the words of Meaker: "The Kymograph registers the precise variations in pressure upon which are based some of the most accurate diagnostic judgments, and while insufflation can be done without this adjunct, I am sure that no one who has learned to use the kymograph would ever be satisfied to work without it."

These views are shared by Bonnet, Mikulicz-Radeki, Gordon King and nearly all investigators who have had considerable experience in methods of utero-tubal insufflation. In my view the use of the kymograph represents an outstanding advance in the investigation of sterility.

<u>Contraindications to Utero-tubal Insufflation.</u>

(1) Inflammation of the Genital Tract. The test should not be carried out in the presence of acute/

acute or subacute inflammations, e.g., endocervicitis, vaginitis, or salpingitis.

(2) Menstruation and the Premenstrual Phase. The possibility of endometrial dislocation and embolism formation contraindicates the use of the test at these times. Further, increased dilatation of the blood vessels would increase the rare chance of gas embolism. Interference with an early pregnancy is obviated by avoiding the premenstrual phase.

(3) Abnormal Bleeding from the Genital Tract. Observations have shown that insufflation in the presence of this condition may favour embolism.

(4) Pregnancy. There is, of course, no point in insufflation when pregnancy exists; but the procedure has often been carried out in error in pregnant women without disturbance to the course of the pregnancy or any ill-effects whatever.

(5) Severe Constitutional Diseases. Cardiovascular disease, severe diabetes mellitus, active pulmonary tuberculosis, and other conditions which contraindicate pregnancy necessarily contra-indicate insufflation also.

(6) Neuroses. Patients with a frankly neuropathic disposition do not stand the test well.

If due regard is paid to the contraindications and to the proper technique the risks of insufflation are negligible. Excessive pressure and rate of flow of gas must be avoided. Only in exceptional cases should a/

a pressure of over 200 mm.Hg., be exceeded. In the conscious patient, severe pain is an indication that no more gas should be passed. Anaesthesia, of course, abolishes this symptom and therefore adds to the element of risk. Occasionally faintness and giddiness may be encountered and, rarely, pelvic infection. Serious sequelae, such as pelvic abscess and even death from gas embolism during or soon after the test, have occurred, though rarely, but usually these mishaps have been due to inattention to essential points of technique.

Hysterosalpingography.

The earliest attempts to visualise the uterine and tubal cavities, and thereby to test tubal patency, were made in 1914. In that year Rubin experimented with collargol, but abandoned its use owing to the irritant reaction on the peritoneum. Other solutions, such as sodium bromide and sodium iodide, were tried but gave similar disagreeable reactions or poor shadows. In 1925, Forsdike obtained satisfactory hysterograms by the use of lipiodol, an iodised oil introduced into surgery by Sichard. Lipiodol has been found to have three outstanding advantages: (a) it is relatively non-irritating, (b) it gives shadows which have proved

to/

to be of considerable value in the investigation of tubal patency, and (c) according to many investigators it is therapeutically effective in a fair proportion of cases.

Hysterosalpingography may be used as a diagnostic aid in several gynaecological disorders, but in cases of sterility its chief value is in the information which it yields about tubal blockage. The chief contraindications to its use, as to the use of insufflation, are as follows: (1) Inflammation of the genital tract, e.g., vaginitis, endocervicitis or salpingitis; (2) pelvic tenderness or swelling; (3) cardiovascular, pulmonary or other serious systemic disease; (4) menstruation.

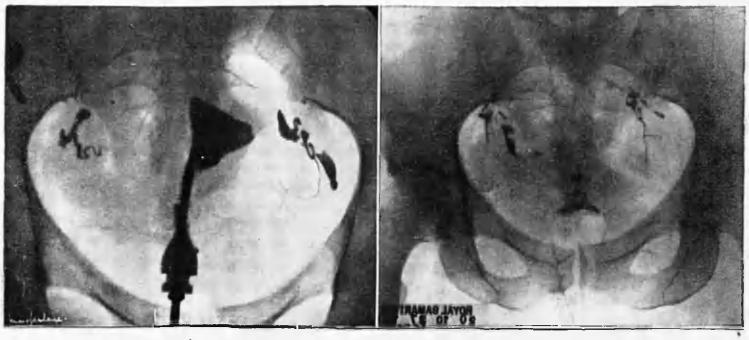
The procedure, even after due observance of the contraindications, is not wholly devoid of risk. Pelvic pain, pyrexia and sepsis in occasional cases have been recorded by many observers. Douay, who with his associates, has made 1,409 hysterograms, has come to the conclusion that the possibility of pelvic abscess or of lipiodol passing into the uterine veins constitutes a real danger which must not be overlooked. Rubin, having used lipiodol in some 150 cases, in all of which insufflation had been performed, stated/

stated that disproportionately greater complications followed the former procedure. He demonstrated, too, that lipiodol may have an occlusive effect in cases of permeable stricture.

In an attempt to obviate the ill-effects of lipiodol, Titus and his co-workers (1938) have described the use of a mixture of mono-iodomethane sulphonate of sodium (40 per cent.) with acacia (20 per cent.). They claim that the use of this non-irritating radiopaque substance has given uniformly satisfactory clinical results.

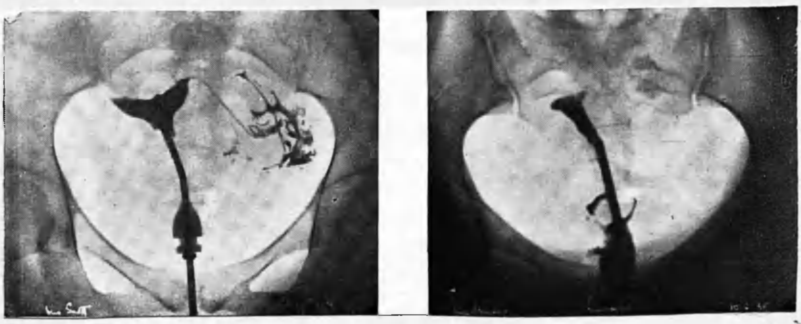
Technique.

It is not necessary to admit the patient into hospital and anaesthesia is very rarely needed. The bowels should have been well emptied, preferably by purgative, but some investigators favour the administration of an enema on the morning of the test. Lipiodol is injected into the uterus from a sterile syringe of the Record type (10 cc. size) by means of a special uterine cannula, the expanded button or acorn nozzle of which is pressed firmly against the external cervical os to prevent leakage. Usually 3 to 7 cc. must be injected. The vagina is lightly plugged with gauze in order to support the cannula, aid/



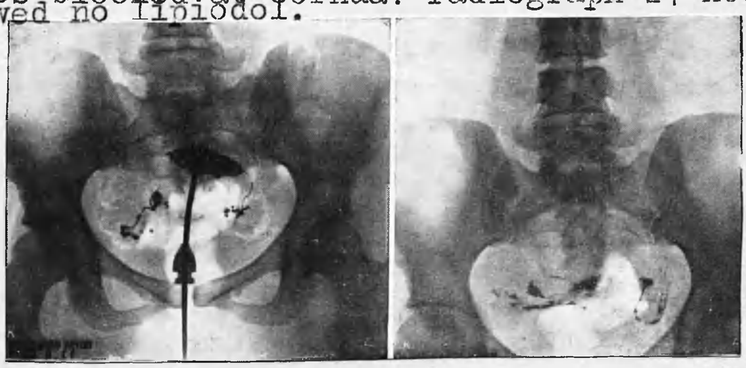
A B

Fig. 20. A. Normal bilateral patency. The triangular cavity of the uterus is larger than usual. B. Later radiograph in same case showing free lipiodol in the pelvis. Kymographic insufflation demonstrated normal peristalsis and patency at pressures of about 80 mm. Hg.



A B

Fig. 21. A. Right cornual occlusion, left tubal patency. The right tube does not contain lipiodol, but the left is full and oil has escaped into the peritoneal cavity. B. Tubes blocked at cornua: radiograph 24 hours later showed no lipiodol.



A. B

Fig. 22. Bilateral patency. A. The appearances indicate possible patency or possible occlusion of the fimbriated end. B. This radiograph, taken twenty-four hours later, shows peritoneal spill, and thus establishes the diagnosis of patency.

aid the obturator action of its nozzle, and prevent leakage of lipiodol into the vagina. The apex of the nozzle indicates the level of the external cervical os.

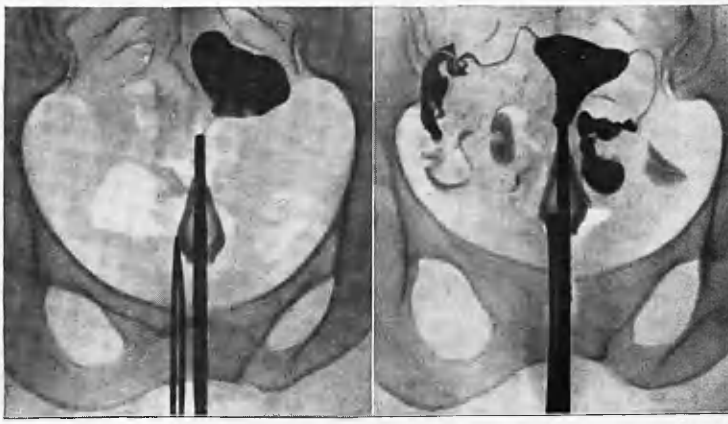
The injection is most suitably made with the patient on a radiological table, so that the passage of the fluid into the tubes can be observed on the screen. It is desirable to take at least two films, one immediately after the oil has been injected and another six to twenty-four hours later. In cases of patency the second film demonstrates the escape of oil through the fimbriated tubal extremities into the pelvic cavity. To depend solely on the photograph taken at the time of injection may lead to erroneous diagnosis. It should be emphasized, too, that the interpretation of hysterosalpingograms requires study and experience.

Characteristic hysterosalpingograms are illustrated in Figs. 20-26. In normal patency the tubes are seen to fill with oil (provided sufficient has been injected) and there is a spill from the fimbriated end either immediately or after a short interval. Occlusions are readily recognized, but must be confirmed by the absence of peritoneal spill in/

(Figs. on this page by permission of Dr. H.W. Post).

A B

Fig. 23. A. Hydrosalpinx of left tube with incomplete block. B. Gonococcal salpingitis with pelvic peritonitis.

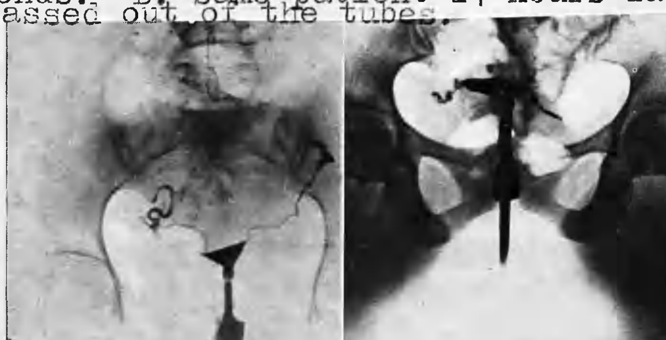


A B

Fig. 24. A. Salpingogram made four days before period was due. Neither tube filled with lipiodol. B. Same patient four days after cessation of period.

A B

Fig. 25. A. Uterine fibroids and dilated tubes occluded at fimbrial ends. B. Same patient 24 hours later. No lipiodol has passed out of the tubes.



A B

Fig. 26. A. Tubes stretched round large fibroid at fundus of uterus. Both tubes are patent. B. Isthmial block following tuberculous peritonitis.

in the later inspection. When the blockage is at the fimbriated ends, the tubes generally show normal filling, and traces of lipiodol may be seen in the lumen for several days. When, however, the blockage is at the isthmus or uterine end, no oil reaches the lumen. In all cases no shadow is seen in the uterus and vagina after twenty-four hours, for lipiodol escapes by gravity when the cannula is withdrawn. Besides patency or non-patency other conditions may be revealed, e.g., abnormal configuration and displacement of the uterine cavity, filiform tubes involving the normally expanded ampullary position, or undue patency and kinking or angulation of the lumen (usually due to peritubal adhesions). In cases of hydrosalpinx, a characteristic picture of discrete drops is produced, the result of the suspension of oil globules in a watery medium within a tubal sac.

Significance of Findings.

The interpretation of the results obtained in the investigation of tubal patency - whether by kymographic methods or hysterosalpingography - is subject to a special difficulty which attends all work on sterility. The clinician has little opportunity to examine, at frequent intervals, women of whose fertility there can be no doubt. Thus, Rubin, in his original paper (1920), described only cases of sterility/

sterility or suspected sterility, with the result that his opinion inclined to what has been called diagnostic severity. The following rules of interpretation, however, have emerged in the course of much work spread over a number of years and performed by many independent authors. Kymographic findings will be discussed first.

(1) A normal curve may be regarded as the most reliable index of adequate tubal function which can be attained by existing methods.

(2) A spastic curve does not necessarily indicate a permanent defect; one and the same subject may yield a spastic curve in one cycle, but a normal curve in the next. Spastic curves show, however, that tubal function may be impaired and suggest the need for a repetition of the test at a later date (one or two months later). If the spastic condition is habitual, the question of treatment must be considered.

(3) Stenosis, too, does not denote sterility, for the question of occlusion does not arise. As in the case of spasticity, the finding should be followed by a repetition of the test and, if necessary, by therapeutic measures.

(4) Absence of oscillation in non-occluded tubes is often associated with the presence of peritubal adhesions or other factors that interfere with the muscular apparatus. The test must be repeated until definite proof of the condition is obtained. If the condition is found in two or three consecutive tests, impaired tubal function may be assumed and surgical or endocrine treatment must be considered.

(5) A single negative result is not a reliable guide to the condition of the tubes. In some cases spastic states are found which resolve either at high pressure or spontaneously. The possibility of a spastic condition being just too pronounced to react to the highest pressure that can safely be applied can never be excluded. Such a condition may simulate occlusion. The possibility of mechanical faults is another reason for repeating the test in cases of apparent non-patency. Moreover, there is always the chance that the first insufflation may have resolved the condition.

If occlusion is found, further investigation by hysterosalpingography becomes necessary. Some investigators, indeed, prefer to use the latter procedure from the first. Speaking generally, the lipiodol test, carried out after a "negative" kymographic examination, serves a twofold purpose: (i) It confirms the condition of occlusion and thus affords a firmer basis for further measures, medical or surgical. (ii) It gives exact information about the site of the obstruction revealed by the kymograph.

The presence of tubal occlusion indicates sterility. But diagnosis and treatment are often effected by one and the same step, a given test (insufflation or injection of lipiodol) both revealing and removing an obstacle to fertilization.

As/

As a result of cumulative experience with uterotubal insufflation during the past twenty years, Rubin (1940) is now able to estimate the etiologic importance of tubal obstruction in sterility. A general idea of its incidence may be obtained from an analysis of 593 replies to a questionnaire embracing 86,113 insufflation tests made in various parts of America and abroad. According to these data, there were complete tubal obstruction in 31 per cent. of the cases and partial tubal obstruction in 9 per cent. Rubin's own series of 5,269 insufflations showed an incidence of complete obstruction in 32 per cent., and of partial obstruction in 33 per cent.

(3) Does the Uterine Endometrium Undergo Normal Development?

The functional test to be discussed under this heading needs little comment. Its purpose is to discover whether the endometrium is in a healthy condition and whether the changes of the secretory phase are not only present but sufficiently well developed to permit the nidation and subsequent development of the ovum. Examination of the specimen obtained by endometrial biopsy usually suffices to answer these questions.

Normally/

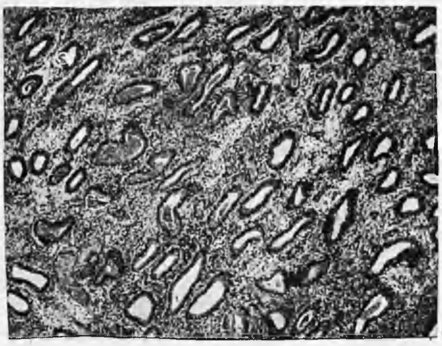


Fig. 27. Section of endometrium showing incomplete differentiation. This deficiency is held to indicate a tendency to miscarriage. (After Mason, 1937).

Normally the signs of the secretory phase are very clearly developed, but in some women it is found that differentiation is limited to a few glands only (see Fig. 27). Mason (1937) has shown that miscarriage often occurs in women in whom such incomplete differentiation is observed; and his findings suggest that steps for the prevention of miscarriage are necessary in such cases. My own experience favours Mason's view, but is not sufficiently extensive to warrant a definite opinion about the incidence of miscarriage in relation to the endometrial condition during the secretory phase.

(4) <u>Are the Endocrine Conditions of Fertility Present?</u>

The answer to this question turns largely on the analysis of the hormone content of the urine collected at certain stages of the menstrual cycle - comparison with the normal excretion often yielding indications of the functional condition of the ovaries and the pituitary and thus indirectly of the reproductive system as a whole. But the procedure, though important, is subject to errors of both technique and interpretation which seriously limit its value in the assay of fertility.

(5) Does Insemination take place in an Adequate Manner and the Appropriate Time?

No investigation of sterility or lowered fertility is complete unless it is ascertained whether or not the spermatozoa and ovum can meet. This inquiry must be divided into two related but independent questions.

(a) Does coitus take place at the time of ovulation?

(b) Do the spermatozoa reach the uterus or is their passage obstructed?

(a) Time of Intercourse.

It is well known that in the human subject ovulation normally occurs spontaneously - i.e., that it is not (as in the case of the rabbit in which ova are released after coitus only) automatically synchronized with insemination. This independence of ovulation and insemination would have little significance if the gametes could, so to speak, lie in wait for each other. But all experimental evidence points to a very short life span for the unfertilized ovum. It may be retained in the tubes for a considerable period, but it loses fertilizability soon after ovulation. Estimates of the duration of this quality (based on experiment by carefully timed artificial insemination) vary with the species but, considering/

considering the technical difficulties, agree remarkably closely. A few examples are given in Table .

TABLE ..I..

Survival of Ovum after Ovulation.

Compiled after Hartman (1932).

Species.		Duration of Survival.
Rabbit	... ...	4 to 5 hours.
Opossum	... ...	Under 24 hours.
Sow	... ...	Under 24 hours.
Mouse	... ...	Under 24 hours.

As there is no reason to assume that the human ovum is more resistant than that of the species mentioned, it may be concluded that fertilization occurs either within twenty-four hours after ovulation or not at all. The view formerly held that an ovum released in one cycle can be fertilized in the next is no longer tenable. Similarly, the general view about the survival of spermatozoa has changed greatly since the days when it was thought that live spermatozoa could be found in the female genital tract three weeks after the last preceding intercourse. It is now held, with Hartman (1932), that the cases adduced in support of the former view involve "moral rather than physiological issues."

In the ferret spermatozoa remain motile for four days after copulation; in the human species they certainly retain motility for five days or slightly more/

more (Haussman, 1879). But the survival, as defined by motility, is only of limited interest in this connection. It must be pointed out that fertilizing capacity and motility are not identical characteristics, the latter persisting after the former has been lost. Rabbit semen loses its fertilizing capacity in vivo in under two days, though under special conditions it may retain this capacity in vitro for a day or two longer. Both in vitro and in vivo, however, motility may persist for three to four days.

It is impossible to give equally precise data for human species, but the general similarity between the viability curves of human and rabbit semen suggest that in man, too, insemination and ovulation must be closely related to each other in time if fertilization is to be secured.

Inquiry often elicits the fact that this essential condition is not fulfilled. Three types of incomplete or wholly deficient synchronization of intercourse with the fertile phase are found among uninformed patients.

(1) Infrequent Sexual Intercourse. Many investigators have on record cases of "undersexed" couples who have intercourse not more often than once a month (on an average), and yet have never thought of this fact as a possible cause of sterility.

In/

In some of these cases the subnormal sexual activity is but one manifestation of general disturbances in the reproductive system; but sexual activity may be at a very low level even in fertile men and women, and in such cases proper timing of intercourse is often the only treatment required.

Very occasionally it is found that though intercourse takes place but seldom the husband is a confirmed masturbator. Close inquiry into matters not apparently related to fertility is necessary in the investigation of such cases.

(2) Religious Observances. These are responsible in some cases for failure to relate sexual intercourse to the occurrence of ovulation. Kurzrok (1928) reported two such cases among orthodox Jews who had observed the restriction of the Mosaic law regarding intercourse during the ritual "unclean" period (i.e., the days immediately following the cessation of the menstrual flow). Normally such restrictions do not hinder fertility, for the "unclean" period ends before the ovulatory phase begins. In Kurzrok's cases, however, the cycles were short and it therefore seemed likely that the "unclean" periods might overlap with the periods of potential fertility.

In/

In both cases discontinuance of the religious observance was followed by conception.

(3) Erroneous Beliefs about Fertile Period.

In some cases it is found that intercourse has been carefully timed by conscientious couples in terms of erroneous information about the place and duration of the fertile period in the cycle.

(b) <u>Transport of Spermatozoa through the Female Genital Tract</u>.

The sexual habits of the couple having been established, it remains to inquire whether or not the spermatozoa can pass safely into the tubes. This inquiry logically begins with the question whether spermatozoa are satisfactorily deposited in the vagina, for even at this stage deficiencies or impairments of the normal process may occur. Three groups of disturbances may be mentioned specially.

(1) <u>Dyspareunia and Vaginismus</u>.

When there is a history of painful intercourse, it is necessary to ascertain if penetration has ever taken place. If it has not, various contributory factors must be considered, such as vaginismus, ignorance of the sexual act, maldevelopment or tumours of the vulva or vagina, the presence of an unusually thick or fibrous hymen, or abnormal disproportion of the penis and vagina.

If penetration has taken place, the cause of dyspareunia may be found in such local lesions of the introitus as inflamed cracks or abrasions, inflamed carunculae/

caruncalae myrtiformes, bartholinitis, vulvitis, tender perineal scar, or too complete perineal repair; or in such intrapelvic conditions as tender, congested or prolapsed tubes and ovaries, with or without malpositions of the uterus. In some cases dyspareunia develops gradually in the course of married life, having its origin in various inflammatory, neoplastic or regressive changes which may be discovered in the course of gynaecological examination. Some causes of dyspareunia - e.g., urethral caruncle or kraurosis vulvae - seldom appear during the reproductive phase.

Examination will, as a rule, reveal whether or not there is present a condition of vaginismus, i.e., protective spasm of the muscles of the pelvic floor. This may be so severe as to involve not only these muscles, but also the adductor muscles of the thigh and even muscles of the back. True vaginismus - i.e., the type that occurs in the absence of a local lesion - concerns the psychologist rather than the gynaecologist. In some cases, however, a closely similar condition develops in the train of a local lesion, serving as a defence mechanism against coitus. It is noteworthy that the removal of the local cause may fail to provide relief; psychotherapy has a part in the treatment of both types of vaginismus.

(2) Errors of Coital Technique.*

It is well known that conception may sometimes follow the ejaculation of semen on to the vulva - that not only an orgasm on the part of the woman but also penetration is unnecessary to fertilization. But it is equally true that fecundation is considerably favoured by the deposition of the semen in the near neighbourhood of the cervix, and also by sexual satisfaction on the part of the woman. A female orgasm synchronous with that of the male, or immediately preceding it, is said by some authorities to set in action certain contractions of the uterus and vagina, as a result of which semen is drawn up into the cervical canal from the pool that has been deposited in the region of the external os. This phenomenon is almost certainly not general, though isolated confirmatory observations have been recorded (Dickinson, 1938); but it is certain that if the semen is deposited near the cervix the journey of the spermatozoa towards their distant goal is greatly shortened in its most perilous portion, namely, in the passage through the vagina. It has repeatedly been shown that spermatozoa may remain alive and active for a long time in the favourable environment of the cervical canal, whereas they rapidly die in the medium of the vagina. The exact duration of life in these two vicinities has been variously estimated by different observers, but it is generally agreed that the great majority of spermatozoa become inert after two hours in the vagina, and that active movements may persist for as long as five days in those spermatozoa that have reached the cervical canal. It is therefore highly probable/

*In the textbook "Sterility and Impaired Fertility" the following section (p. 109-115 in this context) was written by one of my collaborators. I have summarised his contribution here to retain the continuity of the argument.

probable that any condition which favours the rapid transference of the sperm cells from the vagina to the cervical canal is conducive to pregnancy.

Adequate preparation of the woman for coitus, quite apart from its action in favouring the production of an orgasm, has another favourable influence on the spermatozoa. Second only in importance to the secretions of the accessory sex glands of the male, are those of the female. Normal cervical secretions represent a favourable medium for the spermatozoa in their journey towards the ovum. Normally, when at rest, the cervical canal is occluded by a plug of mucoid secretion. Sometimes - but not in the normal woman at the time of ovulation - this is so thick as to constitute an obstacle to the penetration of the spermatozoa, and indeed the rationale of the many operations that are undertaken on the cervix in order to favour pregnancy is not so much that they widen the canal, as that, by improving drainage, they prevent its occlusion by thick mucus. If, however, penetration has been preceded by adequate courtship, the rapid outpouring of the secretions produced by this preliminary excitation may have the effect of dislodging any thick mucous plug in the cervical canal, and of substituting for it a favourable medium for the survival of the spermatozoa. (K. Walker).

Ejaculatio Praecox.

But ignorance and lack of skill are not the only obstacles to the ideal mating that is conducive to fecundation. Many men are physically incapable of prolonging coitus. Ejaculatio praecox is one of the commonest forms of sexual disability to which the male/

male is prone. It is the most frequent cause of disharmony on the physical plane of marriage, and, although not an absolute cause of sterility, must be considered a factor in many cases of childlessness.

A common difficulty in its treatment is the fact that, as a rule, the sufferer from premature ejaculation does not apply for help at an early stage of his disability. By the time he reaches the consulting room, the habit has been firmly established, and to substitute for an abnormal reflex one that is normal is a matter of great difficulty. Only occasionally is there found any associated organic lesion such as a swollen prostate or an enlarged and hyperaesthetic verumontanum. More often than not, all that can be discovered is a slight exaggeration of reflexes and a general state of anxiety. More especially does this anxiety tend to increase at the time of sexual intercourse. Oppressed by a sense of repeated failure in the past, the patient approaches each sexual act with an anxiety that in itself is sufficient to precipitate the dreaded anti-climax. It is not surprising that these cases require a great deal of skill and patience in their handling.

Sometimes/

Sometimes the ejaculation is so premature that it occurs before penetration can take place. John Hunter recommended that semen so lost should be scooped up by means of some such implement as a spoon or a syringe and inserted into the vagina. Some gynaecologists have recommended wives to be prepared for this possibility by having a suitable receptacle available from which the prematurely ejaculated semen can be drawn into a syringe and then re-injected into the vagina. In cases in which treatment for ejaculatio praecox has failed to bring about any improvement, this method may be tried before resorting to cervical insemination. (Kenneth Walker).

Relation of Coital Posture to Fertility.

A question which naturally arises is whether conception is more likely to occur in some coital positions than in others. In former years, the knowledge that an orgasm on the part of the woman was not an essential to conception, and Huhner's observation that whether semen escaped from the vagina after coitus or whether it was retained within it seemed to make little difference, led to an under-estimation of this factor; but it has received more attention since it has been realised that direct emission on to the cervix is favourable to conception.

Van/

Van de Velde (1931) in particular has written on this subject. He points out that, in the normal supine position, in which the woman lies on her back with her legs extended, the semen, when ejaculated from a penis in full penetration, forms a pool in the posterior fornix beyond the cervix. This is especially likely to be so if the uterus is low in position, so as to produce a corresponding deepening of the vaginal vault. It is also likely to happen with slight prolapse associated with a greater or lesser degree of retroflexion of the uterus. If, instead of lying with the legs extended, the woman strongly flexes the thighs, the pelvis is bent forward at a sharp angle to the spine, and at the same time changes occur in the relative positions of the genital organs. Not only is the vagina shortened and the posterior fornix flattened out, but the cervix, instead of pointing backwards, is made to point straight along the vagina. In this way the cervical and the vaginal passages are brought into line, so that the semen is more likely to be ejaculated in a favourable direction. It would appear, therefore, that for most couples the supine position with the woman's thighs fully flexed and separated, and the man lying between them, is the one most favourable to fertility.

While it is important that the question of posture and technique should be considered in any case of childless marriage, a note of warning must be uttered. I have come across instances in which, as a result of their endeavours to carry out the instructions of a gynaecologist, married couples have changed what had previously been a mutual pleasure into a very unpleasant duty. Obeying instructions faithfully, they have set about the sexual act with determination and seriousness, finding consolation only in the thought that, unpleasant although the process might be, it was the means of bringing them nearer to the goal of obtaining a child. Sometimes, indeed, the difficulty in following out instructions was such, that in a little time the male partner was no longer able to fulfil his part of the contract. As a result of his failures, he had lost confidence in his capacity as a husband, and ended by developing a functional impotence. It is very necessary, therefore, that the medical adviser should point out that he is not laying down hard and fast rules, but merely making certain suggestions which the couple can adopt or not, as they think fit. If, instead of being acceptable, these new methods prove/

prove uncomfortable or uncongenial, then they must be abandoned. (Kenneth Walker).

(3) Impairments of Intravaginal Viability.

Once it has been established that insemination takes place with reasonable frequency and with a satisfactory relation to ovulation time, there arises the question of survival of spermatozoa in the vagina. It has already been pointed out that vaginal secretions are often not favourable to the survival of spermatozoa. In most cases all intravaginal spermatozoa cease to move irreversibly within a few hours of coitus (Seguy and Vimeux, 1933; see also Hartman, 1932 for bibliography). Huhner (1928, 1937) who has paid much attention to the problems involved, regards thirty minutes to three hours as a common measure of survival in the human subject, reduction in this period signifying an abnormal condition involving lowered fertility.

Wiesner's observations support the view that spermatozoa survive in the vagina for only a few hours and that the variations found in fertile couples are considerable. In one case, in which the vaginal pool was examined on three different occasions at varying intervals after coitus, it was found that 13 per cent. of the spermatozoa were motile one hour after intercourse and that there was no detectable motility after three/

three hours. In an equally fertile couple nearly 30 per cent. were motile one and three-quarter hours after coitus, but none at all three-quarters of an hour later.

On the other hamd, greatly reduced fertility may be manifested in, and caused by, a reduced period of intravaginal survival. Thus in two cases of female infertility which were examined by Wiesner on several occasions the survival period for all except a few isolated spermatozoa was about three-quarters of an hour; occasionally the period is shorter than thirty minutes. In view of these data it might seem desirable to ascertain in every case, by vaginal examination, whether the survival period of the gametes approximates to the norm; but in practice the need for this procedure does not often arise, for impairment of survival is usually caused by lowered viability of the spermatozoa - i.e., by intrinsic factors located in the gametes themselves and detectable by proper examination of the semen. Intravaginal survival should be tested if the semen analysis fails to give unequivocal evidence about the viability of the gametes, if the volume of the ejaculate is very small or if the vaginal secretion itself appears excessive or otherwise abnormal. The test is neither necessary nor appropriate for the assay of male fertility, although it is still extensively used/

used for this purpose. (Wiesner).

Technique of Post-coital Examination.

The technique of the post-coital examination of the vaginal pool is simple. A speculum is introduced without the use of lubricants and, after exposure of the posterior fornix, a drop of the vaginal pool is transferred to a cover slip and without any delay examined (if necessary on a heated stage or after warming) as a "hanging drop" preparation.

Interpretation of Results.

Little need be said about the interpretation of results. If only a few spermatozoa survive for longer than an hour after coitus the diagnosis is unfavourable, i.e., lowered fertility must be assumed. But it is only in cases in which intrinsic low viability of the spermatozoa can be excluded that this diagnosis concerns the female partner. Even short periods of intravaginal survival do not necessarily signify absolute sterility, for spermatozoa often move very rapidly through the cervix and may be found in the uterus soon after coitus. Some authors, indeed, seem to be of the opinion that very rapid loss of spermatozoal motility in the vagina is not only compatible with fertility, but/

but even represents the norm. Seguy and Vimeux (1933) believe that the acid state of the vaginal pool produces slight acceleration of motility of the spermatozoa, followed by their rapid death. In the opinion of these authors, these conditions cause first, rapid ascent of the spermatozoa to the cervix, and, secondly, the death of those spermatozoa not fitted to withstand adverse influences.

Attention must be directed to a rare but important finding. In some women the spermatozoa are rapidly destroyed by a curious cytolytic process which affects the darkly-stained portion of the head, producing characteristic forms. This intravaginal spermatolysis, which in its initial stages does not interfere with motility, appears within thirty minutes of coitus. Its occurrence may render it impossible to obtain a morphological count in a post-coital specimen. (Wiesner).

(6) Do Spermatozoa pass into the Cervix?

The assumption that uterine peristalsis and possibly aspiration are factors concerned in the transport of spermatozoa from the cervix to the uterus is supported by two observations. First, it is found that inanimate/

inanimate particles deposited in the vagina and on the cervical os may pass fairly rapidly into the uterine cavity. Secondly, spermatozoa have been demonstrated in the cervical canal within forty or fifty seconds of insemination - in some animal experiments virtually immediately after coitus. Such rapidity of ingress could hardly be expected if the transport of the spermatozoa were conditioned entirely by their own motility. On the other hand, the inherent motility of spermatozoa must be regarded as the best established single factor contributing to their ascent into the uterus. Three facts may be cited in support of this view. First, the success attending artificial insemination, when semen deposited in the posterior fornix produces conception without any attendant sexual excitation; secondly, the authenticated cases in which conception has occurred without rupture of a pin-hole hymen; and thirdly, the observation that few, if any, spermatozoa find their way into the cervix in cases of astheno-zoospermia.

Some authors who regard the motility of spermatozoa as essential for proper insemination of the cervical canal have pointed out that the spermatozoa move towards the cervix and not towards the vulva - although their movements in vitro are random. This observation - which is not established beyond doubt - has/

has been explained by the existence of a difference of potential between the cervical os (with its alkaline mucus) and the acid medium of the vagina. The spermatozoal movements are assumed to be directed towards the cervix by this difference - just as they tend to be directed in an electric field in vitro.

Other factors which appear to influence the passage of spermatozoa through the cervix may be discussed very shortly. There is evidence that their passage is facilitated by the lowered viscosity of the cervical mucus which occurs during the ovulatory period. It has also been suggested that the muscular equipment of the abdomen may participate indirectly in the process by producing passive suction on the part of the uterus. Direct ejaculation of semen on the external os has been regarded as an important condition (Meaker, 1934; Hartman, 1932), but that it is not essential is proved by the success of artificial insemination and the fact that conception occurs in cases of unruptured hymen, malposition and other abnormalities. It is probable that the close approximation between the glans penis and the cervix also serves to favour the entry of spermatozoa into the uterus. (Wiesner).

Disturbances of Ingress.

In normal women mated to normal men spermatozoa are found in the cervical canal within a few minutes of coitus. In two cases, in both of which the experiment was carried out three times, active spermatozoa were recovered from the canal well within fifteen minutes of their deposition in the vagina. The specimens were collected from an area situated about $\frac{1}{2}$ cm. from the external os. (Wiesner).

Speaking generally, mere inspection of the cervix does not yield sufficient information about the ingress of spermatozoa. In cervicitis, widespread erosion, widening of the cervical canal, or conditions characterized by excessive mucus formation with the persistence of the mucus plug, no spermatozoa, or only a very few, may be found in the canal even two hours after intercourse; but none of these conditions necessarily prevents their passage. The existence of a pin-hole os need not interfere with the passage of spermatozoa.

Huhner's Post-coital Test.

The post-coital test generally used in the investigation of the cervical passage follows the procedure first described by Huhner; it should be carried/

carried out in every case in which there is reason to doubt the normality or adequacy of spermatozoal ingress in the cervical canal - e.g., in cases of uterine hypoplasia, malposition, persistent mucus plug, etc. The investigation should be preferably carried out at the presumptive ovulatory phase, because it is probable (though the fact has not been established) that the conditions of cervical passage are particularly favourable at this period. The method is as follows:

The patient reports for examination preferably within one or two hours following coitus. A vaginal speculum is introduced without any lubricant and the cervix then dried carefully. The distal part of the canal is cleaned, bleeding being avoided if possible. A piece of mucus is then collected with a narrow wire loop and at once examined.

Interpretation of Results.

It has been mentioned that for one of its original purposes - the investigation of male fertility - this test has been superseded by semen analysis; and such an analysis must supplement, and if at all possible precede, post-coital examination if this is to yield the fullest information of which it is capable.

The/

The interpretation of results is difficult in cases in which the ordinary semen analysis shows the presence of asthenozoospermia, for in these cases failure of ingress may be attributable to the state of the semen rather than to any fault in the female partner. The best course is to repeat the test after, or to postpone it until, treatment of the male has been successful.

If the semen is free of asthenozoospermia and not excessively small in volume, motile spermatozoa should be found in the cervix one hour after coitus. Their number is less significant than their motility, a very few motile spermatozoa being sometimes found in fully fertile cases. If they fail to appear, notwithstanding normal motility in the semen sample, disturbances of cervical function must be suspected; in most of the cases on record the underlying condition was hypoplasia.

When there is evidence of defective ingress, it becomes necessary to discover the responsible factor. So-called "hostility" of endocervical secretions - formerly believed to be important - seems to be rare. But other factors - e.g., malposition, hypoplasia or inflammatory conditions - may be concerned.

Two/

Two errors of interpretation must be guarded against. First, although the test may show absence of spermatozoa in the cervical canal, this event may be exceptional for the patient. This is particularly likely to be the case if sexual excitement, a factor believed to favour the passage of spermatozoa, is absent or diminished owing to the condition of the test. Secondly, a negative result may, on repetition of the examination, be followed by a positive, the very process of examination serving sometimes to remove obstacles - e.g., dense mucus - to the passage of spermatozoa. An obvious analogy is tubal insufflation in which the diagnostic procedure sometimes suffices for treatment too.

(7) Are the Conditions for the Development of the Ovum Maintained at an adequate Level?

The relevance of the tests described under this heading to the study of infertility is perhaps not immediately obvious, for they are carried out when there is a possibility that pregnancy is already established. The tests are concerned, however, not only with the question whether fertilization has taken place,/

place, but with discovering whether there exists a danger of miscarriage.

It is, of course, well known that conception is followed by the excretion of gonadotropic hormone of chorionic origin. Large amounts of this hormone appear in the urine within fourteen days after conception, so that macroscopic changes (blood spots, luteinization) are produced in the ovaries of immature mice by the injection of small volumes of urine (0.1 to 1.0 cc. each on three successive days; Aschheim-Zondek test for pregnancy). In some cases it is found that these volumes of urine fail to produce the typical effect; even much larger amounts or concentrates prepared from them may fail to produce the ovarian changes, though they may evoke certain characteristic uterine responses in the test animals. Women whose urine shows this deficiency soon after the first missed period are much more liable to miscarry than those in whom excretion is normal (Wiesner, 1931; unpublished data). These observations suggest that inadequate maintenance of the condition of pregnancy is associated with deficiency of chorionic excretion. In cases of infertility the tests developed on the basis of these observations assume particular importance, for fertilization by semen of low quality is often followed/

followed by deficient excretion of chorionic hormone, and consequently, as already pointed out, by miscarriage.

S U M M A R Y.

Infertility Factors.

The procedures which have now been described may reveal a number of infertility factors. In some of these, e.g., various types of vaginal and vulval disorders, the causal relation is not obvious but the association with infertility is established by clinical experience, though not by any precise statistical investigation. In others, the disorder is a sufficient - though not necessarily the only - explanation of the infertility. An example of this type is bilateral tubal block. Other infertility factors occupy an intermediate position. Hypoplasia of the uterus, for instance, is often, but not invariably, associated with sterility or lowered fertility and is as much a symptom of the condition as a cause.

Attempts to set out infertility factors in order of importance are on the whole unsatisfactory, for, with rare exceptions, the significance of any one factor depends largely on its combination with others. Thus, malposition of the cervix seems less important

in/

in otherwise healthy women than in those with cervicitis; vulvitis may have little direct influence on reproduction, yet cause sterility by limiting the frequency of sexual intercourse. These important reservations must be borne in mind in assessing the value of the following tentative classification of infertility factors into three groups - slight, severe and absolute.

(i) <u>Factors producing Slight Impairment of Fertility</u>.

(a) Inflammatory conditions of the vagina and the cervix.

(b) Slight inflammatory conditions of the uterus and the adnexa.

(c) Malpositions.

(d) Obstruction of cervical passage by viscous mucus.

(e) Infrequent intercourse.

(ii) <u>Factors producing more Severe Impairment of Fertility</u>.

(a) Advanced inflammatory conditions of the genital tract and the adnexa.

(b) Uterine tumours.

(c) Severe uterine hypoplasia.

(d) Ovarian tumours, cysts and other conditions associated with disturbance of ovulation.

(e) Disturbances of the menstrual cycle associated with certain types of abnormal hormone excretion.

(iii) <u>Factors producing Absolute Sterility</u>.

(a)/

(a) Tubal blockage of the complete type.

(b) General hypoplasia of the genital system.

(c) Certain disturbances of the endocrine conditions of fertility with disappearance of menstrual periodicity (e.g., persistent corpus luteum; excessive oestrogenic in the absence of luteal secretion).

(d) Lack of ovulation.

(e) Deficient response of endometrium to ovarian hormones.

It is inevitable that the interpretation of findings in the wife should turn to some extent on the results of the examination and the assay of fertility in the husband. If the husband is found to be fully fertile, small infertility factors in the wife tend to assume a greater importance; if his fertility is low, the tendency may be to underrate the responsibility of any except the more severe infertility factors in the wife. In general, however, the latter error is seldom committed by experienced workers in this field. They err, very properly, on the side of safety, adopting a diagnostic severity which neglects no factor merely because it seems of little importance in itself.

Integration of Findings.

In many cases it is found that lowered fertility is produced by a combination of unrelated factors; in others the various infertility factors present may be regarded as so many symptoms of one and the same underlying condition. An example in the

first/

first class is a case in which dyspareunia was treated successfully but without resulting conception; further investigation revealed tubal obstruction, and therapeutic insufflation was followed by pregnancy. In the second class a simple example is the combination of hypoplasia of the uterus, blockage of the tubes, partial stenosis of the cervical canal, and the accumulation of tenacious mucus, all of which may represent the effects of deficient ovarian secretion. Wherever possible an attempt should be made to relate the diversity of conditions found on examination to a common underlying cause.

Absence of Infertility Factors.

Not uncommonly even the most scrupulous series of investigations fails to detect the presence of infertility factors. Such negative findings are comparatively unimportant in cases in which the investigation of the husband has discovered signs of lowered fertility; but when the male appears to be fully fertile the absence of manifest infertility factors in the female places the practitioner in a difficult position. He may perhaps resort to the time-honoured diagnosis of incompatibility, but this involves a hypothesis for which there is no foundation in/

in fact. The alternative is to assume either that a technical error in the investigation has resulted in failure to detect a recognized infertility factor or that the infertility is due to disorders which cannot be recognized by any known clinical laboratory tests.

It is very probable that such disorders exist. The fact that the assay of female fertility yields only negative results, serving to exclude anatomical and functional hindrances to reproduction but failing to prove production of viable ova or the existence of adequate conditions for the development of the ovum, was stressed earlier. Both clinical experience and experimental findings support the conclusion that all existing tests for female fertility are crude instruments for the measure of the complexity of factors involved in the mechanism of reproduction. It is significant, to give a single example, that although vitamin E deficiency may cause sterility, it cannot be detected by any of the ordinary methods employed in endocrine or anatomical investigation. Nevertheless, treatment based on the assumption that vitamin E deficiency may be a factor, even in patients receiving a plentiful and varied diet, often results in successful pregnancy to term.

The/

The inevitable conclusion from the fact that the investigation can never prove the existence of fertility is that the presence of infertility factors must be suspected even if their existence cannot be demonstrated. In this field of practice it is a safe rule not to declare any woman normal until she herself has demonstrated the fact by conceiving and carrying to term a viable child.

THE TREATMENT OF FEMALE STERILITY.

Indications and General Procedure.

In many cases no useful purpose is served by the institution of treatment for female sterility, e.g., when sterility of the male partner has been proved to be absolute and permanent or when the patient would suffer more from pregnancy than from continued barrenness. In cases of pronounced male infertility the treatment of the wife should be postponed until that of the husband has established a condition of the semen which does not exclude fertilization.

Very commonly it is advisable to proceed pari passu in both partners. An obvious instance is afforded by cases in which both husband and wife show but minor deficiencies, the sterility of the marriage being attributable to the combination of defects in both/

both partners. Simultaneous treatment is also advisable in cases of suspected dyskyesis, i.e., where conception has presumably taken place on one or more occasions or where the semen is of such a nature as to suggest the danger of early miscarriage. If these conditions are present, measures should be taken for raising the fertility of the husband and, at the same time, for the prevention or treatment of dyskyesis in the wife.

Needless to say, treatment of the wife should be instituted whenever investigation has revealed impairment of her reproductive powers; even relatively minor disorders may repay attention. But some forms of treatment may be advisable even if no specific impairments of fertility can be detected and the general health appears good. This suggestion may seem to depart from established therapeutic principles, for it implies that a "healthy" patient should be subjected to treatment. But undetectable disturbances of oogenesis or of other reproductive functions must always be suspected. Careful stimulation of reproductive functions is harmless and, in not a few cases, produces the desired effect.

The Aims of Treatment.

Meaker's view is that, although even intensive treatment may, indeed usually does, fail to eliminate all sterility factors, the successful treatment of only a few such factors may suffice to restore fertility. It is better practice, therefore, to proceed step by step rather than to plan simultaneous treatment of all the possible causes of sterility detected during investigation. Such restraint should be particularly observed in connection with surgical measures, and not least with the simple but unphysiological procedure of curettage. The gradual elimination of one factor after another, beginning with those most easily attacked, will often eliminate the need for surgical measures. This routine of treatment may involve some sacrifice of time, but it often saves much trouble and expense.

The first essential in the treatment of female infertility is the restoration of general health. Anything that cures the patient may cure sterility. This applies to the removal of septic foci, the treatment of recurrent conditions such as tonsillitis, the relief of digestive disturbances, and the abandonment of noxious habits such as excessive/

excessive indulgence in tobacco or alcohol.

Some workers in this field have rightly stressed the desirability of treating endocrine disorders. In actual practice - as previous workers, particularly Meaker and his associates, have pointed out - thyroid deficiency is probably the most significant of the endocrine disorders associated with subfertility.

Disorders localized in or manifested by the reproductive organs call for special attention. Apart from specific measures designed to stimulate ovarian or uterine function, general gynaecological procedures must be adopted in the treatment of such disorders. It must be borne in mind, however, that disorders of the reproductive system are often but manifestations of a general condition, and, conversely, that many general symptoms such as obesity or disturbances of the vasomotor system have their origin in ovarian or pituitary dysfunction. Purely local treatment of genital disorders is therefore often as inadequate as general treatment.

Therapeutic measures must include careful consideration of psychological factors. Anxiety states may interfere with the normal menstrual cycle. In/

In such cases the excretion of gonadotropic hormone may be excessive and the urine may show reactions suggestive of the menopause. These disappear rapidly and menstruation is established when the anxiety state subsides. Such extreme psychogenic disturbances are not common in sterility cases, but the childlessness of the marriage together with the steps taken to alleviate it often induce a state of mind unfavourable to general recovery and to the specific reproductive functions alike.

In this connection attention should also be drawn to the influence of sexual habits. The importance of this factor is illustrated by the apparent spontaneous alleviation of hypoplasia which sometimes occurs after marriage even in the absence of pregnancy.

Dietetic Adjustments.

In recent years attention has been drawn to the part played by vitamins in the maintenance of reproduction. Vitamin A deficiency may inhibit pituitary function and lead to an interruption of oestrogenic secretion (Parkes and Drummond, 1926). Vitamin E is necessary for the maintenance of the normal condition of the anterior lobe of the pituitary, but its direct influence on the fate of gestation is of even greater significance. In animals, severe Vitamin E deficiency induces/

induces resorption of the foetus; in the human subject a low intake of vitamin E is believed to be responsible for miscarriage. There is no reason to assume that deficiency of vitamin E is responsible for ovarian hypoplasia or the many other conditions for which it is now prescribed, but there is ample evidence that administration of concentrated preparations of the vitamin will counteract the tendency to habitual abortion (Young, 1937; Currie , 1936).

The value of vitamin E therapy is in prevention rather than cure. It should be regularly administered in all cases of female infertility as a precaution against the premature termination of any pregnancy that may occur. But vitamin E can hardly be expected to increase the probability of conception except in extreme conditions of depletion such as rarely, if ever, are met with in clinical practice.

Although absence or pronounced deficiency of vitamin E is the exception in most civilized diets, individual requirements appear to vary greatly, and some subjects may need the addition of vitamin E to a diet which would be fully adequate for others. No method has as yet been established for assessing vitamin E requirements, though a test for the purpose has been suggested. The safe course is to give

generous/

generous doses in suitable cases, e.g., a concentrate equivalent to 2.5 to 5.0 grams of wheat germ oil daily. It is particularly important to prescribe an ample supply of vitamin E in cases of proved dyskyesis or in which the husband shows signs of lowered fertility with consequent danger of miscarriage.

Dietetic treatment is required both in cases of obesity and of malnutrition. General dietetic deficiencies, particularly if long continued, tend to produce external signs of disturbed genital function - e.g., amenorrhoea; but even if these signs do not appear reproductive capacity may be reduced and the diet should be adjusted without delay. Specific dietetic measures such as increase or decrease of a particular dietetic constituent are seldom called for; any of the usual mixed diets, if sufficient in amount and not lacking in first-class proteins, minerals and vitamins, are adequate. None of the diets used in experimental work on animals appear to act specifically on the ovaries or the pituitary; when such animals are reared upon diets which give optimum health and are adequate for all normal metabolic and physiological processes, the fertility is maximal and cannot be increased by any nutritional/

nutritional means.

Limitations of Surgical Methods.

The need for surgical measures, with the exception of tubal insufflation and possibly the correction of uterine malpositions, arises but seldom in the treatment of sterility. This fact must be emphasized, for resort to such measures is still far too common. It is true that in some cases in which cervical amputations and similar drastic procedures are carried out, in the absence of clear indications, the operations are followed by conception; but in a large proportion of these cases simpler procedures would suffice, for surgical measures are presumably often successful only because they indirectly stimulate genital function and induce regeneration (as some believe) which could be just as well achieved by other and less violent means.

Surgical procedures are, of course, required in some disorders and it is generally recognized that dilatation and curettage may promote or restore fertility when all other means have failed. But even when the indications are unequivocal, operative treatment may have to be supplemented by other measures such as endocrine medication. This is true/

true, for instance, of fibromyomata of the uterus, which may develop in the course of protracted disturbances of ovarian secretion, and thus may be associated with sterility which must be attacked not only by removal of the tumours but by correction of the underlying endocrine disorder.

SPECIFIC THERAPEUTIC MEASURES.

So far treatment has been discussed in general terms only. It is now necessary to consider in detail specific measures designed to stimulate ovarian activity, induce the development of the genital organs, and correct other disorders that may underlie or be otherwise associated with female infertility.

Use of Endocrine Preparations.

The use of endocrine preparations has increased greatly since the combination of scientific progress and its industrial exploitation have placed reliable active preparations at the disposal of the clinical worker. But only a few systematic investigations have been published on the use of these preparations for the relief of sterility. Except in the investigations of Clauberg (1936, 1938), Zondek (1935), Hamblen/

Hamblen and Ross (1937), and a few others, the available preparations have been used sporadically or in cases which were not thoroughly investigated before treatment. This is readily understandable in view of the fact that appropriate methods for the analysis of reproductive function are of very recent origin, but it means that the material on which definite conclusions can be based is still relatively small.

General Procedure.

Most of the principles which must be observed in endocrine therapy were either stated or implied in the course of the discussion of the physiology of the menstrual cycle, and only general rules of procedure need be formulated here.

(i) Causes not directly connected with the endocrine system must be eliminated. This postulate, formulated by Meaker, must be observed strictly, for general disorders such as infections or anaemias may lower the reactivity of organs which normally respond to endocrine stimulation.

(ii) Every effort should be made to establish the nature of the endocrine deficiency or disorder. Different endocrine conditions may be manifested in the same external symptoms. A careful differential diagnosis facilitates rational therapy.

(iii)/

(iii) Active preparations must be administered. This condition, though apparently self-evident, is even now not invariably observed. Pituitary powders are prescribed for oral administration in spite of the fact that their content of gonadotropic hormone is destroyed by tryptic digestion. Again, unstandardized preparations are still used to a very large extent because of their deceptive cheapness.

(iv) Dosage must be adequate but not excessive. The level of response varies within very wide limits, and there is no foundation for the comfortable view that rules about dosage can be stated which would be applicable to all patients.

(v) The ultimate criterion in the evaluation of treatment must be clinical. The biological actions of the preparations now in use have been defined by work in animals. Thus oestrogenic hormones have been shown to promote genital development without concomitant stimulation of the ovary except in specific conditions. Hence, it might appear that oestrogenic hormones would not stimulate ovulation, and thus would be of little use in the treatment of infertility.

In/

In some cases an apparently irrational form of treatment is subsequently proved to be physiologically appropriate by the discovery of previously unknown effects. In others it must be assumed that the conditions of animal experiment do not fully reflect the complex conditions in the human subject, in whom a stimulus applied to any part of the reproductive system may conceivably set in train the mechanisms of ovulation or else raise the level of endogenous endocrine activity.

The recognition of these facts affords no general justification for irrational therapy. It simply implies the view that experimental data, such as are obtained in studies of normal animals with uncomplicated, artificially produced, and localized defects, must not circumscribe the clinical application of endocrine products.

Classification and Action of Gonadotropic Hormones.

These are: anterior lobe extracts (ALP); anterior pituitary hormone obtained from human menopausal urine, but also present after oophorectomy and/

and in temporary hyperpituitarism (OO); chorionic hormone of pregnant mares' serum (MS); and chorionic hormone of human pregnancy serum or urine, or of human placenta (PU).

A great volume of experimental work has been carried out with these substances. Most authors, however, have studied their effects on lower animals, e.g., the mouse and other rodents, whose reactions to gonadotropic hormones differ considerably from those observed in Primates (e.g., monkeys). The difference is due not only to the particular form of the sex cycle in Primates, in which the oestrous phase has lost its distinctive character as a separate and almost independent series of changes; but also to the fact that the ovaries of Primates do not react to gonadotropic stimulation by ovulation and luteinization as readily as do the ovaries of rodents. It is easy, for instance, to elicit luteinization in the rodent ovary by administering ALP; but this effect cannot be achieved equally easily in Primates. In view of these differences it is unsafe to draw conclusions about the range of physiological effects of gonadotropic hormones from experiments on lower mammals only; experiments on monkeys are of greater significance because of the close resemblence between the genital functions/

functions in monkey and man.

Action in Immature Primates.

The effects of gonadotropic extracts will be considered in terms of the results obtained by Engle (1932) and Wiesner using immature and mature Rhesus monkeys (see van Dyke, 1936 for bibliography). The animals were kept under identical conditions, observed closely during the course of the experiments, and killed at various stages of the administration of hormone. The organs were sectioned, in some cases serially. The results may be summarized as follows:

ALP. This extract causes secretion of oestrogenic hormone, so that the uterus enlarges greatly and the endometrium develops until the signs of the proliferative phase are fully established. Extravasation of blood takes place in the submucosa. Cessation of the injections or their continuation for a prolonged period leads to bleeding which simulates menstruation but actually represents oestrous bleeding.

Increase in the dose is followed by intensive follicular development. But this is abnormal, for what occurs is cystic degeneration of the ovary, not ovulation and luteinization. If more than about five times the oestrogenic dose, i.e., the dose producing distinct uterine/

uterine effects, is administered, extensive cystic changes result in the ovary.

<u>OO</u>. The gonadotropic hormone from menopausal urine and the urine of oophorectomized women produces in Rhesus monkeys the same reaction as ALP. The uterus undergoes pronounced development, with great proliferation but not differentiation of the endometrium. This reaction corresponds to the condition of the ovary, which contains large, though abnormal, follicles but lacks luteal tissue.

The absence of luteinization is less surprising than in the case of ALP, for OO fails to luteinize even the rat ovary. Perhaps the main significance of the results lies in the fact that the gonadotropic hormone in the urine of oophorectomized women appears to represent a true secretion of the human pituitary, so that its administration may virtually be regarded as substitution therapy.

<u>MS</u>. This hormone causes precisely the same changes as ALP, its action being limited to the promotion of oestrogenic secretion without ovulation or luteinization.

<u>PU.</u> Contrary to previous reports (e.g., by Engle, 1932), the gonadotropic hormone prepared from pregnancy urine or the human placenta stimulates the secretion of oestrogenic hormone by the ovary and thus causes/

causes pronounced uterine development. It also causes <u>some</u> follicles to enlarge, but fails to luteinize them. Most follicles, however, undergo a form of degeneration which differs considerably from that seen after the administration of MS, ALP, or OO. The degenerative process ends in the formation of hyaline bodies which may still retain the circular arrangement of the original follicles but are devoid of any active elements or follicular fluid. The uterus responds to the ovarian changes by growth and by proliferative changes in the endometrium, but owing to the failure of PU to induce luteinization these are not followed by the changes characteristic of the secretory phase.

<u>Comparison of Experimental and Clinical Results.</u>

The experiments described in the preceding paragraphs show that gonadotropic hormones of the type tested cannot be expected to induce ovulation and luteinization in the immature ovary of the monkey - even though their luteinizing potency is well established in other species, such as the rat or the rabbit. The monkey being much more closely related to the human than the rodent, both with respect to the anatomy and the physiology of the genital reproductive system, it must seem doubtful whether luteinization may be expected to result in the human species. In any case, it is necessary to turn to clinical observations/

for decisive evidence on the effect of gonadotropic hormones in human subjects.

The available data are not very extensive, and do not invariably refer to sterile women; moreover, the observers concerned are not in complete agreement. Thus, Zondek (1935) used PU in several cases and claimed to have induced luteinization demonstrated by laparotomy. Hamblen and Ross (1937), however, in a carefully controlled series of six women with anovulatory cycles, showed that only in one case (and that doubtful) was luteinization invoked by MS or PU. The endometrial findings corresponded to the appearance of the ovaries, i.e., a proliferative state was demonstrated by biopsy. Previously, Geist (1933) had failed to obtain follicular stimulation with large doses of PU. Reports of luteinization after administration of PU (Stoeckl, 1934) still await further verification; regressive changes have been reported (Mandelstamm and Tschaikowsky, 1932) which lend additional weight to the experimental observations in monkeys already described.

It might seem, therefore, that the response of the ovary of the human female towards gonadotropic stimuli resembles that of the immature ovary of the monkey; and further that the clinical use of gonadotropic hormones can have but a very limited scope, being/

being restricted to the stimulation of oestrogenic ovarian secretion. But four groups of observations suggest that gonadotropic hormones may be of much greater assistance in the treatment of sterility than these data suggest.

(1) Some authors (Zondek, 1935; Berge, 1935) claim to have cured sterility by the administration of PU in relatively small amounts. Their results are significant, though the preliminary examination was not always sufficient to define the condition of the patient before the administration of the hormone.

(2) There are on record a number of cases in which female sterility responded to treatment with PU, MS, ALP, or mixtures of gonadotropic extracts. In several cases anovulation was diagnosed; the data obtained in the preliminary investigation and the long duration of the previous infertility justify the conclusion that pregnancy was not incidental to, but probably the result of, treatment.

(3) It has been shown in a series of clinical experiment that ovulation can be induced in many women by means of MS (Davis and Koff, 1938). A large dose of MS was administered intravenously either without preliminary treatment or only after a series of preparatory injections of small amounts had been given. In order that/

that an opportunity might be provided for inspection of the ovaries, the patients were chosen from among women who, for various reasons, were about to be subjected to laparotomy. It was found that an intravenous injection of MS was followed, within a short space of time (about thirty hours), by the occurrence of ovulation irrespective of the phase of the cycle at which the injection was administered. If these observations are confirmed they should be of the greatest importance in the treatment of sterility; timed incitement of ovulation will be particularly valuable if combined with artificial insemination. It must not be assumed, however, that this method will be applicable to all cases of anovulation. An examination of the histories of the cases described by Davis and Koff suggests that many, if not all of the patients, would have ovulated spontaneously, although not necessarily at the time at which ovulation was artificially induced.

(4) Hunt (1938) found that sterility was cured, in three patients, by the administration of the serum of pregnant women containing large amounts of chorionic hormone.

The discussion, up to the present point, has centred on the capacity of gonadotropic hormone to induce ovulation and luteinization in the human ovary. But/

But it should be borne in mind that gonadotropic hormones also affect the endocrine functions of the ovary and thus may indirectly evoke uterine development.

Gonadotropic Hormones for Clinical Use.

Dosage.

Unfortunately, it is not possible to set out definite tables of dosage, for the response varies greatly in different persons and at different times. As an example may be mentioned the fact that in sterile women treated for menorrhagia the response to hormone therapy may be considerable in one cycle and absent in another.

XII

A further difficulty arises from the fact that no international unit has as yet been recognized. The commercial preparations are standardized with great care and precision, but the methods of standardization differ widely. It is not surprising, therefore, that great differences have been revealed in the potency of commercial preparations that claim to possess the same number of units of active principle (D'Amour and D'Amour, 1938). Even in the adoption of an international standard, making use of reliable methods of standardization (Parkes et al., 1935; Burn,/

Burn, 1937), would not wholly solve the problem of expressing dosage in precise terms.

Principles of Administration.

The dosage applicable to any given case may be determined by reference to the following:

(a) Treatment should begin, without exception, with small doses and the dose should be raised only if (i) the desired result has not been obtained, and (ii) no adverse general effects have been observed.

(b) Treatment must be controlled by continuous observation. Thus, in cases of hypoplasia involving the ovary, the urine analysis and gynaecological examination should be repeated at intervals; in women with anovulatory cycles another biopsy should be carried out during the first cycle after the institution of treatment; in cases of sterility combined with menorrhagia a careful record should be kept of every menstruation. Conception should be avoided during any cycle in which biopsy has to be carried out. This precaution is desirable in spite of the fact that the use of the biopsy curette often leaves existing pregnancies undisturbed.

Indications for Gonadotropic Therapy.

(a) General.

The general indications for the use of gonadotropic/

gonadotropic hormone have either been described or implied earlier in this discussion. It must be borne in mind that genital disturbances or lack of sexual development are not necessarily due to pituitary deficiency (hypogonadotropism), for in many of such cases considerable amounts of gonadotropic hormone can be demonstrated in the urine.

The general characteristics of hypogonadotropism are lack of genital development (involving the ovaries as well as the uterus), involution of the genital organs, absence of or the presence of small amounts only of gonadotropic and ovarian hormones in the urine, absence of menstrual periodicity or pronounced oligomenorrhoea, and absence of ovulation or inadequate development of the secretory phase.

(b) Specific.

Gross Hypogonadotropism.

Except when preceded by the intensive administration of oestrogenic compounds, gonadotropic therapy is seldom effective in the treatment of primary amenorrhoea and hypoplasia. In our experience it is always desirable to attempt to stimulate genital development by means of oestradiol/

oestradiol before employing gonadotropic hormones. Some authors, however, have reported that satisfactory response may be obtained in cases of hypoplasia by treatment with ALP alone. Following such treatment, they have observed not only uterine enlargement, but also differentiation of previously atrophic endometrium, and even the occurrence of pregnancy (Paynes and Shelton, 1938).

Secondary Hypogonadotropism.

As an example of this condition may be mentioned a deficiency which sometimes occurs after pregnancy and may persist for long periods. In their general features secondary and primary hypogonadotropism resemble each other closely. Uterine hypoplasia, however, is not usually noted in the former, even when the endometrium is atrophic and other signs of impaired ovarian activity (absence of cycle) exist.

Anovulation.

This is perhaps the most important of the conditions requiring treatment by means of gonadotropic hormones. If anovulation is combined with other signs of hypogonadotropism the treatment should follow the lines described in the preceding paragraphs./

graphs. Where, however, genital development is normal and menstrual periodicity unimpaired, one of the two following procedures may be adopted:

(a) Gonadotropic hormone should be injected intramuscularly during the first half of the cycle (seventh to fifteenth day) and may be followed by intramuscular administration of PU during the second half of the cycle. The use of PU is intended to counteract the tendency to abortion which may be present in subfertile couples.

(b) A large single dose of MS (e.g., Serogan or Gonadyl) may be injected intravenously during the mid-menstrual phase. Davis and Koff, as already stated, claim to have produced ovulation by this method. It may be suggested that the intravenous administration of MS calls for precautions against the occurrence of shock (e.g. test for sensitivity on the patient). The intramuscular route may also be tried.

General Survey of Results.

On the basis of existing clinical experience it may be stated that gonadotropic therapy is effective in the conditions discussed in the previous pages; but the available data are by no means sufficient to justify statistical statements about the expectation of success. Neither/

Neither the scope nor the technique of gonadotropic therapy has yet been defined with anything approaching finality.

Oestrogenic Compounds.

The term oestrogenic compounds is now applied to a number of chemically different substances which have in common the capacity to incite uterine development in the immature and the oophorectomized female mammal and to produce the vaginal changes associated with oestrus in lower animals. Although synthetic substances with oestrogenic potency have been prepared, their full clinical significance is as yet doubtful. The only non-synthetic oestrogens in general clinical use are those obtained from the urine of animals (particularly pregnant mares), from the urine of pregnant women, and from the amniotic fluid of cattle. The substances most commonly used are oestradiol (or its derivatives) and the excretion products of oestradiol (such as oestrone), which can be extracted from the urine. Some derivatives of oestradiol, e.g., oestradiol monobenzoate, are far more active than oestradiol itself and are consequently preferred by most clinicians. Oestrogenic compounds are sold under a/

a variety of trade names.

Actions and Administration.

All oestrogenic compounds produce the same effects, but the intensity of these effects varies greatly.

Some derivatives of the pure hormone - e.g., the diproprionate and the benzoate - have a lowered rate of absorption, and this fact accounts largely for their increased activity. When in oily or aqueous solution, oestrogenic hormones are so rapidly absorbed and excreted that attempts have been made to administer them in forms capable of exercising a more prolonged action. It has been found that hormone crystals compressed into tablets and grafted into muscle are absorbed very slowly (Deanesly and Parkes, 1938). Such deposits can produce effects lasting for several weeks, thus obviating the need for numerous injections and saving much trouble.

Range and Activity.

Oestrogenic substances produce changes characteristic of the proliferative phase in the uterus and vagina of the Primate female. The administration of these hormones may also be followed by pseudo-menstruation, that is to say, by bleeding from the/

the developed uterine mucosa resembling menstrual bleeding but actually equivalent to oestrous bleeding. Oestrogenic substances cannot induce the changes of the secretory phase, but they are necessary for the sensitization of the endometrium to progesterone. Although oestrogenic substances in general and oestradiol in particular primarily affect the uterus, the Fallopian tubes, and the vagina, they may, through their action on the pituitary, also produce indirect effects on the ovary.

General Indications for Oestrogenic Therapy.

The indications for the use of oestrogenic compounds are very extensive, oestrogenic therapy having been used widely and on the whole successfully in such different conditions as amenorrhoea of the hypohormonal type and irregular bleeding originating in the hypoplastic endometrium. When such conditions are associated with sterility, prolonged oestrogenic therapy may have to be employed as a preliminary measure before more specific attempts are made to cure the sterility.

On the other hand, the use of oestrogenic compounds is contra-indicated in cases of sterility associated with an excessive output of oestrogenic hormone./

hormone. This applies particularly to women in whom excessive and irregular bleeding, and endometrial biopsy have indicated the existence of a glandulo-cystic hyperplasia.

Specific Indications for Oestrogenic Therapy.

Anovular Cycles without Excessive Excretion of Gonadotropic Hormones.

In some women presumptive absence of ovulation - demonstrated by biopsy and absence of pregnandiol - is associated with the excretion of large amounts of gonadotropic hormone and cannot therefore be referred to any lack of gonadotropic stimulation. In others, however, anovular cycles occur in the presence of normal or possibly even deficient gonadotropic excretion, and in these cases Clauberg's oestrogenic shock therapy may be employed.

This treatment is based on the observation that oestrogenic substances may inhibit the secretion of gonadotropic hormone. Clauberg assumed that the administration of a single large dose (oestrin shock) may be followed, first, by inhibition of gonadotropic secretion and storage of the hormone in the pituitary, and, secondly, by release of a strong gonadotropic stimulus/

stimulus and ovulation. His assumption is supported by the fact that a single oestrin shock may cause stimulation of the testis, and also by the observation that in rabbits it may produce strong ovarian effects (e.g., luteinization). Applying the same technique to human subjects, Clauberg treated cases of anovulatory cycle with considerable success, pregnancy resulting a short time after the institution of treatment. The details of the procedure are as follows:

During the mid-menstrual phase (twelfth day) a single dose (which may, however, be subdivided) of 100,000 or 200,000 international units is injected. The amount required (10 to 20 mg. of oestradiol benzoate) can easily be dissolved in a small volume of oil and injected intramuscularly. Certain adjustments are necessary in cases in which the cycle is of prolonged duration, for the theoretical and experimental foundations of the treatment demand that the shock should be produced during the early mid-menstrual stage in order that pituitary secretion may act on a follicle which has undergone preliminary development.

This form of treatment deserves more extensive trials than it has hitherto received. It may be suggested that, successful treatment of anovulation being in some cases followed by a tendency to miscarriage, the administration of the shock should be followed/

followed by treatment with gonadotropic hormone or progesterone to counteract this tendency.

Hypoplasia of the Uterus and Tubes.

This responds in many cases to the prolonged administration of oestrogenic compounds (Gardiner-Hill and Smith, 1931; Chapman, 1934; Zondek, 1931; Bishop et al., 1935).

Development of the hypoplastic uterus often occurs in treatment with oestradiol, an effect which Clauberg (1936) has demonstrated by striking radiographs. He maintains that the effects of the treatment extend to the tubes, which in cases of infantile uterus often share in the developmental deficiency and are consequently impermeable. The effect of hypoplasia on fertility may therefore be identical with that produced by acquired blockage, and treatment may bring about, not only an enlargement of the uterus, but patency of the tubes.

In this connection it should be added that oestrogenic therapy has proved valuable, not only in congenital occlusion, but in occlusion resulting from inflammatory changes, the growth impulse imparted by the endocrine stimulus apparently bringing about patency of the canal, irrespective of the origin of the occlusion (Clauberg).

Dosage./

Dosage. Conflicting views are held about dosage. Siebke (1934) believes that 0.1 mg. of oestrone given daily by mouth will cure hypoplasia; others are of the opinion that dosages amounting to 10 mg. of oestradiol benzoate per week are necessary.

Cases of hypoplasia generally need prolonged treatment, sometimes lasting for three to six months.

Inflammatory Conditions of the Tubes.

Such conditions may subside spontaneously, but improvement may be materially hastened by the administration of large doses of oestrogenic hormone (100,000 to 300,000 international units a week). Clauberg's (1938) important observation that even inflammatory lesions may respond to such treatment serves to underline the conclusion that oestrogenic therapy should always be tried before resorting to surgery, and that it should be continued during convalescence in cases in which operative treatment proves unavoidable.

Dangers of Oestrogenic Therapy.

These need cause little apprehension, assuming they are used with care. It is true that in experimental animals the administration of very large/

large doses of oestrogenic hormones has induced abnormal conditions - even chromophobe adenomas - of the anterior lobe of the pituitary gland. These findings, however, have very little clinical significance, for the doses were relatively much larger than those employed in human subjects. What is still more to the point, no reports of similar effects in human subjects have yet been published.

It is, of course, recognized that large doses of oestrogenic compounds may produce sterility in rodents, probably through the suppression of the pituitary gonadotropic secretion; and that in pregnant rodents such doses may cause abortion. But these observations, though highly significant in the study of reproductive physiology, have no direct bearing on the therapeutics of sterility, for neither sterilization nor abortion need be feared from the doses used in the treatment of the human female.

Progesterone.

It should be recalled that progesterone can only act on the uterus when this has been sensitized by the previous secretion or administration of oestrogenic hormone. The substance is now available in pure crystalline form, prepared either by extraction of/

of corpora lutea of animals or from natural sterols (cholesterol, stigmasterol). It can be obtained from the latter either by direct degradation of the side chain of the molecule or by more complex methods involving the intermediate formation of an androgenic compound. The biological activity is the same whatever the method of preparation, for the chemistry of progesterone is now precisely known and its manufacture can be accurately controlled.

The standardized commercial preparations of progesterone are oily solutions of the crystalline hormone - standardized in terms of international units, 1 mg. of the crystalline substance representing 1 unit - and they are all administered in the same way, namely, by intramuscular injections.

Statements in the literature dating from before the discovery of progesterone suggest that corpus luteum preparations may be active by mouth; but such reports must be accepted with some reserve. Peroral administration of progesterone in rabbits fails to produce the typical effects of this hormone; a synthetic compound (Pregneninolol), however, is active when given by mouth and may yet replace progesterone (Clauberg and Uestun, 1938; Zondek, 1939). In the doses generally employed progesterone seems to have no toxic or other side effects.

Indications for Administration of Progesterone.

Repeated Early Miscarriage.

Though it is difficult to assess the results statistically, progesterone appears to be of value in the prevention of abortion. It may therefore be used as an alternative to chorionic hormone in the treatment of established or suspected dyskyesis. The indications and mode of administration may be summarized as follows:

(a) Cases in which endometrial biopsy shows the occurrence of ovulation but leaves doubts about the intensity of the endometrial development (Mason, 1937). In these cases progesterone may be given during the second half of the cycle (from the fourteenth day onward) until menstruation occurs. If fertilization takes place and pregnancy is established, the treatment is continued for three to six months or replaced by the administration of chorionic hormone (PU).

(b) Cases in which dyskyesis may be expected on account of the condition of the semen. Treatment follows the same lines as in (a).

(c) Cases in which pregnancy is already established but in which the urine test or the reproductive history suggests the possibility of miscarriage.

Theoretically, it should be possible in non-pregnant women to adjust the dosage in each case, for the intensity of the response could be gauged by the repetition of biopsies in successive cycles. But the practical difficulties and disadvantages of such a procedure/

procedure rule it out completely, and needless to say, there could never be any question of adopting it in women already pregnant. Fortunately, the system of dosage arrived at empirically has proved satisfactory.

In most cases two weekly doses of 2 to 3 mg. seem to suffice.

Amenorrhoea of the Hypo-hormonal Type with Hypoplasia of the Uterus.

The oestrogenic treatment of hypoplasia of the uterus and endometrium associated with amenorrhoea of the hypo-hormonal type should be followed by the administration of progesterone. Such combined treatment reproduces the conditions of the normal menstrual cycle, and in cases of amenorrhoea serves to evoke both progestational development and menstruation (Kaufmann, 1932).

SURGICAL AND OTHER GYNAECOLOGICAL METHODS.

It may be stated as a general principle that major operative measures should not be employed for the treatment of sterility in women until (a) the male factor has been evaluated, and (b) non-operative and minor operative measures have failed. In this context the term "minor operative measures" is used in a wide sense./

sense. It includes tubal insufflation, intra-uterine injection of iodized oil, and the minor gynaecological procedures used in the treatment of some cases of dyspareunia and uterine retrodisplacement. When such treatment is ineffective, major operative measures may afford the only reasonable chance of restoring fertility.

The following measures are discussed in this section:

(i) Dilatation and curettage.
(ii) Treatment of dyspareunia and vaginismus.
(iii) Correction of uterine position.
(iv) Removal of fibromyomata.
(v) Restoration or improvement of tubal patency.
(vi) Intra-uterine transplantation of the ovary.
(vii) Ovarian surgery.
(viii) X-ray therapy.

(i) Dilatation and Curettage.

For many years this procedure has been used almost universally in the treatment of female sterility. In many cases it has been and is resorted to without any previous investigation and for no better reason than that it is sometimes followed by pregnancy within a short time. This apparent empirical justification is unsatisfactory, for the operation appears to act as a non-specific stimulus producing irritation and ultimately regeneration of the endometrium which can often be attained/

attained by more physiological methods - e.g., by the administration of oestrogenic compounds. It is only in rare instances that curettage reveals the presence of an unhealthy endometrium; and in the few cases in which it results in the removal of an obstructing cervical mucous plug some less drastic procedure - e.g., tubal insufflation or the passage of a sound - would obviously serve at least as well. It is probable that the use of dilatation and curettage will progressively diminish as the systematic application of other, particularly of endocrinological, methods increases.

(ii) Treatment of Dyspareunia and Vaginismus.

The treatment of dyspareunia is that of its cause. A fibrous or inelastic hymen should be excised. Tender carunculae myrtiformes usually have to be removed. Acute Bartholin abscesses should be incised and drained; but for chronic abscesses the best treatment in most cases is excision.

Enlargement of the vaginal introitus may in some cases be attained by the introduction of graduated glass dilators; but if this simple measure fails and the introitus remains so small that painless coitus is impossible, a perineoplasty should be carried out. The simplest operation of this type is by means of a vertical incision in the mid-line of the vaginal orifice into the perineum, the incision being then sutured transversely./

versely. Alternatively, the muco-cutaneous junction of the vagina and perineum may be incised transversely, the perineal muscles separated laterally with the fingers, and the incision then sutured.

For lesser degrees of developmental abnormality, e.g., vaginal septum, minor operative procedures may suffice, but for the major abnormalities extensive plastic operations, e.g., reconstruction of the vagina, may be necessary. Since many of these cases are associated with developmental abnormalities of the uterus or adnexa it is essential to determine the condition of these structures before any major plastic operation for the relief of sterility is undertaken.

Vaginismus.

Although true vaginismus is psychogenic, the milder forms often respond to local treatment. A useful measure is the application by the patient herself of a suitable local anaesthetic - e.g., a solution containing 10 per cent. cocaine. While this treatment is in progress the husband should use a condom in order to avoid diminution of penile sensitiveness. Gradually the concentration of the local anaesthetic is reduced, preferably without the knowledge of the patient, and ultimately, in successful cases, a bland ointment may be substituted and the use of the condom abandoned.

An/

An alternative procedure is to inject hypodermically a suitable anaesthetic oil, e.g., proctocaine 4 to 8 c.c., close to the vaginal introitus. Such measures are seldom useful, however, in severe or true vaginismus, which usually calls for some form of psychotherapy.

(iii) <u>Correction of Uterine Position.</u>

Most authorities now regard backward displacement as unimportant, provided that the tubes are patent and that there is no associated dyspareunia due to prolapse and tenderness of the ovaries. The association of backward displacement with distortion and thence apparent blockage of the tubes has been referred to. In such cases bimanual reposition of the uterus should be attempted, if necessary under anaesthesia. If the attempt is successful and repetition of the insufflation test shows that the patency of the tubes has been restored, an effort should be made to maintain the uterus in an anteverted position by means of a Hodge pessary. Only if this fails should a suspensory operation be undertaken.

In cases in which a retrodisplacement is "fixed" by pelvic adhesions, extensive operative treatment involving freeing of the uterus, tubes and ovaries and shortening of the round ligaments may be called for. Such/

Such shortening of the round ligaments is usually required in cases in which persistent dyspareunia is an associated symptom. During the operation it is useful to test the tubes for patency by inflating them from the uterine end, and for this reason an intra-uterine cannula should be placed in position before the operation starts. Inflation from the abdominal ostium is also useful if there is reason to doubt the patency of the tubal canal.

In considering the desirability of corrective measures, the condition of the patient must be viewed as a whole. Thus, displacement associated with hypoplasia should not be treated by correction of position only, but preceded and accompanied by dilatation of the cervix and suitable endocrine treatment.

(iv) Removal of Fibromyomata.

Fibromyomata are often associated with sterility and in some cases, by their action in distorting and obstructing the tubes or uterine cavity, may be responsible for it. In his study of the association between fibromyomata and sterility, Giles (1919) computed that 85 per cent. of the women in whom these tumours were present were either completely childless (60 per cent.) or had had no child for a number of years (25 per cent.). He concluded/

concluded that "the uterus that could have become pregnant but has not done so is the one that pays the penalty." From a less teleological point of view it may be argued that the correlation of the two phenomena arises from the fact that fibromyomata are conditioned partly and often, if not entirely and always, by disturbances of ovarian secretion - particularly it would appear by prolonged excessive secretion of oestrogenic hormone. They are thus not only associated with a condition which may underlie reduced fertility but may themselves serve still further to reduce it by causing what Meaker describes as "uterine blockade" or obstruction of the tubes.

Operative treatment is directed mainly to cases in which infertility appears to result from the mechanical effects of fibromyomata. In such cases - e.g., those in which nidation is prevented by a submucous tumour or in which repeated miscarriages have resulted from the presence of an interstitial tumour - a carefully executed myomectomy is often followed by successful pregnancy. It is, indeed, surprising how often a uterus distorted by numerous tumours and subjected to considerable trauma by myomectomy not only regains an approximately normal form but proves functionally adequate for a normal gestation. The cases in which success should be/

be least expected are those in which the tumours are of the subperitoneal type.

On the subject of technique it need only be said that in many cases it proves possible to remove quite a number of fibromyomata, both interstitial and submucous, through a single incision into the anterior wall of the uterus.

(v) <u>Restoration or Improvement of Tubal Patency</u>.

In considering measures to this end it must be recalled that tubal obstruction may be the sole cause of sterility or only one of several causes, and that it may represent a symptom rather than a cause. Thus, it may be due to inflammatory changes, either within the lumen or peritubal, or to endocrine deficiency (e.g., in cases of hypoplasia). The choice of treatment must therefore turn largely on the differential diagnosis. For example, an uncomplicated genital hypoplasia involving the tubes, and thus associated with tubal blockage, calls for endocrine treatment and not - at any rate in the first place - for surgical intervention.

The surgical procedures may be classified as follows:

(a) Uterotubal insufflation.
(b) Injection of a radiopaque oil (e.g., lipiodol).

(c)/

(c) Salpingostomy.
(d) Ovarian transplantation.

(a) Uterotubal Insufflation.

Uterotubal insufflation was first devised and used for diagnostic purposes, but its therapeutic value soon became evident. In some cases it was found that after a single insufflation blocked tubes became normally patent and some hitherto barren women conceived. Nevertheless, the systematic use of therapeutic insufflation was much delayed by the resistance of some investigators, who occasionally experienced mishaps or apprehended dangers resulting from the dilatation of the tubes or from the possible activation of quiescent foci of infection. Within recent years it has been established that the dangers are negligible as long as due account is taken of the obvious contra-indications, such as acute processes and pelvic swellings.

Both the principles of the method and its limitations may be readily understood if two of its effects are borne in mind. First, uterotubal insufflation resembles the clearance of other passages, in that it may remove mechanical obstructions, such as accumulated mucus or fine internal adhesions. Secondly, it may resolve muscular spasm. The second effect can often be demonstrated objectively and clearly by the use/

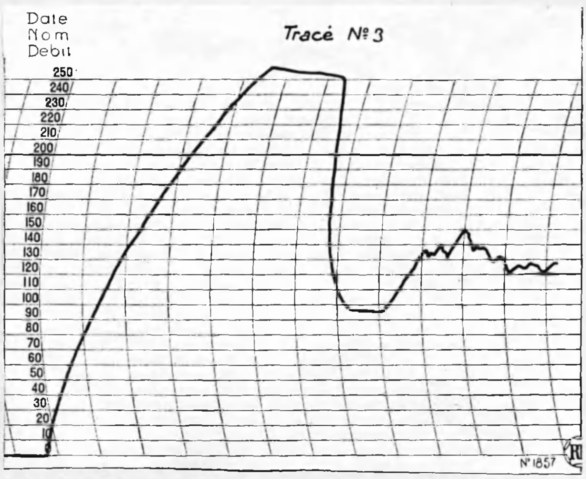


Fig. 28. Kymographic tracing, by means of Bonnet's apparatus, from a case in which the pressure of gas rose to 250 mm. Hg. It was maintained at that level, indicating complete tubal blockage. After about half a minute the pressure suddenly and unexpectedly fell, denoting the establishment of patency. Normal tubal peristalsis then began and continued around 130 mm. Hg. This tracing illustrates a therapeutic effect of insufflation. (By kind permission of Professor L. Bonnet).

use of the kymographic method, a lower pressure being needed at the second than at the first insufflation, even if a prolonged interval separates the two. Thus, spasm may be detected as well as cured by a single insufflation. This response of spasm to insufflation is an established fact, however obscure its aetiology may be. (See Fig. 28).

A single insufflation may not, however, succeed in resolving partial obstruction or spasm; in fact the procedure may have to be repeated several times over a period of weeks or months before the desired result is achieved. No definite rule can be given either about the number of insufflations that should be carried out or about the intervals that should elapse between them. But attention may be drawn to the special value of the kymograph in cases in which insufflation has to be repeated, for it provides permanent records by which the progress of the treatment can be judged. It may be added that the general remarks on diagnostic insufflation apply to therapeutic insufflation also; it should not be employed during the pre-menstrual phase of the menstrual cycle.

The indications for therapeutic insufflation fall into two groups: (1) stenosis, spasm or occlusion of the tubes; and (2) normal tubal patency. It is difficult to offer any precise explanation of the undoubted/

undoubted efficacy of insufflation in a considerable number of cases in the second group. It may act by producing dilatation of the cervical canal, with associated reflex stimulation of ovarian function, or by removing an obstructing cervical mucous plug; or it may act as a useful stimulus on tubal peristalsis.

Results of Insufflation.

The mechanical effect of tubal insufflation in restoring partial or complete tubal patency has already been discussed; it may be added that in many cases improved tubal motility can also be demonstrated after one or more insufflations. Therapeutic success, however, is not proved by the demonstration of mechanical effects, however impressive these may be. The true value of therapeutic insufflation must be assessed both by the frequency with which it is followed by conception and by the establishment beyond reasonable doubt of a relation between the effect and its apparent cause. To provide a standard by which it may be decided whether or not pregnancy is directly attributable to insufflation, Rubin (1932) has laid down the following conditions:

(1) The age of the patient should be thirty years or over.

(2) Pregnancy must follow within two months of insufflation.

(3) Marriage should have lasted three years or more.

(4)/

(4) The patient must not have been treated by any measure other than by insufflation.

(5) The insufflation should have been carried out within the first two weeks of the last regular period or in the pre-ovulation stage.

(6) The patient must not have taken contraceptive precautions for at least one year before insufflation.

Rubin's statistics and conclusions (1932) may be summarized shortly. Of 398 patients (244 with "primary" and 154 with "secondary" sterility) who became pregnant after insufflation, 123 (21.6 per cent.) had peritubal adhesions or stenosed tubes. In this series 67.6 per cent. of the pregnancies occurred during the first six months following insufflation, 42.2 per cent. within two months, and 27.9 per cent. within one month. Of the 244 patients with "primary" sterility and the 154 with "secondary" sterility who became pregnant, 22.1 per cent. and 44.1 per cent. respectively had been married for over five years before treatment by insufflation. The treatment was successful in twelve women who had been sterile for more than fifteen years. In 247 of the 398 successful cases (62.1 per cent.) insufflation was the only treatment employed.

The combination of insufflation with pelvic diathermy appears to have been successful in the hands of some workers in a relatively high proportion of cases. Thus/

Thus Mintz (1936) reports that in forty-four cases of tubal obstruction subjected to such combined treatment patency was established in twenty-five. In nine of the twenty-five successful cases pregnancy occurred and resulted in living children; in two others pregnancy was followed by miscarriage.

(b) Injection of Radiopaque Oil (e.g., Lipiodol).

This procedure, designed for diagnostic purposes, may also be used therapeutically. In some cases a single injection for hysterosalpingography is followed by pregnancy; in other cases pregnancy follows repeated injections. According to some authors the injection of iodized oil serves not only to resolve minor obstructions in the tube, but to stimulate genital function and to exert a mildly antiseptic effect on the uterine and tubal mucosa. Reports in the literature (Béclère and François, 1932; White, 1939) indicate that the expectation of success is in the same order as in cases treated by insufflation.

The use of hysterosalpingography for diagnosis has already been described. Radiographic control is also required when the injections are made for therapeutic purposes, and not more than one injection per month is advisable. The occurrence of untoward/

untoward reactions and possible dangers following the injection of iodized oil into the uterus and tubes have already been discussed. Titus and his co-workers claim that the non-irritating mixture of mono-iodomethane sulphonate of sodium with acacia used by them is entirely free of such disadvantages. It is still premature, however, to say whether it is as effective for therapeutic as for diagnostic purposes.

(c) Salpingostomy.

Plastic operations on the tubes, aiming at the restoration of a free passage, should be used as a last resort only. The following essentials should be satisfied before the operation is undertaken:

(1) Except in such conditions as severe congenital abnormality, neoplastic deformity, or flattening of the tubes, caused for example by fibromyomata or by ovarian tumours, other therapeutic measures such as endocrine treatment, insufflation and diathermy must have failed to restore patency.

(2) The condition causing obstruction of the passage must be chronic and must not have shown recent acute exacerbation.

(3) The patient must have been kept under observation for a period of several months. Periodic re-examination is necessary, for even large and bilateral adnexal masses may subside without causing permanent blockage of the tubes and without preventing the ultimate occurrence of pregnancy.

Observance/

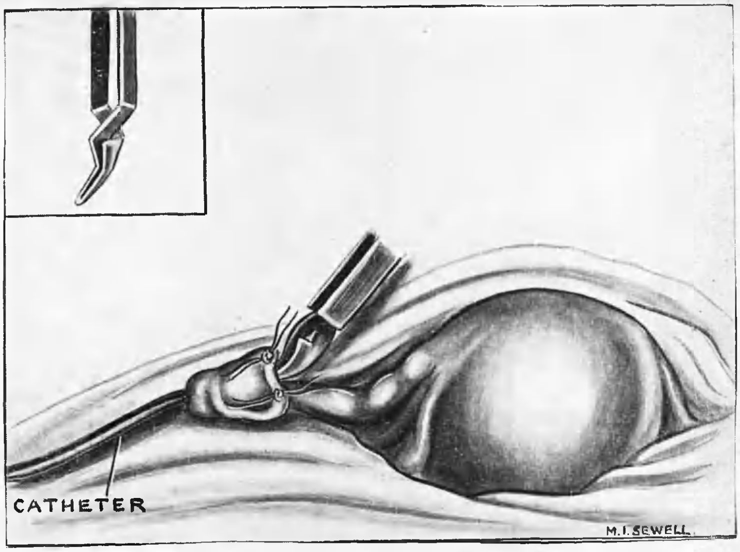


Fig. 29. Salpingostomy. Formation of circumcision cuff.

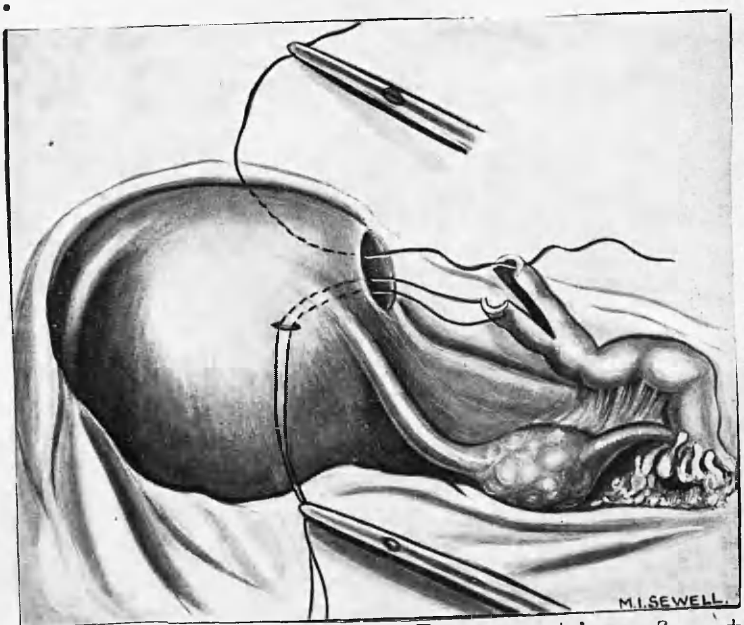


Fig. 30. Salpingostomy. Preparation for tubo-uterine implantation.

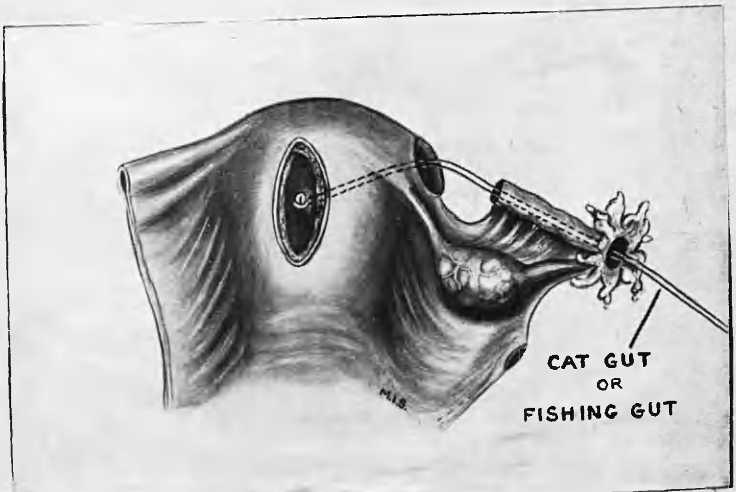


Fig. 31. Salpingostomy. Completion of tubo-uterine implantation.

are needed (Chalier, 1937; Hanak, 1938). The factors that determine choice of procedure are the condition of the tube and the site of blockage.

Blockage at the Fimbrial End. In this condition the circumcision cuff method gives the most satisfactory results. The tube is first opened and the distal portion then folded back over a special Bonney forceps. A small rubber catheter is passed into the lumen and the serosal edge is sewn back on to the peritoneal surface of the tube so as to form the cuff. The essential features of the method are shown in Fig. 29. (Lane-Roberts).

Blockage at the Uterine End. In this condition some form of tubal implantation is required (see Figs. 30 and 31). This may be preceded by (a) resection and anastomosis, (b) coring out the angle of the uterus, or (c) splitting the fundus laterally and antero-posteriorly.

Whatever the method employed, the essential principle of the operation is that the tube, from which the occluded portion has been excised, is brought into the uterine cavity. During the progress of the operation tubal patency must be tested, and to this end an inflation cannula should be placed in position before the abdominal incision is made. By means of a small rubber bulb/

bulb inflator inserted into the tubal ostium it is also possible, and desirable, to verify tubal patency from the fimbrial end. When the operation is completed a length of catgut or fishing gut should be passed through the new lumen into the uterine cavity and removed from the cervical canal ten days after the operation. While the salpingoplasty is in progress haemostasis is much facilitated by the use of ring forceps on the main arterial supply of the uterus. The lightest possible suture materials should be used on the peritoneal surface. (Lane-Roberts). A variation of this method has been described by Cullen (quoted by Engelmann, 1927).

Von Graff (1936) published a review of the seventy uterine implantations recorded in the literature; it appears that these were followed by pregnancy going to term in twenty-three cases. Forsdike (1936) gave details of ten isthmial operations involving excision of part of the isthmus with anastomosis of the two ends, implantation of the ampullary end into the uterine wall, and a sliding of the fimbrial end to the cornual extremity. Before closing the abdomen he insufflated the tubes, but even at a pressure of 300 mm. Hg. no air passed the junction, although in some of the cases it escaped at the site of the anastomosis. Further attempts/

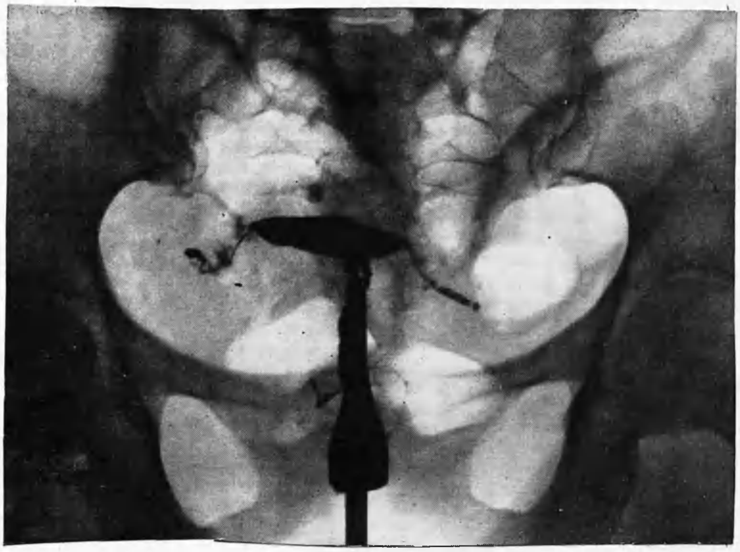


Fig. 32. Bilateral obstruction of the tubes in the region of their distal thirds. The extravasation of the iodized oil with a resultant hazy outline is one of the typical appearances in inflammatory conditions of the tubes. At operation gross inflammatory changes were found in and around the right tube, and moderate inflammatory changes and adhesions in the region of the ostium of the left. (This and Fig. 33 by kind permission of Dr. H.W. Post and Mr. V.B. Green-Armytage).

Fig. 33. Same patient as in Fig. 32. The right tube has been excised and a salpingostomy performed on the left which is now seen to be patent. There was a successful pregnancy in this case.

attempts at insufflation three weeks later also proved negative. Forsdike concluded that operations on this part of the tube offer no reasonable prospect of relieving sterility. Other gynaecologists, however, e.g., Bonney and ~~Green~~-Armytage, are more optimistic and have recorded a number of successful plastic tubal operations. Bonney (1937) had 18 per cent. of successes from salpingostomy and recorded five pregnancies following double and single implantation of the tubes with or without simultaneous salpingostomy. Green-Armytage (1937) performed salpingostomy in twenty-five cases (see Figs. 32 and 33), and tubal uterine implantations in three; there were four successful pregnancies in the former series and one in the latter.

Many authors have pointed out such dangers of salpingostomy as resuscitation of quiescent infective processes. Nevertheless, since the pioneer operations of Martin (1895) and McNaughton-Jones there have been many reports of cases in which the procedure has been attended with complete success. In a large series (Solomons, 1935), thirty of 366 women became pregnant after the operation; in sixty-eight other cases tubal patency was established but conception did not occur. In the women who became pregnant/

pregnant the excision was carried out at the fimbrial end in eighteen cases, at the isthmus in four cases, and at the interstitial portion in six cases. Two tubal pregnancies occurred, both after isthmial excision. In the sixty-eight cases in which, though tubal patency was established, conception did not occur, the excision had been carried out at the fimbrial end in fifty-six cases, at the isthmus in four cases and at the interstitial portion in eight. In another series comprising 818 cases, there occurred fifty-four pregnancies, but only thirty-six of these resulted in live children (i.e., one live child for every 22.5 operations).

Any estimate of the expectation of success must take account of the fact that the series which are recorded in the literature are, in general, those in which there have been a high proportion of good results. The probability that a given operation will result in the restoration of fertility is presumably much lower than the available figures suggest. On the credit side, however, it may be pointed out that tubal patency restored by salpingostomy may persist for long periods, if not permanently.

(d) Other Plastic Operations on Tubes.

Excision of one tube with concomitant

removal/

removal of the ovary of the opposite side does not always cause sterility in animals. The ovum may migrate from one side of the body to the other and reach the contralateral tube, just as particles of charcoal injected anywhere into the abdominal cavity may be found after a very short time in the uterus and cervix. Advantage may be taken of this migratory capacity in the ovum when a diseased tube has to be excised on one side of the body and a diseased ovary on the other. Dienst (1927) described a case in which he removed an unhealthy left ovary and excised the right tube. He then mobilized the left tube and attached its fimbrial end in the neighbourhood of the right ovary. The operation was completely successful and was followed by a restoration of fertility.

(e) Ovarian Transplantation with Plastic Operation on Tubes.

A number of cases have been recorded in which the ovary has been transplanted into the tubal lumen after salpingoplasty with a view to increasing the chances of the ova finding their way into and through the shortened tube. Several successes have been recorded, but in general the results are unsatisfactory and the procedure cannot be recommended (Martin, 1922).

(vi)/

(vi) Intra-uterine Transplantation of the Ovary.

This operation is seldom performed, for suitable cases are very few and results, both from the point of view of persistence of the graft and of successful pregnancy, are poor. It is generally agreed that transplantation should never be attempted in cases in which salpingoplasty is possible.

The technique of the operation must be adjusted to the individual case, but the essential procedure is to attach a small piece of ovary, containing as much cortical tissue as possible, to the endometrium by the least possible number of fine catgut sutures, access to the uterine cavity being obtained by an incision through the anterior wall.

Animal experiments (Wiesner, 1922; Przibram, 1922) indicate that the following conditions must be fulfilled if intra-uterine ovarian grafts are to maintain their functional state:

(1) The endometrium and the uterus must be well developed; thus the ovary of the rat can be grafted most easily into the puerperal uterus.

(2) The graft must be small in relation to the size of its bed; small grafts are more easily vascularized than large ones.

(3) A small amount only of ovarian tissue,

if/

if any at all, must be left at the original site; if a large amount remains, the graft is unlikely to take.

(4) Local reactions must be minimized by using as few sutures as possible; no sutures should pass through the germinal epithelium of the graft.

Intra-uterine ovarian grafting was first performed by Martin in 1895; the patient produced a live child. Bainbridge and Frank (quoted by Englemann, 1927) also reported successes. Of the forty-five cases described by Estes (1924) four became pregnant. Gellert (1923) published reports of two successful cases. Other authors, however, have stated that the intra-uterine grafts made by them have maintained their endocrine function but not served to restore fertility.

It may be suggested tentatively that ovarian grafts might have more chance of survival if, during the critical post-operative period when a grafted material either takes or perishes, uterine development is stimulated by oestrogenic treatment. Animal experiments also suggest that the development and regeneration of grafts is promoted by gonadotropic stimulation.

(vii) Ovarian Surgery.

This has an important bearing on the prevention/

vention of sterility. It cannot be too strongly emphasized that whenever possible some residue of healthy ovarian tissue should be left in the course of ovarian operations, not only in the hope of maintaining endocrine stability, but also for the preservation of potential fertility. Even very small residues may develop into larger and functional organs provided that an area of the cortex is unaffected. Such regeneration may possibly be stimulated by post-operative gonadotropic therapy.

It will be noted that a healthy residue was specified. There is evidence that a diseased ovary may inhibit the function of the healthy ovary of the other side. If, then, the ovary is grossly diseased, and the chances that any residual tissue would be healthy are small, the safest course is to remove it completely. Fortunately, as long as gonadotropic secretion is normal, removal of one ovary is usually followed by compensatory hypertrophy of the other.

(viii) X-ray Treatment.

So-called stimulating doses of X-rays have been employed in attempts to stimulate ovarian function. Irradiation has been directed either to the ovaries or to the pituitary. The utility of this method is extremely doubtful, particularly as much

safer/

safer and more easily controlled endocrine methods of stimulation are now available. In careless hands X-ray therapy may result in destruction of fertility.

ARTIFICIAL INSEMINATION.

(Kenneth Walker and B.P. Wiesner).

The fact that artificial insemination is discussed here must not be taken to mean that the procedure is adopted exclusively for the treatment of female infertility. In fact it is often resorted to on account of deficiencies in the male.

The procedure involves the deposition of semen, by means of suitable instruments, into the vagina, the cervical canal or the uterus, or its introduction into the tubes by pressure (insufflation method). It is practised widely and increasingly in animal husbandry, a field in which it offers many advantages over natural insemination. The semen produced at a single ejaculation can be diluted, divided into smaller samples and made to serve for the impregnation of several females, thus greatly increasing the number of offspring that can be bred from a sire in any one season. By modern means of transport it can be carried over great distances and used, as in Russia, for the improvement of poor or impoverished stocks. These procedures, of obvious genetic/

genetic and economic value, have no immediate application in the human subject, proposals to use semen of high biological value for mass insemination - the so-called "eutelegenesis" advocated by Brewer (1936) and Muller (1936) having met with little favour.

The recognized indications for artificial insemination may be summarized as follows:

(1) Impotence and other conditions - e.g., hypospadias or severe dyspareunia - in which normal deposition of the semen in the vagina cannot be effected (Hotchkiss, 1936; Engelmann, 1927).

(2) Cases in which, impregnation by the husband's semen being impossible (e.g., in azoospermia or severe teratozoospermia), it is decided to use "foreign semen," i.e., semen obtained from a donor. This procedure, though only seldom adopted, is becoming slowly but increasingly popular in the United States. A detailed report of a case in which it was utilized has been published by Hotchkiss (1936).

(3) Oligospermia associated with sterility. Owing to the small volume of semen, the vaginal pool which forms after insemination is liable to be acid in reaction and thus unfavourable to the survival of an adequate number of spermatozoa. Cervical insemination secures the deposition of the spermatozoa in a more favourable medium. This method has obvious advantages over the pre-coital use of alkaline douches, which are sometimes prescribed in such cases as a means of counteracting the vaginal acidity.

(4) Oligozoospermia or asthenozoospermia.

In/

In these conditions artificial insemination should be preceded by centrifugation in order to increase the density of the sperm population in the material introduced into the cervix. There is no evidence that, carried out carefully, this procedure damages the spermatozoa.

(5) Impairment of cervical passage. Artificial insemination may be carried out in this condition, but in most cases methods less troublesome both to the practitioner and the patient can be adopted.

Technique.

Timing of Insemination.

The systematic use of artificial insemination is too recent to permit any statement about an optional procedure, and the following remarks should be regarded as suggestions.

In view of the short survival period of spermatozoa in the female genital tract, insemination should be carried out as near to the presumptive time of ovulation as possible. The fulfilment of this condition forms one of the greatest difficulties in the successful application of insemination. The discussion earlier of the value and limitations of the existing methods for the detection of ovulation points to the conclusion that, although more recent developments promise well for the future, there does not yet exist any universally applicable clinical method for determining ovulation time with any degree of precision.

As/

As a rule general principles must still be relied on rather than specific tests, though the latter may be of help in arriving at a decision. Of the general principles the most important is that ovulation tends to occur during the mid-menstrual phase and most often approximately two weeks before the onset of an expected period. The first insemination should therefore be carried out at this time; but if the husband's potency permits repetition of insemination on one or more occasions, the procedure should be carried out just before, during and shortly after the middle of the cycle.

Provision must be made for the abnormally early or late occurrence of ovulation in some women. If conception does not occur after a series of artificial inseminations performed during the mid-menstrual phase, the dates should be changed first to the earlier part of the cycle and then, should conception still not occur, to the later part, i.e., between the fourteenth and the eighteenth day.

The signs and symptoms which are sometimes helpful in determining suitable dates of insemination were discussed earlier.

Collections of Specimens.

Semen should be collected, preferably as a masturbation/

masturbation specimen, after a period of continence which must be adjusted to the individual. It should be delivered into a dry clean specially prepared glass container, if possible within a very few minutes of insemination. Such a short interval may not be essential to success, but our knowledge of the duration of fertilizing capacity in human semen is too incomplete to warrant risks in such a vital matter.

If for any reason it is impossible to obtain a masturbation specimen, semen may have to be collected from the vagina after coitus. In this case it should be drawn up into a sterile dry pipette, contact between the seminal fluid and the rubber bulb being avoided. The pipette, like any other glass material, should be washed for prolonged periods before use.

The use of condom samples for insemination is deprecated. It is true that artificial insemination in animals often proves successful when semen has been collected in an artificial vagina made of rubber; but the semen in such cases is usually of high quality. In many cases of artificial insemination in the human subject this is not the case, and any procedure which may reduce the viability of the spermatozoa should be avoided.

Preparation/

Preparation of Semen.

When the semen is normal and insemination is carried out because of sex difficulties such as dyspareunia, no special preparation of the semen is needed. It is deposited in the vagina or the cervix immediately or as soon after ejaculation as possible. Similarly the semen need not be specially prepared in mild cases of oligospermia. In pronounced oligozoospermia, however, the semen should be transferred to a dry and sterile centrifuge tube with a cone-shaped bottom and centrifuged at high speed (at least 2,500 revolutions per minute) for several minutes. The spermatozoa are thus concentrated in a small volume at the bottom of the tube and form a more densely populated specimen for insemination.

Introduction of Semen.

(a) Vaginal Insemination. This procedure, resorted to when the semen is normal, calls for very few precautions. A dry unlubricated vaginal speculum is placed in position and any excess of vaginal secretion is removed by means of a wide-mouthed pipette. The semen is then drawn up in a pipette prepared for the purpose. This is inserted through the speculum which is then withdrawn, leaving the pipette in such a position that its opening lies in the immediate vicinity of the external os. After withdrawal of

the/

the speculum the semen is ejected into the vagina. This order of procedure is adopted in order to avoid the risk of an outflow of semen at the moment at which the speculum is removed.

(b) Cervical Insemination. For this procedure it is usual to employ centrifuged semen. The cervix is first cleaned but without the use of antiseptics. In some cases it is advisable to free the cervix of mucus, e.g., when a viscous plug is present. Nearly all the supernatant fluid left above the sediment of spermatozoa is then drawn up into the pipette and discarded. With the same pipette the sediment is stirred gently into the small volume of liquid remaining (about 0.15 to 0.2 c.c.) and this concentrate is then drawn up into the pipette. Care must be taken to avoid compressing the rubber bulb forcibly, lest the semen should travel to the upper end of the pipette and into the bulb. The mouth of the pipette is inserted into the os and the semen concentrate is delivered with very gentle pressure into the cervical canal. A slight loss of material is inevitable.

Needless to say, a similar procedure may be adopted with semen which does not show oligozoospermia, but this does not need centrifugation. In fact, cervical insemination has been commonly used by German workers in cases of dyspareunia and in other circumstances in which the normality of the semen has not been in question. Some surgeons do not use pipettes for cervical insemination but prefer either syringes with long blunt cannulas or special glass instruments.

(c)/

(c) Intra-uterine Insemination. This method has been used by German and Italian workers. The procedure is practically identical with that described in (b). It is doubtful whether it is justified or even helpful, except possibly in women with extremely narrow cervical canals. Kurzrok (1937) states that intra-uterine insemination is sometimes rendered difficult by the fact that seminal fluid may stimulate uterine contractions which result in its expulsion.

(d) Tubal Insemination. This method has been described in American and German papers (Dickinson, 1922; Sellheim, quoted by Engelmann, 1927). It aims at delivering the semen under gas pressure directly into the tubes. The method has no physiological basis; it has not been extensively tried and in the present state of experience it cannot claim any advantage over cervical insemination.

(e) Deposition Method. Pust (1914) described a method whereby a cervical occlusive cap was used for securing close contact between the entrance to the cervix and the seminal pool. The semen was deposited into the cap which was then placed in position over the cervix. The method appears to have no advantages.

Post-Operative Procedures.

No special precautions need be taken after the completion of insemination and the woman may leave immediately or after a short rest. It may not be out of place, however, to repeat the warning about miscarriage after conception resulting from subfertile semen. It is my practice to prescribe injections of

chorionic/

chorionic hormone during the second half of any cycle during which insemination has been carried out.

Results.

Engelmann's very comprehensive review (1927) surveyed 185 recorded cases with sixty-five successes; but it should be pointed out, first, that a large number of unsuccessful attempts have not been reported in the literature, and, secondly, that in many of the published cases the semen employed was normal, the reason for insemination having been impotence of the husband. Comparatively few case reports have appeared since the publication of Engelmann's review (e.g., Hotchkiss, 1936; Seguy and Vimeux, 1933).

The results are of greatest interest in cases in which the semen is of low quality. Walker and Wiesner have used artificial insemination in twenty-three cases in which treatment of men suffering from teratozoospermia. and oligozoospermia was followed by reduction in the number of abnormal forms without a corresponding increase in the sperm count. Concentrates of semen were used in all except one of the cases, the sediment obtained by centrifugation being deposited on to the external os or, more frequently, within the cervical canal. In most cases the procedure was unsuccessful, but in six cases conception took place after five to twenty-one attempts. In one/

one of these cases fertilization may have been produced by semen which was obtained from the vagina after intercourse on the fifteenth day of the cycle; but insemination was repeated with a masturbation sample on the seventeenth day and it may have been then that conception occurred.

Of the unsuccessful cases some may be omitted from consideration since the patients did not consent to the frequent repetition of the procedure which may be necessary for success; but in nine cases there were eleven to twenty-six attempts at insemination without any success.

The future of the method must depend largely on whether it will become possible precisely to synchronize the occurrence of ovulation with the deposition of semen. This end may perhaps be attained either by the discovery of more accurate methods than are at present available for determining ovulation time or by the adoption of methods for inducing ovulation at will.

PART II.

INTRODUCTION.

The series which I propose to describe now and which forms the basis of this study, consists of five hundred consecutive and unselected patients who have been under my care or observation from July 1933 to February 1943, and who complained of the infertility of their marriage. No cases of "relative sterility" nor any with a history of miscarriage are included.

It is proposed to deal with the subject in the following order:-

1. The age incidence of the patients and the duration of marriage:
2. Analysis of the tubal status -
   (a) Tubal insufflation - number performed, complications which may arise and details of insufflation findings;
   (b) Hysterosalpingography, similarly:
3. Endometrial Biopsy.
   (a) Number performed - general observations;
   (b) Details of cases exhibiting anovular cycles;
   (c) Details of endometrial tuberculosis:
4. Examination of the Husband.
5. Treatment.
6. Results of Follow-up.

The age incidence is as follows:-

Age.	No. of Patients.	Percentage.
Under 20 years	7	1.4
20-30	326	65.2
30-40	163	32.6
Over 40 years	4	0.8

These figures show no features of note, corresponding to the expected finding that about two-thirds of the patients are in the 20-30 years age-group.

The duration of marriage is shown below:-

Duration of Marriage.	No. of Patients.	Percentage.
Under 1 year *	23	4.6
1-5 years	322	64.4
5-10 years	134	26.8
Over 10 years	21	4.2

* This, of course, refers to the date when first under observation: subsequently it was learned that eight of them had the same complaint a varying number of years later.

The above table calls for little comment except possibly that one might have expected a relatively higher incidence in the 5-10 years group. It illustrates the fact which/

which is a matter of common clinical observation that a large number of couples, when their marriage has proved infertile after five years, do not seek medical advice on this point, but seem to have reconciled themselves to infertility. This matter will later be commented upon when the results of treatment are discussed.

The routine of investigation employed, briefly stated, was as follows: (1) complete history and physical examination, (2) tubal patency tests by insufflation (since early 1937 almost wholly by the kymographic method), and (3) endometrial biopsy. Hysterosalpingography was performed in many of the patients, mainly for correlation with insufflation results and to determine the site of blockage in non-patent tubes. The husbands were examined and semen tests performed in as many cases as possible by Dr. W.S. Mack at Glasgow Royal Infirmary.

The investigations will now be described: it is proposed firstly to deal with the results of studies of tubal patency and function.

ANALYSIS OF THE TUBAL STATUS.

The methods employed in investigating the status of the Fallopian tubes were (1) peruterine insufflation with carbon dioxide gas, both with and without/

without the aid of a kymographic apparatus and (2) the injection of lipiodol into the uterus and tubes - hysterosalpingography. A detailed account of the findings now follows.

Tubal Insufflation.

In 20 patients of the total series, a diagnosis of the tubal status was not made, for one or other of the following reasons: (1) stenosis of the cervical canal or internal cervical os, or (2) nervousness or apprehension on the part of the patient, or (3) failure to return for further study - this was sometimes due to the patient living a considerable distance out-of-town. Thus, the total number of patients whose tubes were insufflated amounted to 480. Whenever possible, two tests (or more) were done at varying intervals, as it was considered that a definite diagnosis, more especially in cases of suspected blockage, could not be made on the result of one test. This view received strong support as the result of subsequent tubal investigations and in the light of follow-up results. This will be referred to later. One insufflation, only, was performed in 248 patients. The remainder (232) had two or more insufflations: in most instances this was done simply as a confirmatory/

tory procedure, often to compare the findings with and without anaesthesia, but, in 22 patients, six or more insufflations were done for reasons of study and experiment. The figures in this group are as follows:-

Six	insufflations	were	performed	in	11	cases;
Seven	"	"	"	"	4	"
Eight	"	"	"	"	2	"
Nine	"	"	"	"	1	case;
Twelve	"	"	"	"	1	"
Fourteen	"	"	"	"	1	"
Twenty-three	"	"	"	"	1	"
Twenty-five	"	"	"	"	1	"

Fuller details and the results of these studies will be described later.

The total number of insufflations performed in the whole series is 1,003.

Complications were rare, much the commonest being momentary faintness; this generally occurred when the patient (not anaesthetised) sat up too quickly. Four patients had a more severe fainting attack which necessitated their detention for 1-2 hours. None insufflated at the out-patient department had to be admitted on the same day to hospital as a result of the procedure, but three patients who developed salpingitis or a more extensive pelvic infection and had subsequently to be admitted to hospital call for more detailed consideration. The following brief details/

details give the essential features in these cases:

(a) Leslie, Case 169. She was aged 27 and married 5 years when she was first insufflated on January 8th, 1937. Tubal patency was diagnosed. 18 days later the test was repeated with the same result. On the conclusion of the test endometrial biopsy was performed. Three days later both insufflation and biopsy were repeated. On the evening of the same day menstruation commenced and continued for the usual period of 3 days. On the following day she was admitted urgently to hospital with acute salpingitis; her temperature was 100.6°. Slight elevation of temperature continued intermittently for 16 days. She remained in hospital for 4 weeks.

Four and a half years later she reported that she was well, menstruation was regular and painless, and that she had not become pregnant.

(b) Barclay, Case 247. She was aged 28 and married 5 years when she was insufflated on January 19th, 1938. Tubal blockage was diagnosed. Fourteen days later (menstruation being due in 3 to 4 days), endometrial biopsy was performed. Two days later menstruation commenced and on the second day was accompanied by severe pain. The flow had its usual duration and the pain seemed to subside. However, about seven weeks later she reported to hospital with recurrence of the pain: examination revealed a large cystic swelling on the left side of the uterus. Her temperature was 99.2° and did not rise above this figure while she was under observation. She remained in hospital for nine days and went out of her own accord against medical advice. Seven weeks later she was admitted urgently to the

Western Infirmary, Glasgow, and operated upon at once. "The peritoneal cavity was found to be filled with pus and a large mass, the size of a cocoanut, was seen lying just below the umbilicus. Widespread adhesions to abdominal wall, pelvic wall, ovaries and colon were present. The mass was opened and a large quantity of pus evacuated." Pathological report - "In film, pus cells are fairly abundant. A few degenerate bacilli of indeterminate nature are found, chiefly intracellular. No tubercle bacilli found. No growth on culture. The wall of the abscess is of fibrous tissue and the lining is of acutely necrotic caseous material. In a few places the appearances are suggestive of tuberculosis, but no tubercle bacilli have been seen in sections." She was dismissed well, four and a half months later. A follow-up letter, three years later, failed to trace her.

(c) Jennings, Case 418. This patient was aged 30 and married almost 4 years when she was insufflated on November 18th, 1940. Tubal blockage was diagnosed. Four days later hysterosalpingography (lipiodol) showed bilateral tubal blockage at the fimbrial ends. Nine days later menstruation commenced and was apparently normal. Three days after its completion, another kymographic insufflation was performed, with the same result as before. Sixteen days later she was admitted to hospital with salpingitis and mild pelvic sepsis. Her temperature was elevated for 3 days - highest 100.6°F. - and she was dismissed well at the end of 9 days. One year later she wrote that she was well, menstruation regular and not painful and that she had not become pregnant.

Although/

Although the incidence of this serious complication is low (three times in the series of 480 patients, in a total of 1,003 insufflations), its occurrence means that every possible precaution should be taken to avoid the introduction of infection or its spread from a dormant tubal condition. A warning might be taken from case (a), namely that insufflation and biopsy should not be performed together at the premenstrual phase of the cycle. It has already been pointed out, of course, that it should be a general rule not to insufflate the tubes shortly before a 'period' is due. In Case (b) it is a mere matter of conjecture as to whether infection was introduced at the time of insufflation or at the time of endometrial biopsy, fourteen days later. In fact, the pathological findings at operation, subsequently, suggest that one or other procedure (or both) may have 'lit up' a general tubercular salpingitis. Case (c) is complicated by the fact that two insufflations were performed with a lipiodol injection interposed. No endometrial biopsy was performed. There, again, one assumes that the second insufflation was responsible. I had hoped to test the patency of the tubes in Case (a) after an interval of over a year in order to determine if patency were still/

still present, but the patient wrote to say that she was unable to call at the hospital. Whether or not infection had sealed the tubes cannot, therefore, be answered, but no pregnancy had occurred. In the other cases this possibility did not arise since non-patency already existed.

In concluding this consideration of the risk of salpingitis and pelvic infection after insufflation, it may reasonably be stated that, in view of its rarity and also since this complication occasionally occurs even after a dilatation and curettage under the strictest aseptic conditions, the risk is negligible. In 1932 Rubin reported that in his earlier cases he had three instances of "mild pelvic irritation," but that in his next 2,800 insufflations there were no unpleasant symptoms. The danger of embolism is also negligible. I have not encountered it in over one thousand insufflations. In Rubin's analysis of over eighty-six thousand insufflations done by various investigators, there is no record of its occurrence. It may safely be said that this complication can be dismissed from consideration, if the test is done correctly and in properly selected cases.

The tubal status of the 480 patients of the series is briefly summarised later. Since March 1937 the/

the kymograph has been used in conjunction with tubal insufflation and it may here be stressed that its value cannot be overestimated. The following figures include investigation both with and without its aid (Kymograph in 75 per cent. of cases).

Tubal Status of 480 Patients.

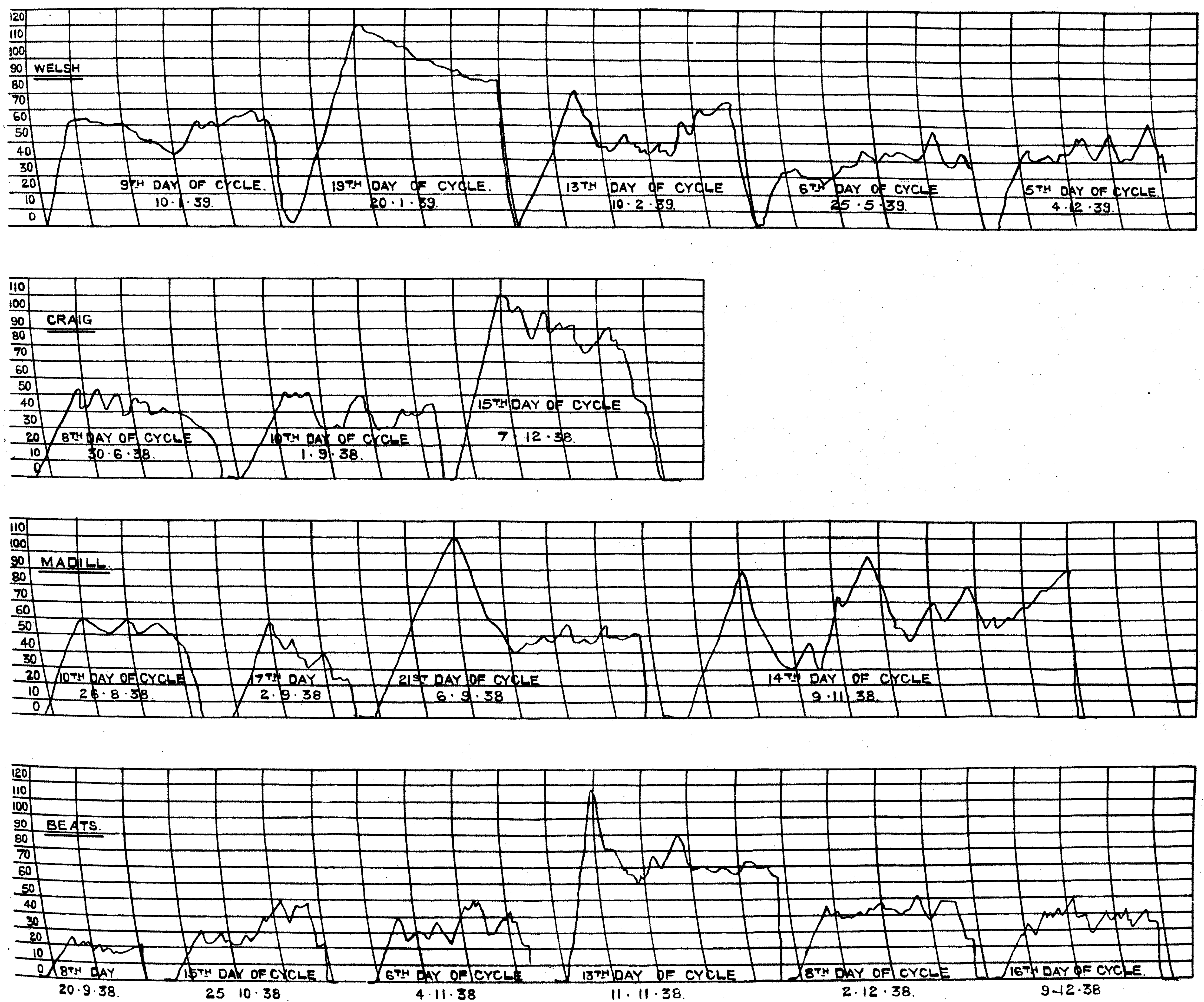
	Number of Patients	Percentage
Normal Patency	283	58.9
Non-patency	182	38.0
Spasm-normal patency	12	2.5
Peritubal adhesions and tubal strictures	3	.6

More detailed consideration may now be given to the features of note in each of these groups (I) Normal patency, (II) Non-patency, (III) Spasm-normal patency, and (IV) Peritubal adhesions and tubal strictures.

(I) NORMAL PATENCY.

In 75 per cent. of these 283 cases gas passed through the tubes at a pressure below 120 mm. Hg. Patency below 50 mm. Hg. or above 170 mm. Hg. was uncommon and did not amount to more than 5 per cent. of the total. There seems little point in more fully analysing these pressure findings or in reproducing the/

PLATE I.


WELSH
9TH DAY OF CYCLE. 10·1·39.
19TH DAY OF CYCLE. 20·1·39.
13TH DAY OF CYCLE 10·2·39.
6TH DAY OF CYCLE 25·5·39.
5TH DAY OF CYCLE. 4·12·39.
CRAIG
8TH DAY OF CYCLE 30·6·38.
10TH DAY OF CYCLE 1·9·38.
15TH DAY OF CYCLE 7·12·38.
MADILL.
10TH DAY OF CYCLE 26·8·38.
17TH DAY 2·9·38
21ST DAY OF CYCLE 6·9·38
14TH DAY OF CYCLE 9·11·38.
BEATS.
8TH DAY 20·9·38.
15TH DAY OF CYCLE 25·10·38
6TH DAY OF CYCLE 4·11·38
13TH DAY OF CYCLE 11·11·38.
8TH DAY OF CYCLE 2·12·38.
16TH DAY OF CYCLE. 9·12·38
0
10
20
30
40
50
60
70
80
90
100
110
120

the many and varied kymographic tracings. The pattern of the latter has already been described (page 88) and illustrated (Figs. 15, 16 and 17). But there are two sub-groups which may repay more detailed study and which it is proposed to describe now;

A. Cases in which six or more insufflations were performed.

B. Cases in which one (or more) of the insufflations showed apparent non-patency.

A. <u>Six or more insufflations</u> (9 Patients).

<u>Case No. 245</u>. <u>Welsh</u>.
First insufflation, 20.12.37, under anaesthesia, without kymograph - gas passed at 80 mm. Hg. Five further insufflations without anaesthesia were done with the aid of the kymograph at intervals until 4.12.39. The tracings show normal tubal patency, with slight variations in appearance: in all of them gas passed and contractions were recorded below 120 mm. Hg. (Plate I).

<u>Case No. 246</u>. <u>Craig</u>.
First insufflation, 13.1.38, without kymograph and without anaesthesia - gas passed at 80 mm. Hg. Five further insufflations without anaesthesia, with kymograph, until 7.12.38. Three characteristic tracings are shown in Plate I. These illustrate only one noteworthy feature, namely, that although patency and tubal peristaltic waves are present around 50 mm. Hg. in the first two tracings, the more rapid passage of gas in the third (evidenced by the more vertical ascent line) is followed by/

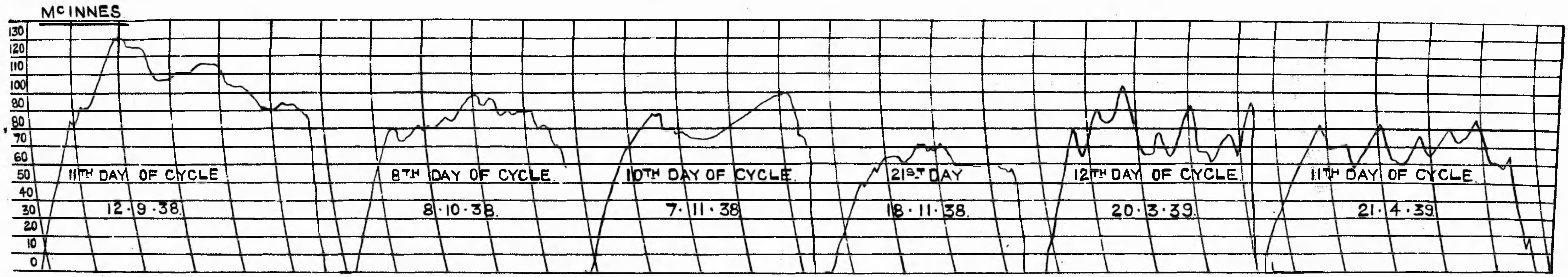
by patency around 110 mm. Hg. and tubal waves around 90 mm. Hg.

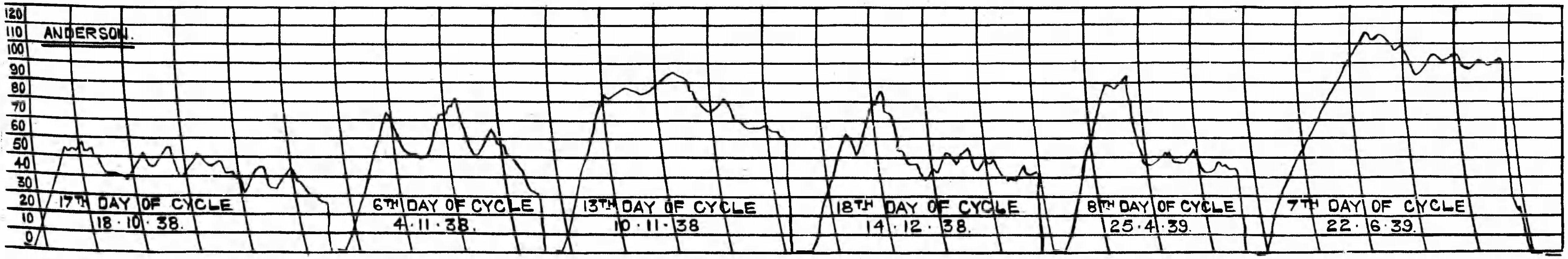
Case No. 269. Madill.
First insufflation, 11.4.38, no anaesthetic, kymograph, - gas passed at 80 mm. Hg. Six further kymographic insufflations without anaesthesia until 6.9.38. Four of the tracings are shown in Plate I and the points of interest are: the first shows rather flat waves (10th day of menstrual cycle), the second shows more active, deeper peristaltic waves (17th day of cycle), the third a moderate degree of spasm, followed by a pressure drop of 70 mm. Hg. with waves around 50 mm. Hg. (21st day of cycle) and the fourth very active, deep waves (14th day of a cycle two months later - ? ovulation time).

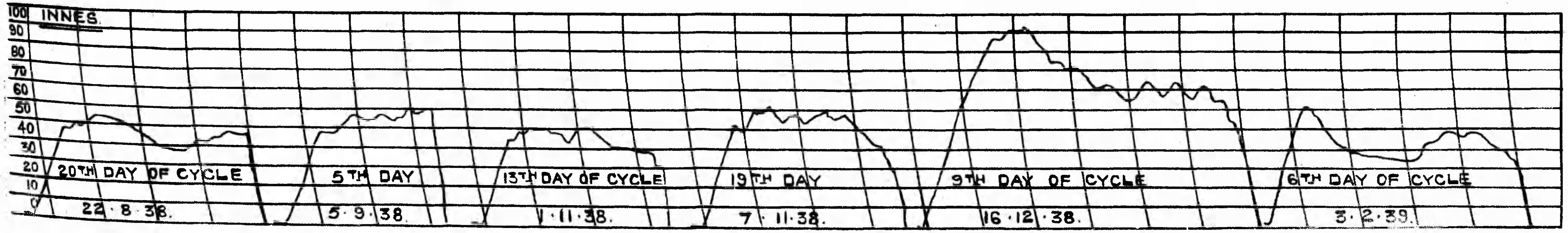
Case No. 307. Beats.
First insufflation, kymographic, 20.9.38, no anaesthetic - gas passed at 25 mm. Hg. Five further kymographic insufflations without anaesthesia until 9.12.38. All six tracings are shown in Plate I: all but one indicate tubal patency at pressures below 50 mm. Hg. The similarity in the tracings is noteworthy. The exception shows patency at 120 mm. Hg. and a mild degree of spasm with a fall of pressure of 50 mm. Hg., and normal waves following. On this occasion gas was purposely passed into the uterus at a speed much faster than was customary in order to study the effect. This case is of much interest not only because it shows patency at an unusually low level, almost identically reproduced in four subsequent insufflations at intervals, but also because of the unusually rapid onset and severity of shoulder pain experienced by the patient on sitting up after each test. Ten days after the last insufflation,

menstruation/

PLATE II


McINNES
130
120
110
100
90
80
70
60
50
40
30
20
10
0
11TH DAY OF CYCLE
12·9·38.
8TH DAY OF CYCLE.
8·10·38.
10TH DAY OF CYCLE.
7·11·38
21ST DAY
18·11·38.
12TH DAY OF CYCLE
20·3·39.
11TH DAY OF CYCLE.
21·4·39


120
110
100
90
80
70
60
50
40
30
20
10
0
ANDERSON.
17TH DAY OF CYCLE
18·10·38.
6TH DAY OF CYCLE
4·11·38.
13TH DAY OF CYCLE
10·11·38
18TH DAY OF CYCLE
14·12·38.
8TH DAY OF CYCLE
25·4·39.
7TH DAY OF CYCLE
22·6·39.


100
90
80
70
60
50
40
30
20
10
0
INNES.
20TH DAY OF CYCLE
22·8·38.
5TH DAY
5·9·38
13TH DAY OF CYCLE
1·11·38.
19TH DAY
7·11·38.
9TH DAY OF CYCLE
16·12·38.
6TH DAY OF CYCLE
3·2·39.

menstruation occurred. (Before her next 'period' was due she became pregnant).

Case No. 325. McInnes.

First insufflation, kymographic, 12.9.38, no anaesthetic - gas passed at 130 mm. Hg. Five further kymographic insufflations until 21.4.39: these showed patency around 80-90 mm. Tracings shown in Plate II. The only feature of interest is that the first four tracings showed a rather flat type of wave whereas the last two showed them to be deep and well-formed. The former type may be encountered in patients with scanty or irregular menstruation and who are excessively stout, as was the case in the patient under study. The alteration in the character of the tracings could not be correlated to any of the phases of the menstrual cycle. Two possibilities suggest themselves (1) that the improvement in tubal function was spontaneous and (2) that it was due to repetition of insufflation.

Case No. 328. Anderson.

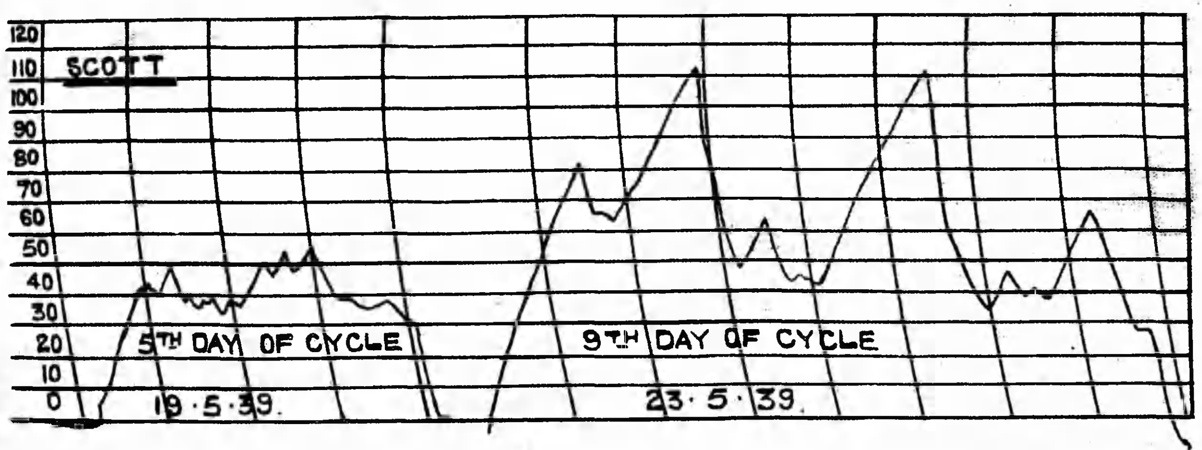
All six insufflations were kymographic and without anaesthesia. The first was on 18.10.38 and the last on 22.6.39. The tracings are reproduced in Plate II. Although all exhibit slight differences in patency levels, the extremely close resemblance between the fourth and fifth (at four and a half months interval) is very striking. The former was obtained on the eighteenth day of a menstrual cycle and the latter on the eighth.

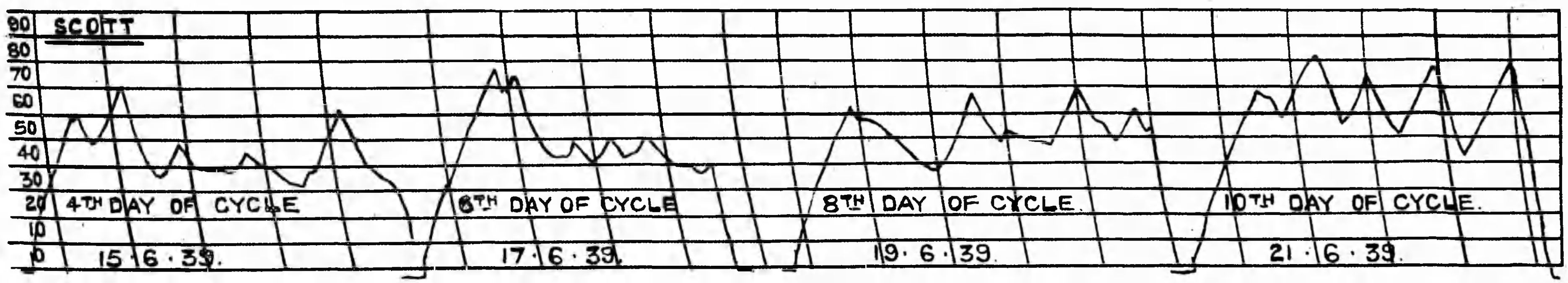
Case No. 407. Scott.

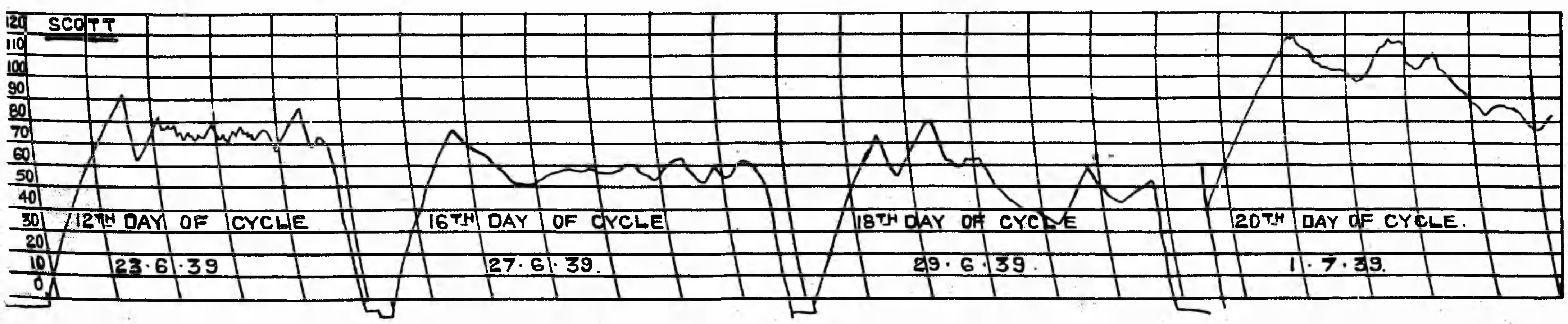
Twenty-three kymographic insufflations were performed without anaesthesia between 19.5.39 and 28.12.39. They fall into three groups, viz.,

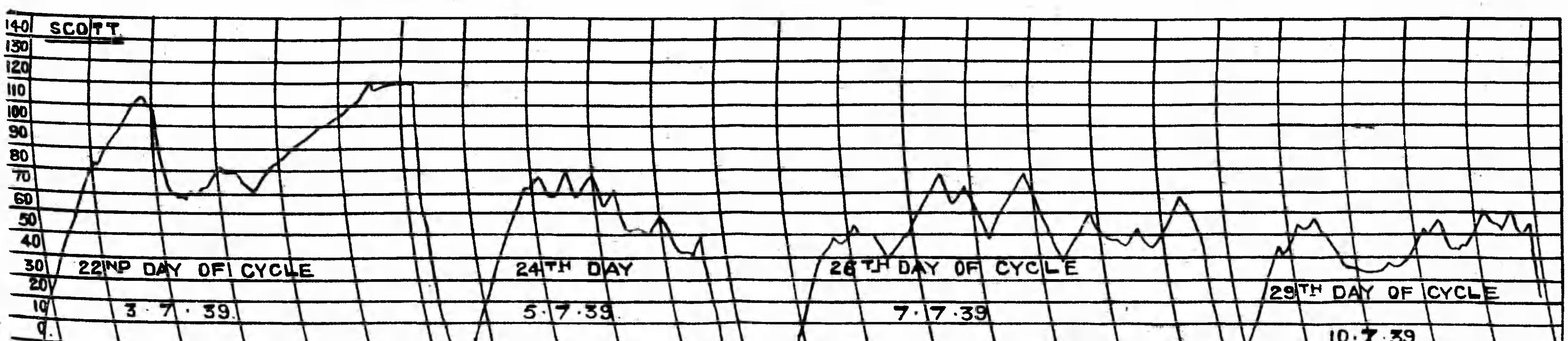
1./

PLATE III.


SCOTT
120
110
100
90
80
70
60
50
40
30
20
10
0
5TH DAY OF CYCLE
19.5.39.
9TH DAY OF CYCLE
23.5.39.


SCOTT
90
80
70
60
50
40
30
20
10
0
4TH DAY OF CYCLE
15.6.39.
6TH DAY OF CYCLE
17.6.39.
8TH DAY OF CYCLE.
19.6.39.
10TH DAY OF CYCLE.
21.6.39.


SCOTT
120
110
100
90
80
70
60
50
40
30
20
10
0
12TH DAY OF CYCLE
23.6.39
16TH DAY OF CYCLE
27.6.39.
18TH DAY OF CYCLE
29.6.39.
20TH DAY OF CYCLE.
1.7.39.


SCOTT
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0.
22ND DAY OF CYCLE
3.7.39.
24TH DAY
5.7.39.
26TH DAY OF CYCLE
7.7.39.
29TH DAY OF CYCLE
10.7.39.

1. Two in May 1939.
2. Twelve in June and July 1939 (intermenstruum).
3. Nine in December 1939.

The complete set of tracings is illustrated in Plates III and IV.

The insufflations in the first group were simply diagnostic and routine. During the tests, however, it was apparent that the patient was a very suitable subject psychologically and physically, for a contemplated study of tubal behaviour by means of frequent insufflations throughout a menstrual cycle. She was asked to report on the day after her next menstruation concluded: menstruation - from 11.6.39 until 14.6.39.

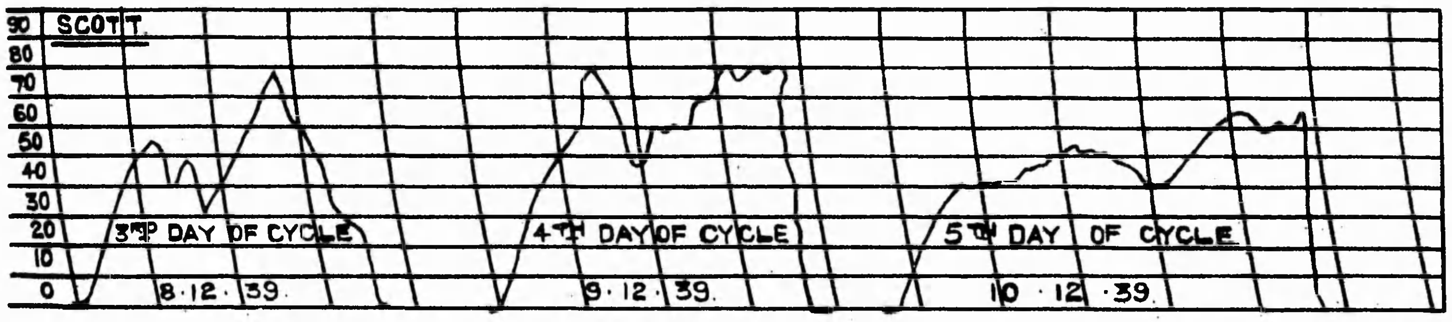
The first insufflation of the series was on 15.6.39 and it was repeated every alternate day until 10.7.39, with two exceptions - domestic reasons prevented her attendance on 25.6.39 and also on 9.7.39, but the latter omission is compensated for by an insufflation on the following day, which was two days prior to menstruation.

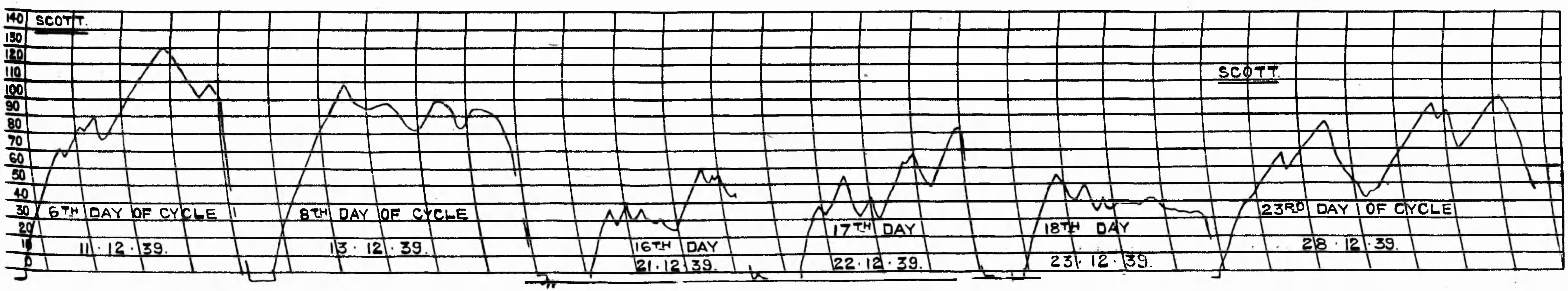
In all but two instances, frequent and active tubal peristalsis is present with patency and waves within the pressure limits of 50 and 80 mm. Hg. The exceptions occur on the twentieth and twenty-second day of the cycle, when patency is shown around 120 mm. Hg. and the tubal contractions are infrequent and of low amplitude. A striking tracing is that of 23.6.39 (12th day of cycle), showing unusually frequent peristalsis although of low amplitude (?ovulation).

Six months later it was decided to repeat a series as a basis for comparison. She was asked to report on the day following the conclusion of a menstrual

period/

PLATE IV


SCOTT.
90
80
70
60
50
40
30
20
10
0
3RD DAY OF CYCLE
8·12·39.
4TH DAY OF CYCLE
9·12·39.
5TH DAY OF CYCLE
10·12·39.


SCOTT.
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
6TH DAY OF CYCLE
11·12·39.
8TH DAY OF CYCLE
13·12·39.
16TH DAY
21·12·39.
17TH DAY
22·12·39.
18TH DAY
23·12·39.
SCOTT.
23RD DAY OF CYCLE
28·12·39.

period (5.12.39 - 7.12.39). As she had been quite undisturbed by the previous series, it was decided to try a patency test every day. Unfortunately, she was unable to attend as arranged and only nine tests were performed until menstruation intervened on 30.12.39, viz.:- December 8th, 9th, 10th 11th, 13th, 21st, 22nd, 23rd and 28th.

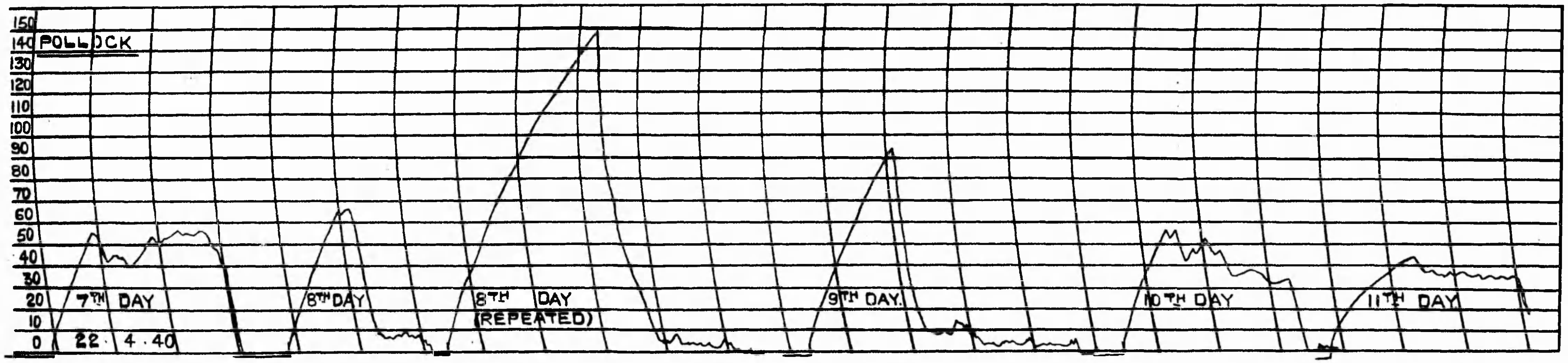
In this group, too, patency was established usually between pressures of 50 and 80 mm. Hg. with active peristaltic waves. More detailed comparison of both series, however, does not show any noteworthy cyclical correspondence. It is to be noted that the rate of flow of gas was at the constant figure of 30 ccs. per minute at every test.

Case No. 411. Innes.
All six insufflations were kymographic and without anaesthesia. The first was on 22.8.38 and the last on 3.2.39. The tracings are reproduced in Plate II. Only one of them shows active peristaltic waves, the others being very like each other showing patency around 50-60 mm. Hg. with rather feeble contractions.

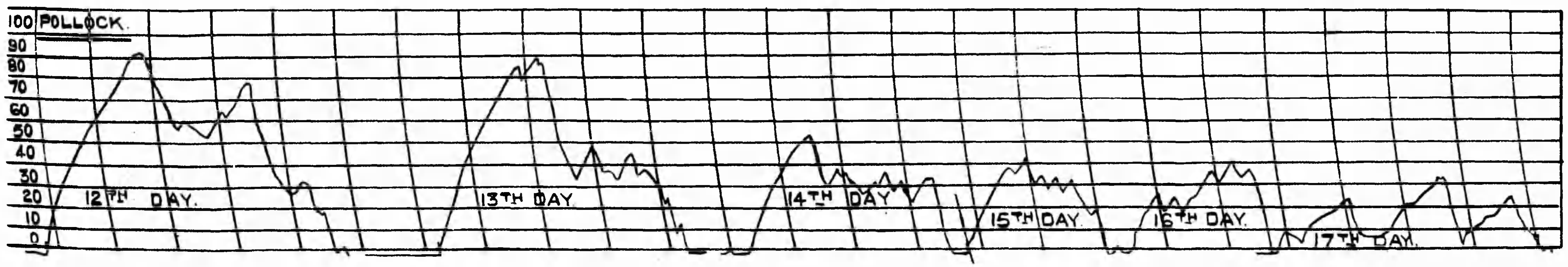
Case No. 474. Pollock.
Twenty-five kymographic insufflations were performed without anaesthesia between 4.3.40 and 17.10.41. After the first test she was asked to report on the day following a menstrual period. Thereupon a series was commenced on 22.4.40 and an insufflation was done every day until 9.5.40, on the evening of which day menstruation recurred. Plate V illustrates these eighteen results in a daily investigation of tubal behaviour in a complete menstrual cycle. This as far as can be ascertained from a study of the literature

and/

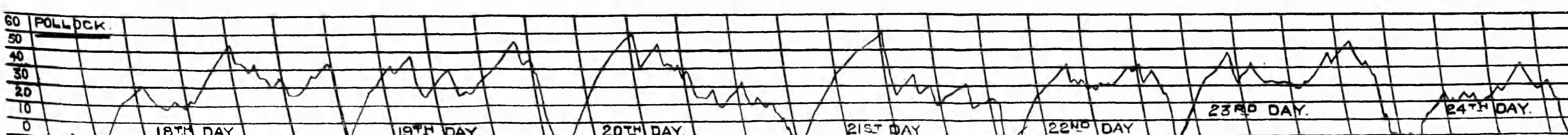
PLATE V.



POLLOCK
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
7TH DAY
22 . 4 . 40
8TH DAY
8TH DAY (REPEATED)
9TH DAY.
10TH DAY
11TH DAY



POLLOCK.
100
90
80
70
60
50
40
30
20
10
0
12TH DAY.
13TH DAY
14TH DAY
15TH DAY.
16TH DAY.
17TH DAY.



POLLOCK.
60
50
40
30
20
10
0
18TH DAY
19TH DAY.
20TH DAY.
21ST DAY
22ND DAY
23RD DAY.
24TH DAY.

and a personal communication from Rubin (Dec. 20, 1941), is the first occasion on which it has been done.

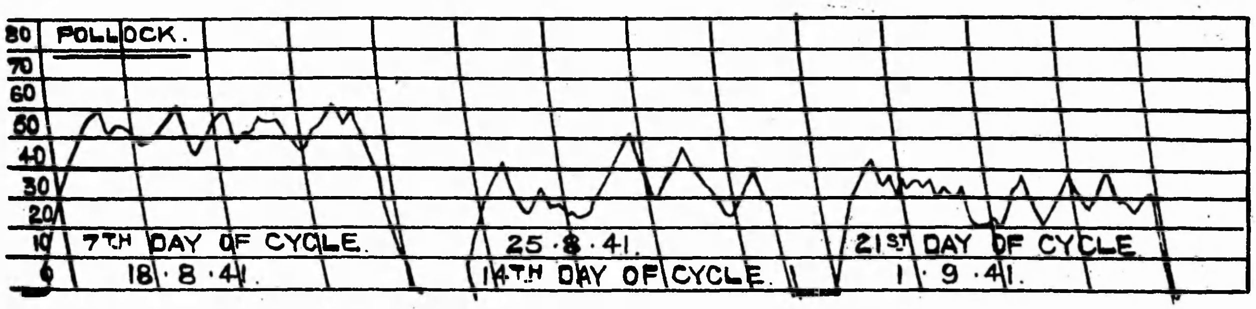
The similarity of most of the tracings throughout the cycle is striking and gives little indication that their appearance is influenced by or can be correlated to phases of endometrial or ovarian activity. A marked degree of spasm, followed by numerous waves, at very low pressure, is shown in the tracings of 23.4.40 (8th day) and 24.4.40 (9th day) and in a less typical form on the 12th and 13th days, but this does not recur. Since the rate of flow of gas was kept constant throughout (30 ccs. per minute) - this is an important advantage of the Bonnet kymographic apparatus - and no variation in procedure or circumstances was introduced throughout the series, it is difficult to explain why spasm occurred on two, only, of the eighteen days. With the exception of the four insufflations specified above, on all occasions gas passed below 60 mm. Hg.

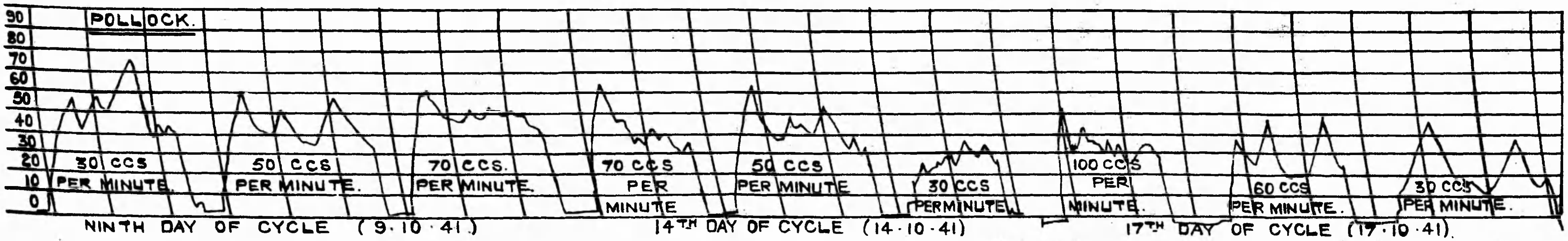
Some sixteen months later the patient reported to me, and the opportunity was taken of doing three insufflations at weekly intervals during a menstrual cycle. These are shown on Plate VI and represent the findings on the seventh, fourteenth and twenty-first days of the cycle. There is little difference in them except that the contractions on the fourteenth day are fewer but more pronounced. All bear a close resemblance to the findings in the larger series already described.

Two months later the following experiment was done. One one occasion insufflation was performed with gas passing at 30 ccs. per minute, immediately followed by gas at 50 ccs. per minute and immediately

thereafter/

PLATE VI


POLLOCK.
80
70
60
50
40
30
20
10
0
7TH DAY OF CYCLE.
18 · 8 · 41.
25 · 8 · 41.
14TH DAY OF CYCLE.
21ST DAY OF CYCLE.
1 · 9 · 41.


POLLOCK.
90
80
70
60
50
40
30
20
10
0
30 CCS PER MINUTE.
50 CCS PER MINUTE.
70 CCS. PER MINUTE.
70 CCS PER MINUTE
50 CCS PER MINUTE
30 CCS PER MINUTE
100 CCS PER MINUTE.
60 CCS PER MINUTE.
30 CCS PER MINUTE.
NINTH DAY OF CYCLE (9 · 10 · 41)
14TH DAY OF CYCLE (14 · 10 · 41)
17TH DAY OF CYCLE (17 · 10 · 41).

thereafter at 70 ccs. per minute. Five days later this was repeated, but with gas-rates in the reverse order. Three days later, a further test was done with rates of 100, 60 and 30. The results of these three tests were as follows: the first showed little appreciable difference in the tracings: the second and third showed a slight fall in the level at which patency was established when the rate of flow of gas was decreased. (Plate VI).

Summary.

1. Nine patients showing normal tubal patency were insufflated on six or more occasions.

2. One of them was insufflated twenty-three times and another twenty-five.

3. No ill-effects of any kind were produced either at the time or subsequently.

4. No great difference, either in the level at which patency is established or in the appearance of tubal contraction waves is usually seen in any given patient when insufflation is repeated even after several months.

5. Increase in the rate of flow of gas may be followed by a marked increase in the patency - pressure level and more active, deeper peristaltic waves. This, however, is not invariable.

6. Around ovulation-time (presumed), more active or more frequent peristalsis may be seen. This, also, is not invariable.

7. There is no indication that there is any constant close correspondence between the type of kymographic tracing/

tracing obtained (tubal patency and peristalsis) and the endometrial cycle or ovarian hormonal activity.

B. <u>Cases of normal patency which have shown at one insufflation (or more) apparent non-patency.</u>

In the course of repeated insufflations it became apparent that a number of cases of definite patency - confirmed, in all but three cases by the occurrence of 'shoulder-pain,' or subsequent pregnancy, or by the demonstration of pneumoperitoneum, or hysterosalpingography, - exhibited apparent non-patency on occasion. A study of this group (25 patients) may throw some light on this anomalous finding and may be of assistance in obviating a possible source of error. The findings may be summarised as follows:

(1) In nine patients, two tests, only, were performed, one showing patency and the other non-patency: in fifteen patients - three tests, two showing patency and one non-patency: in one patient - four tests, three showing patency and one non-patency. Thus, none of the "patency-cases" showed "non-patency" more than once.

(2) Anaesthesia was employed in twelve of the group, when insufflation showed "non-patency." In a further two, with anaesthesia, patency was shown, but/

but without it, non-patency. The remainder (11) had no anaesthetic at any insufflation.

Only in one instance of "non-patency" was insufflation performed premenstrually.

The conclusions that may be drawn from a study of this small group are (1) in cases of tubal patency, and isolated or occasional finding of apparent non-patency may occur and this equally in anaesthetised and non-anaesthetised subjects, and (2) the result of a single insufflation, with or without anaesthesia, showing apparent non-patency cannot be depended upon.

This latter conclusion will receive further consideration later when the results of insufflation are compared with (1) hysterosalpingography and (2) the incidence of pregnancy.

(II) NON-PATENCY.

The pattern of the tracing obtained in complete tubal blockage has already been described (page 89) and illustrated (Fig. 14).

There is no variation in this pattern and therefore no further analysis or study is indicated except to say that of 182 cases exhibiting non-patency, 105 were insufflated once only, 42 twice and the remainder (35) three times or oftener. Five cases were insufflated on six occasions or more: the following is a brief summary of them.

Case No. 103. McRuvy.

Seven insufflations were performed between 30.1.36 and 6.11.39. On the first occasion an anaesthetic was used but not on the others. The first three insufflations were done without the kymograph. All showed non-patency.

Case No. 279. Sharpe.

Six insufflations were performed without anaesthesia between 16.3.38 and 9.10.41, the first without the aid of the kymograph and the others with it. All showed non-patency under anaesthesia. The uterus was found to be very hypoplastic.

Case No. 288. Simons.

Eight kymographic insufflations between 9.5.38 and 9.5.39 without anaesthesia. On two occasions the pressure of gas was raised to 230 mm. Hg. All showed non-patency.

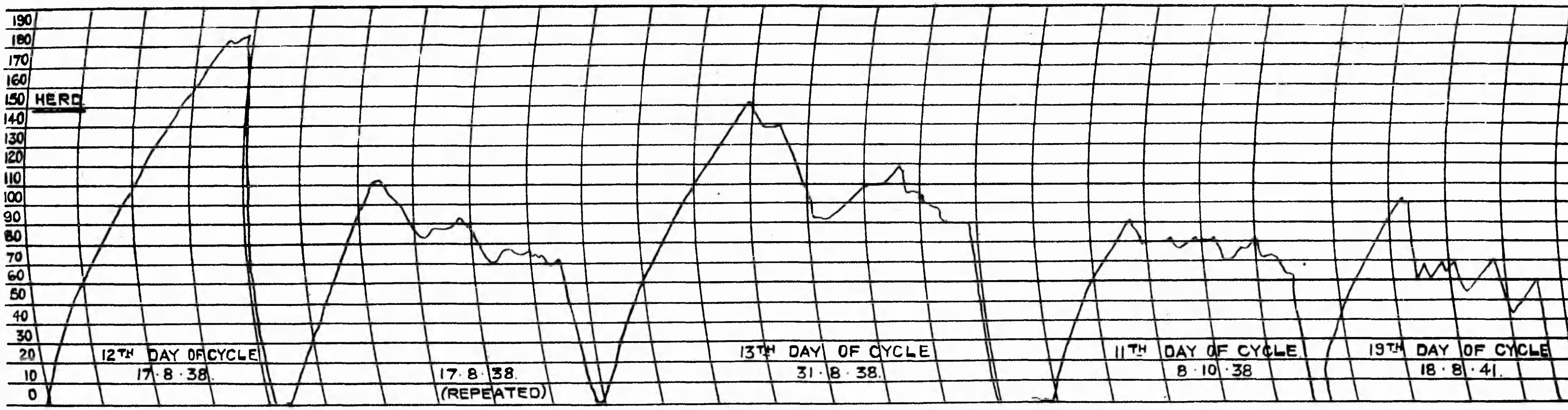
Case No. 338. Forrest.

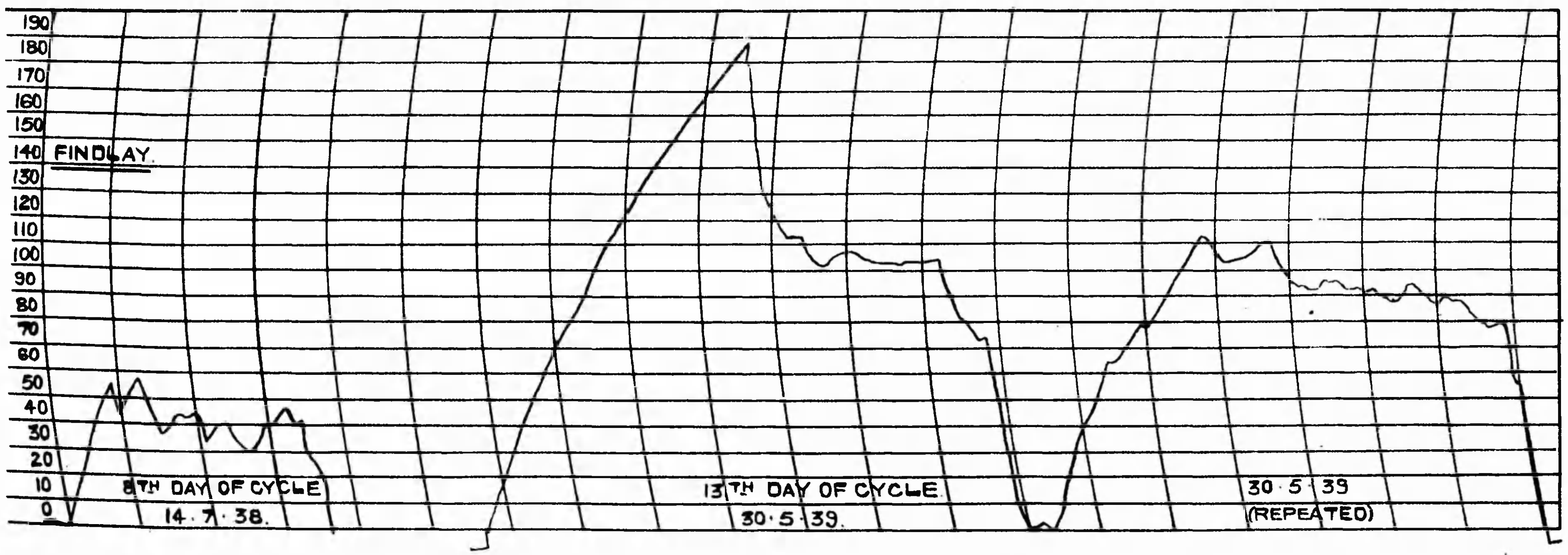
Six kymographic insufflations without anaesthesia were performed between 14.2.39 and 8.2.40. All showed non-patency. (This case will be referred to later as showing tuberculosis of the endometrium).

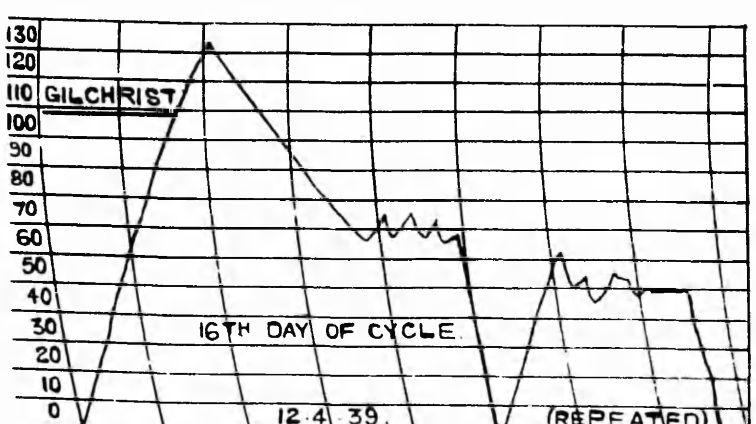
Case No. 445. Kennedy.

Seven kymographic insufflations were performed without anaesthesia between 15.8.39 and 2.9.41. All showed non-patency.

PLATE VII.


HERD
12TH DAY OF CYCLE
17·8·38.
17·8·38.
(REPEATED)
13TH DAY OF CYCLE
31·8·38.
11TH DAY OF CYCLE
8·10·38
19TH DAY OF CYCLE
18·8·41.


FINDLAY.
8TH DAY OF CYCLE
14·7·38.
13TH DAY OF CYCLE.
30·5·39.
30·5·39
(REPEATED)


GILCHRIST
16TH DAY OF CYCLE.
12·4·39.
(REPEATED)

Non-patency of the tubes is undoubted in these five cases, but, as a matter of interest, hysterosalpingography was performed (in four of them) and confirmed the insufflation findings. All had treatment during the course of these insufflations in an endeavour to restore tubal patency, but without avail: this will be discussed later. None became pregnant. Nor, indeed, was there any reason to doubt the diagnosis of non-patency in any case which was insufflated thrice or oftener, i.e. by a contrary finding on salpingography or by the recurrence of pregnancy. Only once when insufflation twice showed non-patency was the finding shown to be erroneous, but a single result was disproved subsequently in six cases by lipiodol and in twenty-seven cases by pregnancy ensuing. These cases will be discussed more fully later, but the conclusion already arrived at in another group of cases is corroborated in this group, namely, that one cannot depend on the accuracy of a single insufflation which shows non-patency.

(III) SPASM-NORMAL PATENCY.

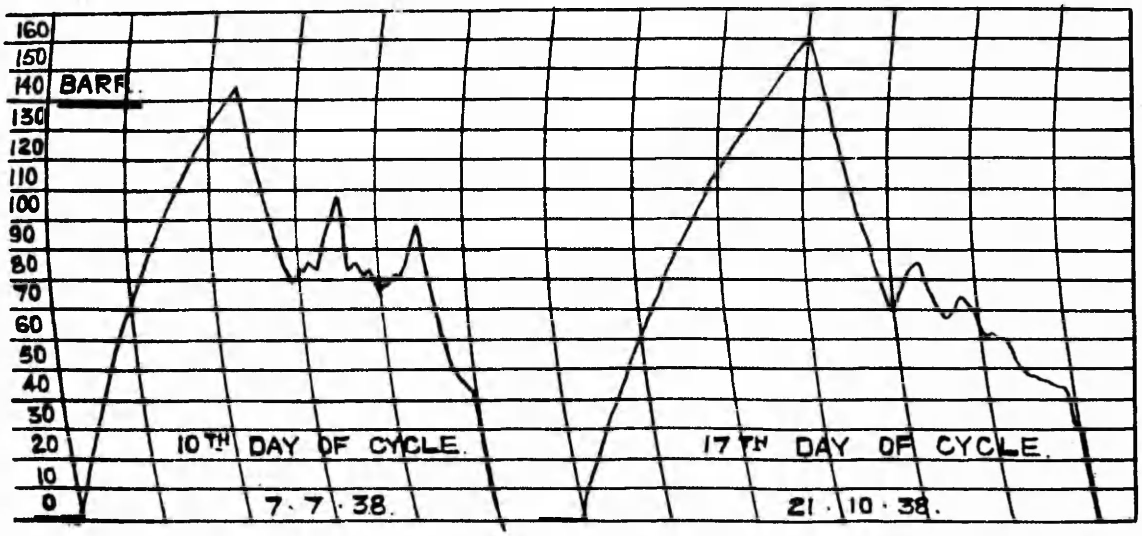
Twelve patients are in this category. The following brief details give the main results of insufflation.

Case No. 218. Herd.

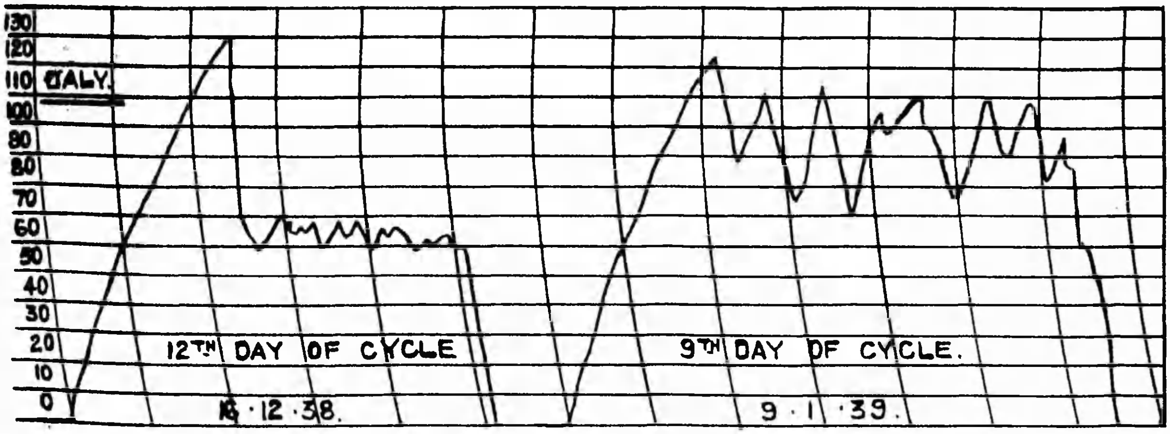
Six insufflations without anaesthesia between

30.9.37/

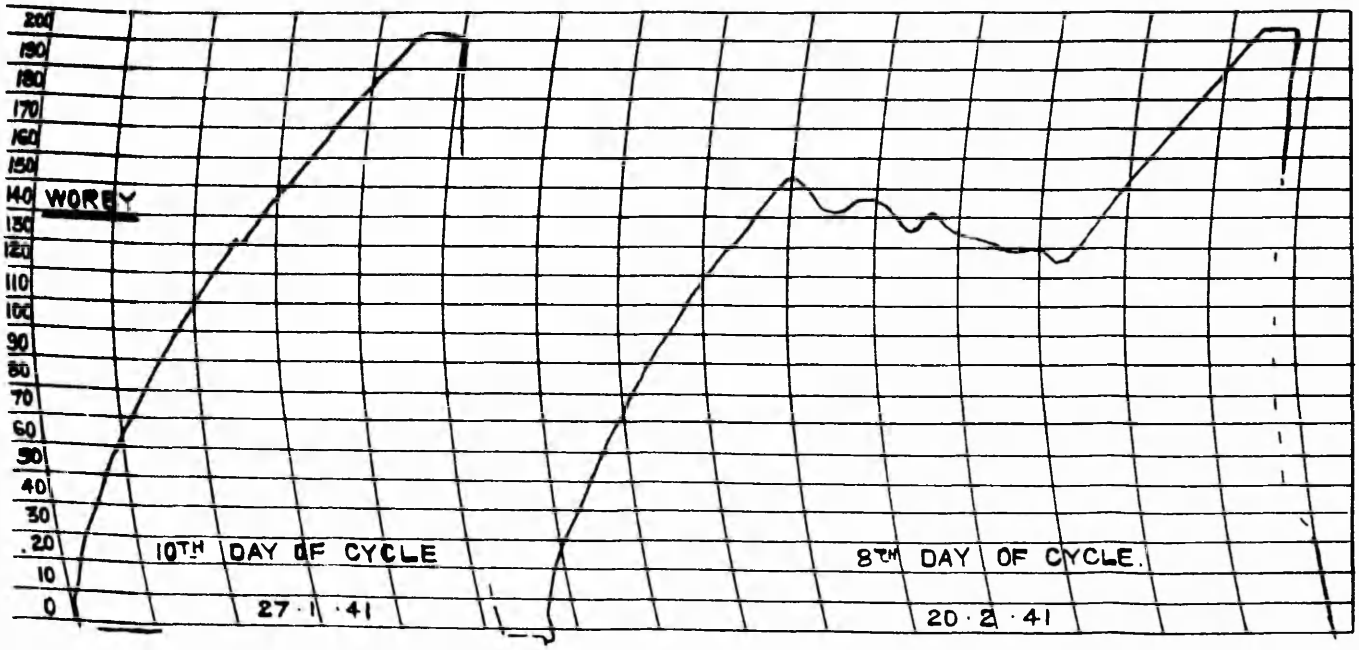
PLATE VIII



160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
BARF.
10TH DAY OF CYCLE.
7 · 7 · 38.
17TH DAY OF CYCLE.
21 · 10 · 38.



130
120
110
100
90
80
70
60
50
40
30
20
10
0
ITALY.
12TH DAY OF CYCLE
16 · 12 · 38.
9TH DAY OF CYCLE.
9 · 1 · 39.



200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
WOREY
10TH DAY OF CYCLE
27 · 1 · 41
8TH DAY OF CYCLE.
20 · 2 · 41

30.9.37 and 18.8.41: the first two results doubtful on account of cervical leakage, but regarded as suggestive of non-patency. Four subsequent kymographic insufflations are illustrated on Plate VII. The first shows patency around 180 mm. Hg., immediate repetition of the first showing contractions around 100 mm. Hg.: the second, patency at 150 with a fall of pressure to 90 and thereupon contractions: the third is normal and shows no spasm: the fourth, patency at 100 with a fall to 60 and then normal contractions.

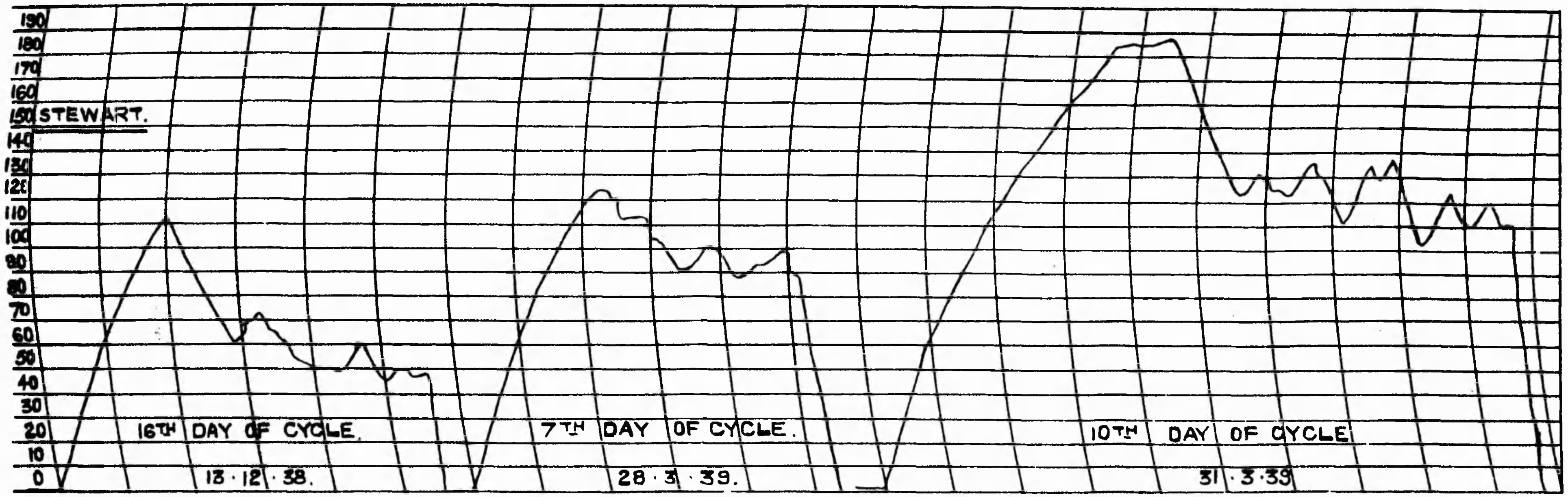
Case No. 222. Findlay.

Three insufflations without anaesthesia between 7.10.37 and 30.5.39: at the first, without kymograph, gas passed at 150 mm. Hg.; the second shows normal patency and contractions; the third is a very good example of spasm, the pressure rising to almost 200 mm. Hg. before uterotubal tone is overcome: there is a rapid fall to 110 mm. Hg. at which normal contractions occur - immediate repetition of the test shows active contractions around 110 mm. Hg. and absence of spasm. (See Plate VII).

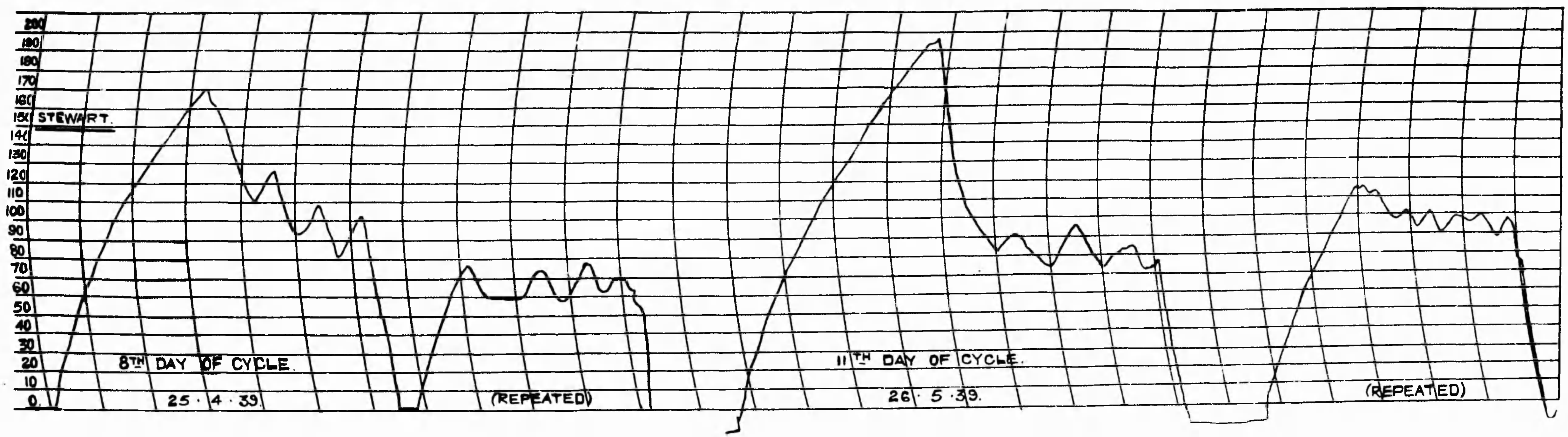
Case No. 242. Gilchrist.

Six kymographic insufflations without anaesthesia between 14.12.37 and 15.9.41: only on one occasion, 12.4.39, was spasm exhibited; pressure rose to 130 mm. Hg. and then fell rapidly to 70 mm. Hg., with the/

PLATE IX.



STEWART.
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
16TH DAY OF CYCLE.
18 · 12 · 38.
7TH DAY OF CYCLE.
28 · 3 · 39.
10TH DAY OF CYCLE
31 · 3 · 39



STEWART.
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0.
8TH DAY OF CYCLE.
25 · 4 · 39
(REPEATED)
11TH DAY OF CYCLE.
26 · 5 · 39.
(REPEATED)

the onset of normal contractions: immediate repetition of the test showed patency and contractions around 50 mm. Hg. (Plate VII).

Case No. 282. Barr.

Two kymographic insufflations without anaesthesia; in the first, 7.7.38, pressure rose to 140 mm. Hg. and then fell rapidly to 80 with the onset of contractions: a somewhat similar tracing was found on 21.10.38 - pressure rose to 160 and rapidly fell to 70: both are illustrated in Plate VIII.

Case No. 303. Daly.

Five kymographic insufflations without anaesthesia between 18.10.38 and 13.8.41: two tracings are reproduced on Plate VIII, the first (16.12.38) - twelfth day of cycle - illustrating spasm and the second (9.1.39) - ninth day of cycle - showing extremely deep contractions.

Case No. 322. Stewart.

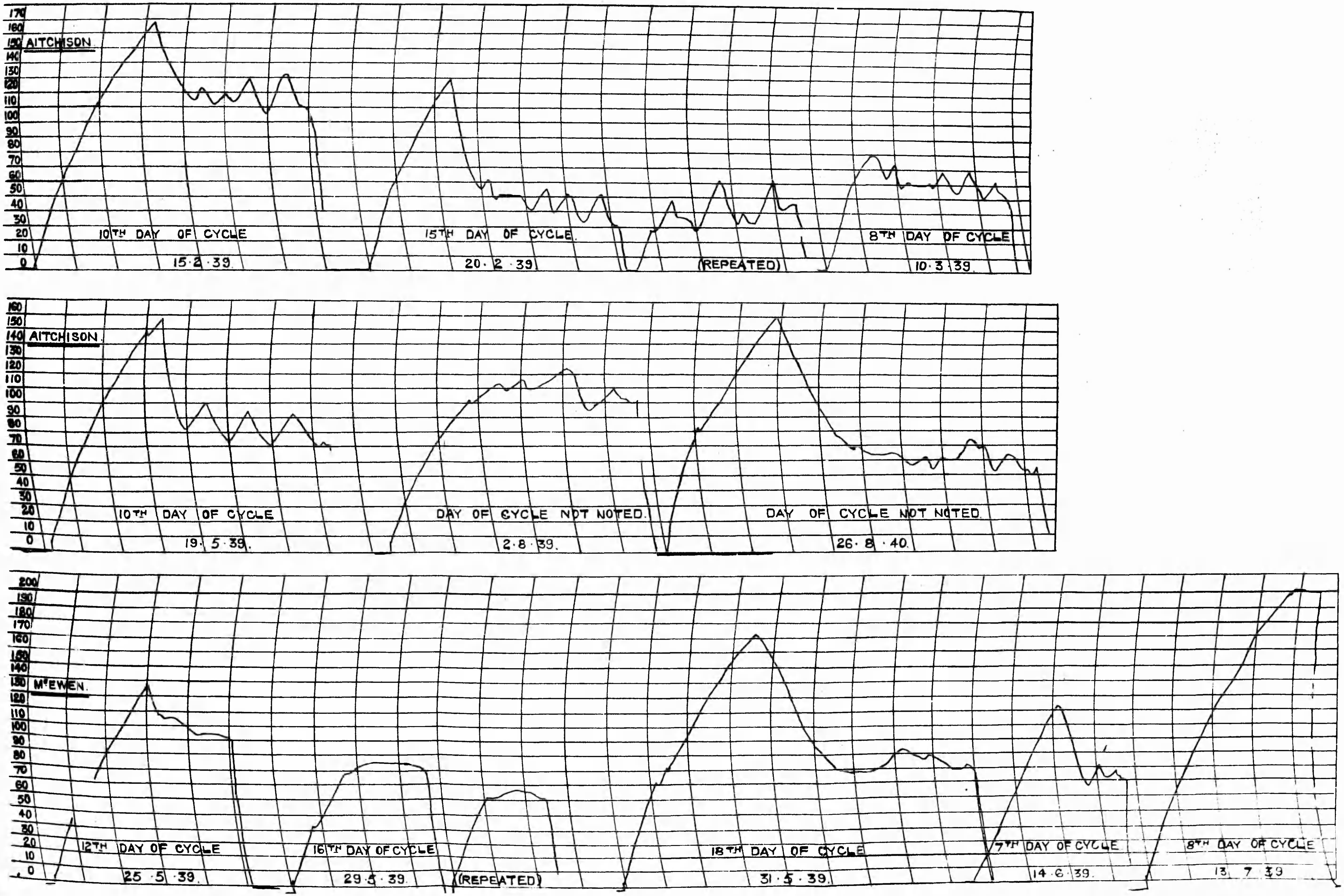
Twelve kymographic insufflations without anaesthesia between 10.10.38 and 13.11.39: five are illustrated on Plate IX: one of them (28.3.39) shows normal patency, but the others illustrate, especially 26.5.39, a very high degree of tubal spasm.

Case No. 350. Aitchison.

Nine insufflations without anaesthesia between 14.12.38 and 26.8.40, the first without kymograph and the others with it: six tracings are

illustrated/

PLATE X.


AITCHISON.
10TH DAY OF CYCLE
15·2·39.
15TH DAY OF CYCLE.
20·2·39
(REPEATED)
8TH DAY OF CYCLE
10·3·39.
AITCHISON.
10TH DAY OF CYCLE
19·5·39.
DAY OF CYCLE NOT NOTED.
2·8·39.
DAY OF CYCLE NOT NOTED.
26·8·40.
McEWEN.
12TH DAY OF CYCLE
25·5·39.
16TH DAY OF CYCLE
29·5·39.
(REPEATED)
18TH DAY OF CYCLE
31·5·39.
7TH DAY OF CYCLE
14·6·39.
8TH DAY OF CYCLE
13·7·39

illustrated on Plate X: four exhibit spasm, while two show normal tubal patency.

Case No. 395. Worby.

Two kymographic insufflations without anaesthesia, (1) 27.1.41 - apparent blockage at 200 mm. Hg.; (2) 20.2.41 - apparent patency at 150 mm. Hg. with tubal contractions and then rise of pressure to 200 mm. Hg., presumably due to spasm (Plate VIII).

Case No. 396. McEwen.

Five kymographic insufflations without anaesthesia, between 25.5.39 and 13.7.39: all are illustrated on Plate X: they show interesting variations in type.

Case No. 426. Sibbald.

Two kymographic insufflations without anaesthesia, the first on 4.7.39 and the second, three days later: both tracings shown on Plate XI, illustrating patency at very high pressure and clearly demonstrating spasm.

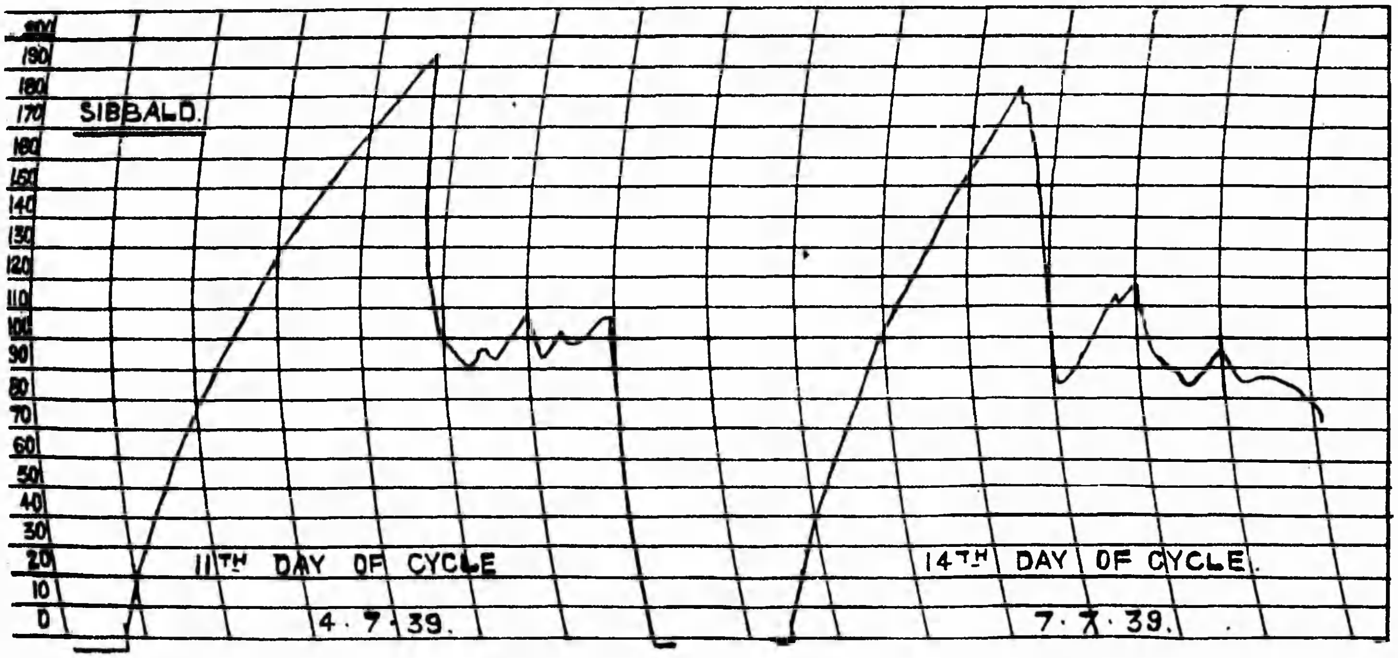
Case No. 455. Bradley.

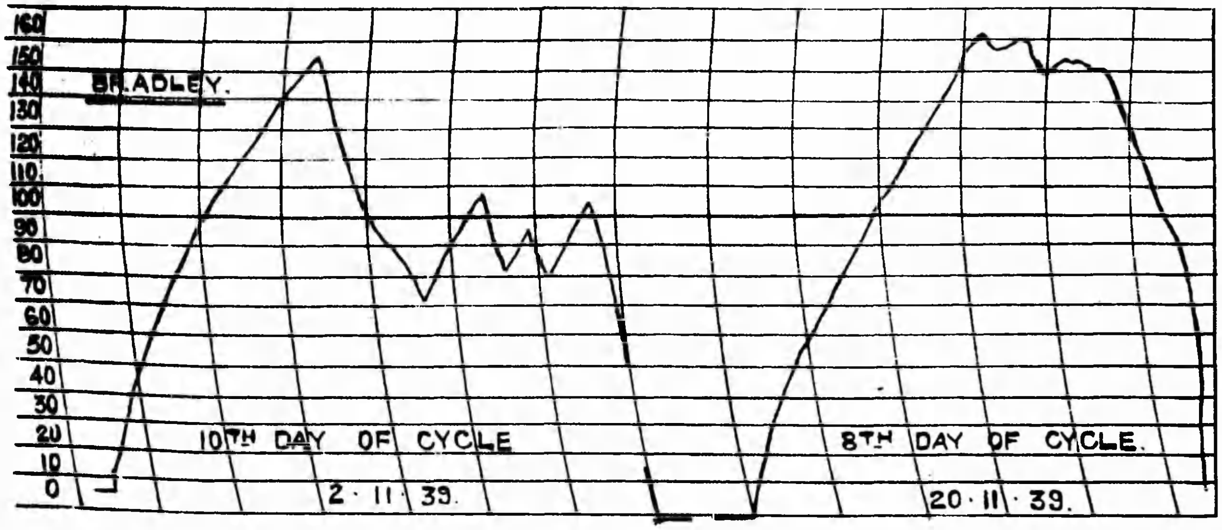
Two kymographic insufflations without anaesthesia; the first, 2.11.39, shows spasm with patency established about 150 mm. Hg., while the second, 20.11.39, shows no spasm but patency around 160 mm. Hg. (Plate XI).

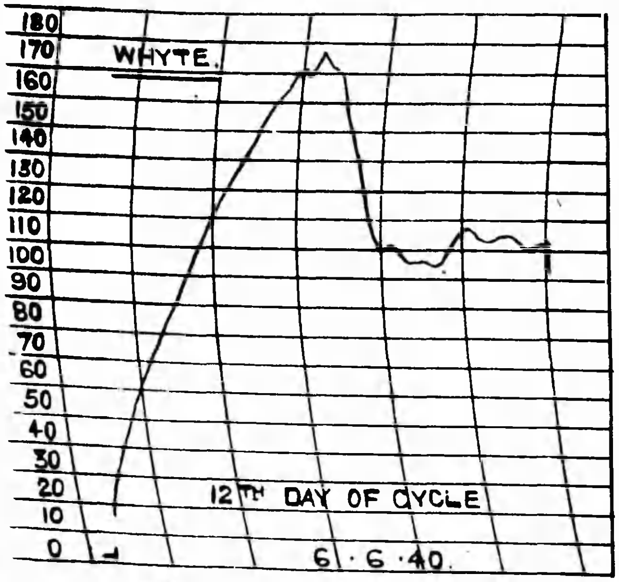
Case No. 488. Whyte.

Only one insufflation in this case (kymographic and without anaesthesia) - see Plate XI: pressure rose to

PLATE XI.


SIBBALD.
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
11TH DAY OF CYCLE
4 · 7 · 39.
14TH DAY OF CYCLE.
7 · 7 · 39.


BRADLEY.
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
10TH DAY OF CYCLE
2 · 11 · 39.
8TH DAY OF CYCLE.
20 · 11 · 39.


WHYTE.
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
12TH DAY OF CYCLE
6 · 6 · 40.

180 mm. Hg. and then rapidly fell to 110 when normal contractions commenced.

Three features of importance emerge from a study of this group,

(1) cases of tubal spasm may show, on occasion, apparent non-patency at 200 mm. Hg. (high degree of spasm),

(2) similarly, these cases may show occasional normal patency without spasm, and

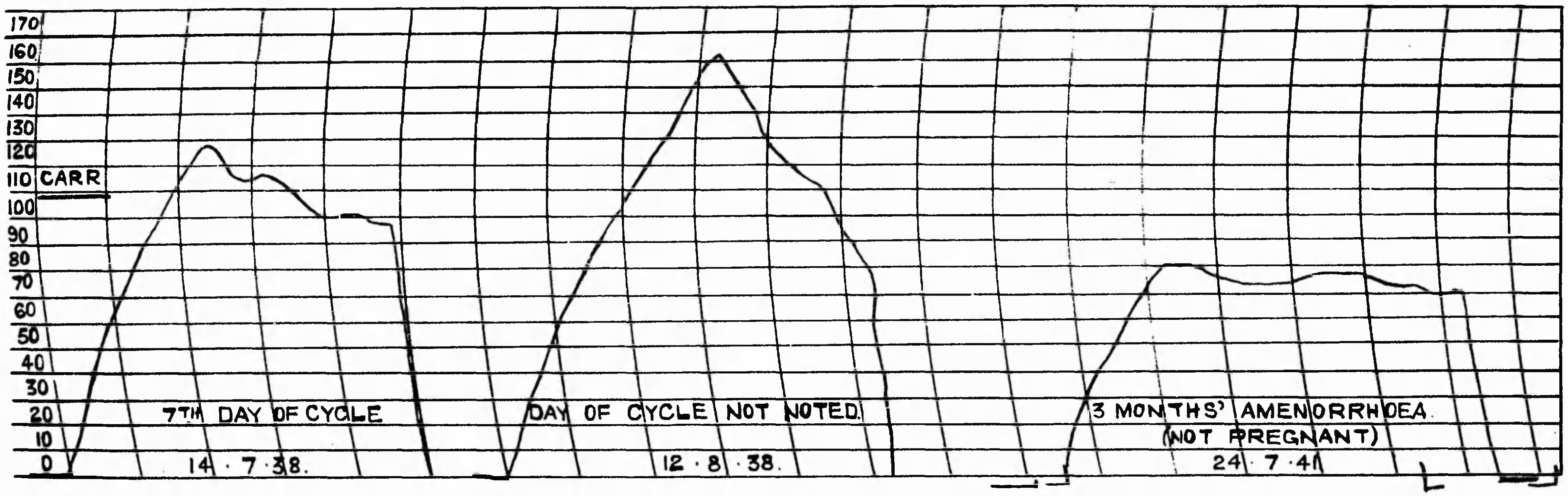
(3) the condition does not seem to predispose to infertility since five of the twelve (Cases 282, 322, 350, 395 and 396) became pregnant. (Moreover the husband of case 222 showed complete azoospermia on two tests). This incidence of fertility compares favourably with that of 75 in 235 normal-patency cases traced.

(IV) PERITUBAL ADHESIONS AND TUBAL STRICTURES.

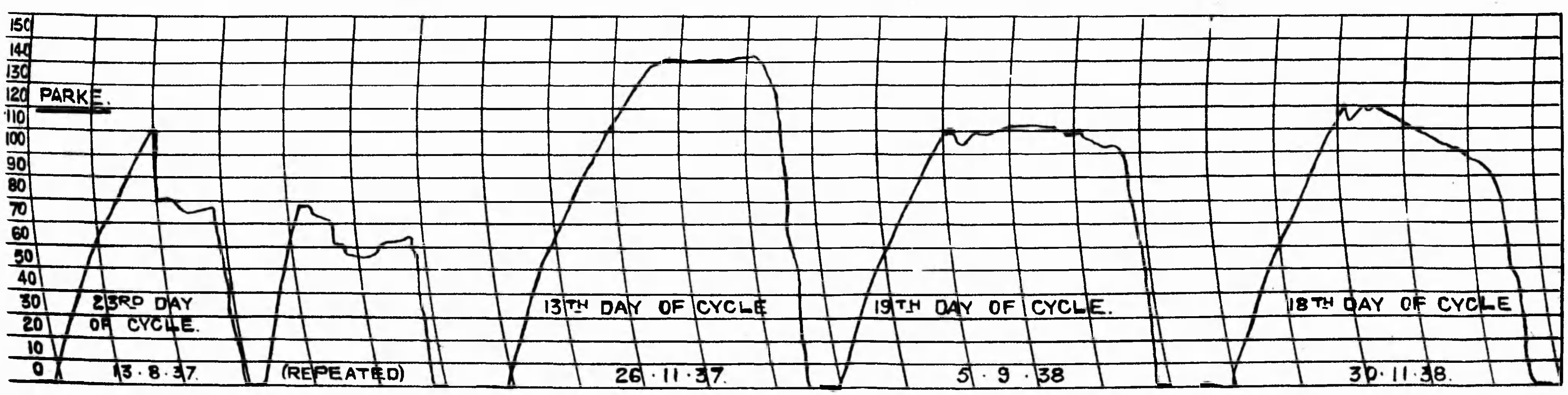
Although a number of cases showed minor degrees of tubal stenosis as evidenced by patency at high pressure and/or absence or gross diminution of peristaltic waves, only three showed noteworthy degrees of this condition.

It will be remembered that all cases of gross tubal disease were excluded from insufflation and no cases of relative sterility were included in the series: it is therefore not surprising that this investigation revealed so few cases of adhesions or strictures. The following is a brief summary of these cases:

PLATE XII



170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
CARR
7TH DAY OF CYCLE
14 · 7 · 38.
DAY OF CYCLE NOT NOTED.
12 · 8 · 38.
3 MONTHS' AMENORRHOEA.
(NOT PREGNANT)
24 · 7 · 41



150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PARKE.
23RD DAY
OF CYCLE.
13 · 8 · 37.
(REPEATED)
13TH DAY OF CYCLE
26 · 11 · 37.
19TH DAY OF CYCLE.
5 · 9 · 38
18TH DAY OF CYCLE
30 · 11 · 38.

Case No. 17. Carr.

Four insufflations between 26.1.35 and 24.7.41: the first with anaesthesia but without the kymograph showed patency at 60 mm. Hg.: the other three are illustrated on Plate XII - the first shows patency at 130 mm. Hg. with poor waves, the second at 160 with no waves and the third at 80 with very poor waves.

In 1932 she was operated upon in Glasgow Royal Infirmary. The following were findings on laparotomy: "The ileum and its mesentery were studded with miliary tubercles: the hepatic flexure was bound down by adhesions: the appendix was thickened and adherent retrocaecally." Appendicectomy was performed. Ultimate diagnosis, "Tabes mesenterica."

This may be related to the present abnormal state of her Fallopian tubes. Pregnancy has not resulted (seven years follow-up).

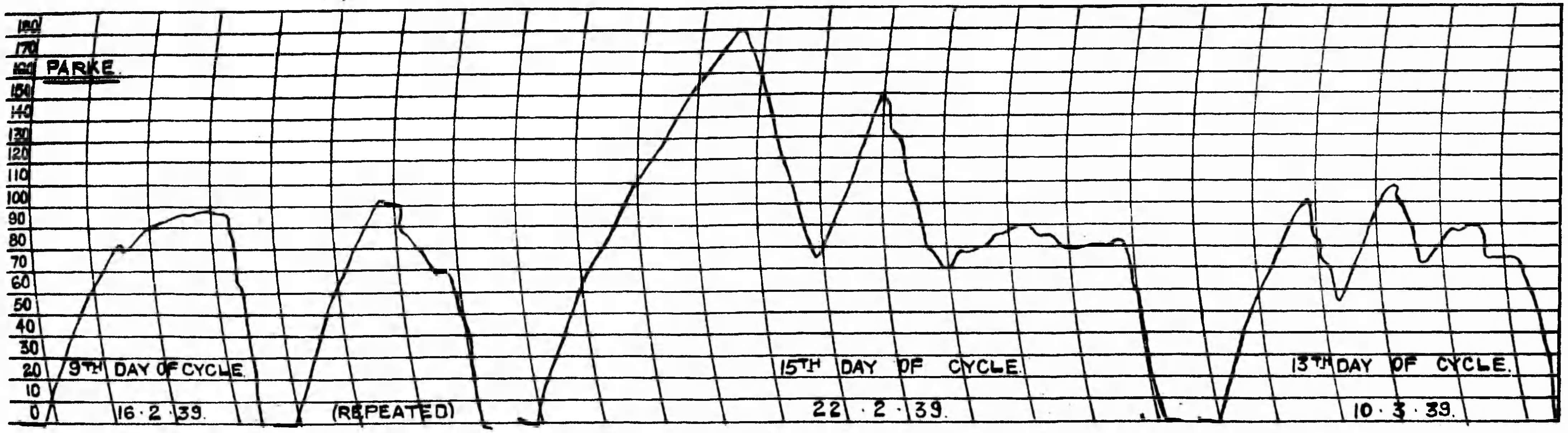
Case No. 81. Brown.

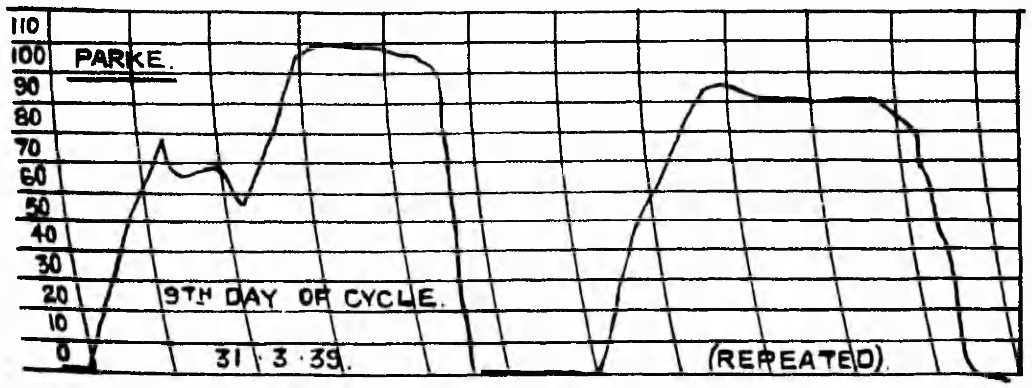
Two insufflations (without kymograph):
(1) 25.7.35, under anaesthesia - gas at first failed to pass, but repetition showed patency at 130 mm. Hg;
(2) 2.4.37, without anaesthesia - gas passed at 160 mm. Hg.

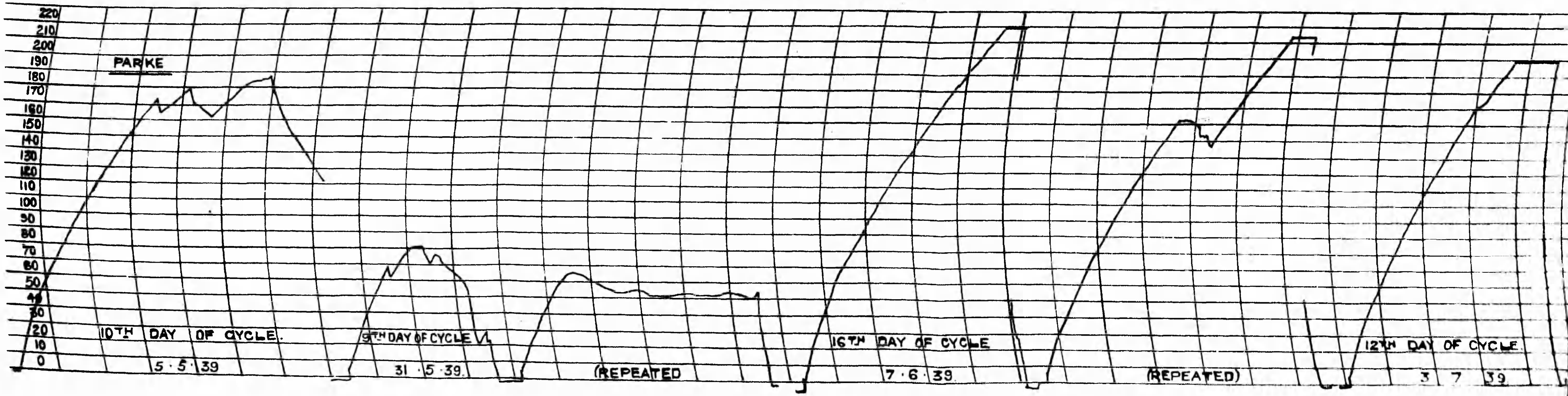
The patient states that she was operated upon "at the age of five years for peritonitis."

There/

PLATE XIII.


PARKE.
9TH DAY OF CYCLE.
16·2·39.
(REPEATED)
15TH DAY OF CYCLE.
22·2·39.
13TH DAY OF CYCLE.
10·3·39.


PARKE.
9TH DAY OF CYCLE.
31·3·39.
(REPEATED)


PARKE
10TH DAY OF CYCLE.
5·5·39
9TH DAY OF CYCLE
31·5·39.
(REPEATED
16TH DAY OF CYCLE
7·6·39.
(REPEATED)
12TH DAY OF CYCLE.
3 7 39

There are no tracings in this case.

Case No. 193. Parke.

Fourteen insufflations without anaesthesia between 28.5.37 and 3.7.39: the first two, without kymograph, showed patency at 190 mm. Hg. and 180 mm. Hg. respectively; the remainder showed very diverse findings and are illustrated on Plates XII and XIII. She had a course of pelvic diathermy - to be discussed later - from 6.9.38 to 15.10.38.

This patient was operated upon in the Royal Samaritan Hospital on 30th December, 1935, for chronic appendicitis. The following were the findings: "The ovaries are adherent to the pelvic wall and to the posterior aspect of the uterus: the tubes are patent: the appendix is inflamed and bulbous."

The general features of her case are those of gross tubal dysfunction, but with some measure of patency. This dysfunction is almost certainly due to peritubal adhesions. Over four years after her first insufflation she was still not pregnant.

Pneumoperitoneum.

Radiographs for the purpose of demonstrating pneumoperitoneum were made in fourteen patients, immediately after insufflation. In all cases of tubal patency (eleven), gas was seen between the liver/

PLATE XV.

PNEUMOPERITONEUM.

The photographs illustrate the rapid absorption of CO_2 gas under the diaphragm. The topmost was taken within five minutes of insufflation, the middle fifteen minutes later and the lowermost a further fifteen minutes later.

liver and diaphragm. Photographs illustrating pneumoperitoneum and absorption of carbon dioxide gas are seen in Plate XV.

Hysterosalpingography.

Lipiodol was injected into the uterus and tubes and radiographs then taken in 114 patients on whom one or more insufflations had already been performed: in fifteen of them a further lipiodol examination was made at an interval (varying from several weeks to several months) and in one case the test was performed on three occasions with an interval of three weeks between the first and second, and four months between the second and third. Thus, in all, 131 lipiodol injections were made. In every instance, an X-ray photograph of the pelvis was taken immediately after lipiodol injection and another either twenty-four or forty-eight hours later. A number of representative hysterosalpingographs are shown in Figs. 34-55.

Complications were uncommon and similar to those observed during and immediately after tubal insufflation, much the most frequent being momentary faintness. Their general incidence was a little higher than on insufflation and the complaint of abdominal or pelvic pain during the injection was definitely more frequent./

Fig. 34. Black.
Case 9.

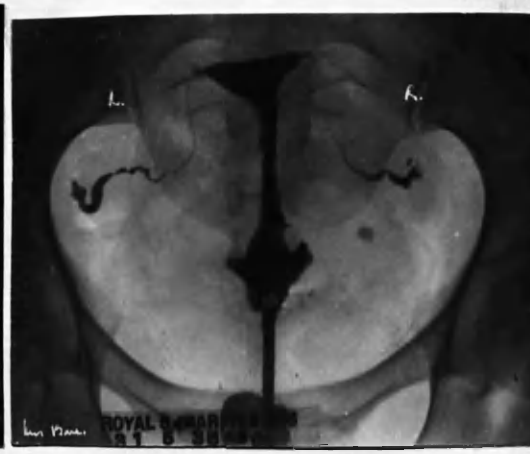


Fig. 35. Barr.
Case 282.

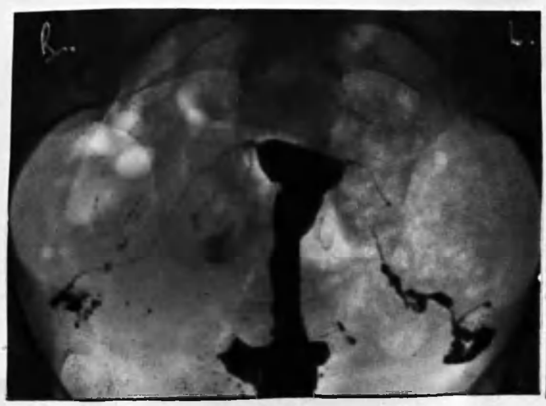


Fig. 36. Cromie.
Case 238.

Fig. 37. Fraser.
Case 257.

Fig. 38. Garrett.
Case 258.

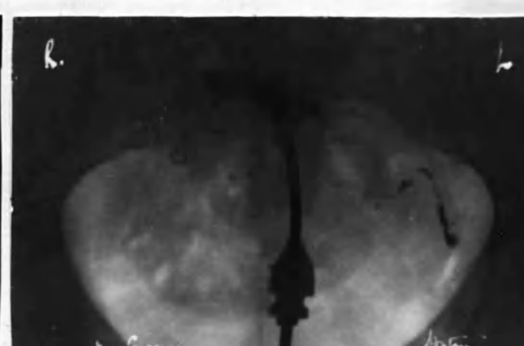


Fig. 39. Green.
Case 212.

REPRESENTATIVE HYSTEROSALPINGOGRAPHS.

Fig. 40. Halliday.
Case 295.

Fig. 41. King.
Case 292.

Fig. 42. Laird.
Case 194.

Fig. 43. Lindsay.
Case 165.

Fig. 44. Miller.
Case 275.

Fig. 45. Phelan.
Case 253.

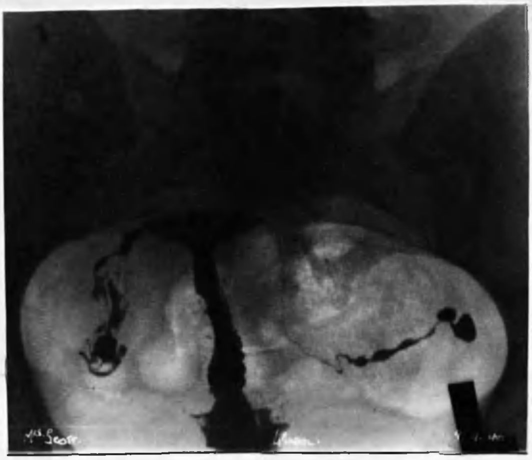


Fig. 46. Scott.
Case 407.

Fig. 47. Simons.
Case 288.

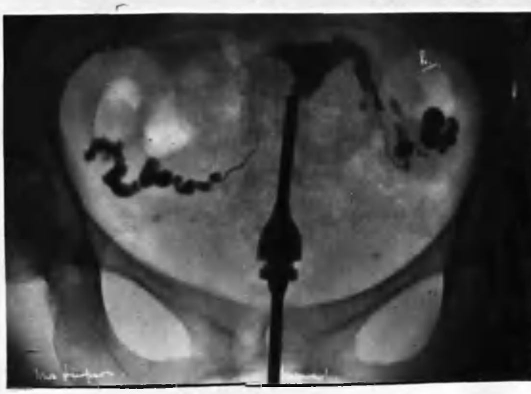


Fig. 48. Simpson.
Case 271.

Fig. 49. Welsh.
Case 245.

Fig. 50. Wilson.
Case 201.
Tubes appear blocked but 24 hours later spill seen at left fimbrial end.
2 insufflations showed patency.

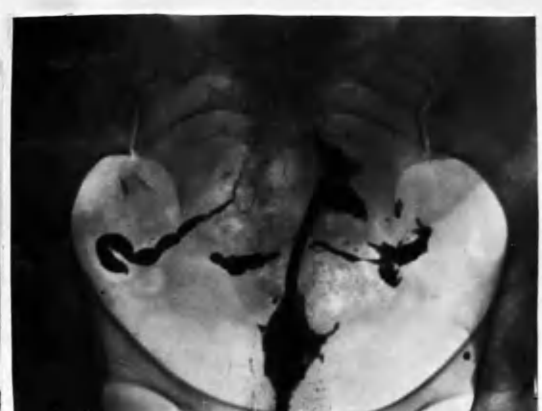


Fig. 51. Young.
Case 290.

Fig. 52. Miller.
Case 185. 1/11/38.

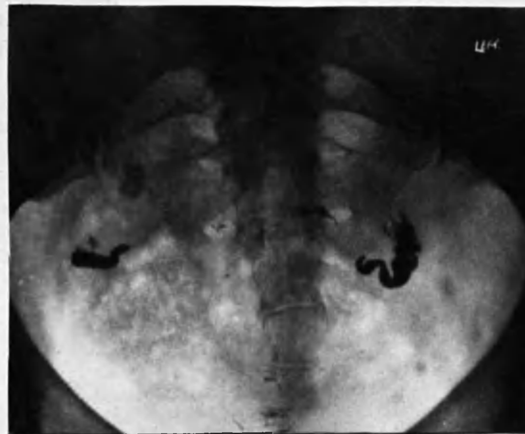


Fig. 53. Miller.
Case 185. 2/11/38.

Lipiodol remains in the tubes after 24 hours but there is no spill (non-patency).

Fig. 54. Wallace.
Case 285.
Although the tubes appear normal, radiograph 24 hours later shows no spill - blockage confirmed by insufflations.

Fig. 55. Early.
Case 425.
Subsequent to operation for bilateral hydrosalpinx (portions of tubes removed).

frequent. On a few occasions the pain was sufficient to make the completion of the test unsatisfactory or impossible and this accounts for some of the 'unsatisfactory' findings in the analysis of results. Before these are described, brief reference may be made to two sequelae, (1) in one patient, lipiodol appeared to have entered uterine veins; this, at any rate, is suggested by the appearances in the X-ray films: fortunately, this caused no upset whatever: and (2) one patient developed pelvic sepsis: further details of this case will now be described:

Bell. Case 274. This patient was aged 26 and married three years when she was insufflated on May 5th, 1938. Tubal blockage was diagnosed. Nineteen days later the diagnosis was confirmed by the injection of lipiodol. Neither procedure caused any upset. Some three months later another kymographic insufflation showed non-patency of the tubes. Four days later - there was no complaint - a second hysterograph was done which showed blockage at each fimbriated end. Twenty-three days later she was admitted to hospital, suffering from salpingitis and complaining of pain in the right side of the abdomen of three weeks' duration. Her temperature was 99.2^{o} and remained elevated slightly for forty-eight hours. She was treated with Prontosil

and/

and the usual measures, and was dismissed well after three weeks' stay in hospital. During this time a pelvic radiograph showed traces of lipiodol in the neighbourhood of the right tube. Three months later a radiograph still showed traces of lipiodol in the same site. Over three years later she wrote that she had remained well, that menstruation had been regular and painless and that there had been no pregnancy.

It was rather disturbing to find that she had developed sepsis, presumably arising at her second injection which, of course, was not essential for diagnostic purposes but was performed as a matter of interest and for comparison.

Radiographs of this case are shown in Figs. 67 and 68.

The results in the series of 114 cases were as follows:-

Bilateral tubal patency was revealed in	... 59	cases.
Unilateral patency " " "	... 7	"
Non-patency " " "	... 40	"

The test proved unsatisfactory in eight cases.
Further study of the non-patent group shows, firstly, that it formed 37.7 per cent. of the total (comparing very closely with the figure of 38.0 per cent. arrived at by insufflation in 480 patients, already described) and, secondly, that the blockage appeared to be at the fimbriated/

fimbriated ends in twenty-two cases, at the uterine ends in thirteen and at one end of one tube and the other end of the other in five cases.

Comparison of insufflation results with those of lipiodol shows that patency demonstrated by insufflation was confirmed by lipiodol in fifty-four of the sixty cases. The discrepancy in the remaining six cases, which showed tubal patency with lipiodol but non-patency with insufflation, merits further consideration: in each instance only one insufflation had been performed, anaesthesia having been employed on three occasions; the evidence of the passage of lipiodol through the tubes seems incontrovertible (see Figs. 56-61); three of the six cases became pregnant (18 months, 6 months, and 48 months later respectively); unless one assumes a patency-establishing effect of a single insufflation in each of these cases, the only conclusion appears to be that the lipiodol results were correct and the insufflation ones were not. Thus, hysterosalpingography has demonstrated an erroneous insufflation-finding of non-patency in six of a group of sixty cases (10 per cent.). This finding confirms the view expressed earlier, in considering the results of repeated insufflations, namely, that reliance cannot be placed upon a single insufflation finding of non-patency.

Causative/

Tubal patency demonstrated by lipiodol in six cases in which insufflation showed non-patency. (Radiographs taken in each case 24 hours later showed lipiodol free in pelvis).

Fig. 56. Baim.
Case 302.

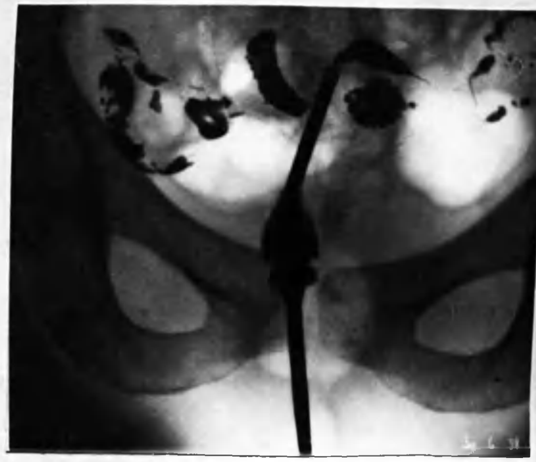


Fig. 57. Bennett.
Case 300.

Fig. 58. Bonnar.
Case 438.

Fig. 59. Cook.
Case 156.

Fig. 60. Stewart.
Case 131.

Fig. 61. Vertis.
Case 200.

Causative factors of this error may be, (1) a very high degree of tubal spasm (or utero-tubal tone), or (2) error in technique e.g. (a) the tip of the cannula may not be free in the uterine cavity, but may be impinged on the wall of a stenosed cervical canal, or (b) failure to make certain that there is no blockage in the insufflation apparatus.

Further comparison of the results shows that in all seven cases showing unilateral patency with lipiodol, insufflation gave evidence also of patency, in one case, (Worby, Case 395, already described and illustrated in the "spasm group"), at a high pressure level and exhibiting spasm. Too much reliance, however, should not be placed on the radiological appearance of unilateral patency, since the apparent failure of lipiodol to enter a tube or pass through it may be due to insufficiency either in the amount of lipiodol or its pressure. This possibility is illustrated in reviewing those cases which erroneously showed apparent non-patency with lipiodol and also in several of the patients who had hysterographs repeated. The latter are illustrated in Figs. 67-81. Instances of unilateral tubal patency are shown in Figs. 86-90.

Of the forty cases showing non-patency after lipiodol, thirty-six had given the same result on insufflation./

Four Cases showing Tubal Blockage - no Lipiodol free in pelvis 24 hours later - insufflation showed patency.

Fig. 62. Brophy.
Case 294.

Fig. 63. Buchanan.
Case 318. 17/1/39.

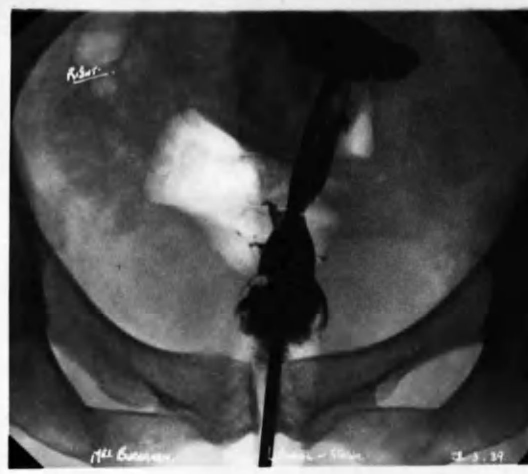


Fig. 64. Buchanan.
Case 318. 21/3/39.
(Early pregnancy - uterine cavity enlarged).

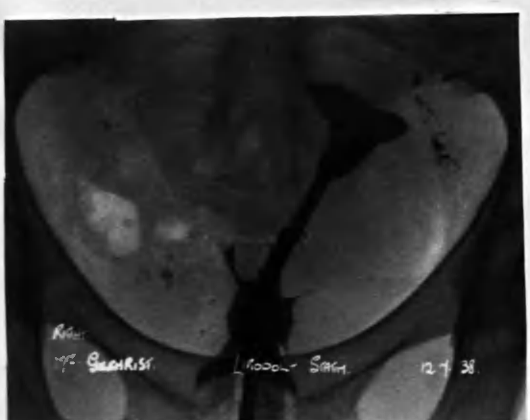


Fig. 65. Gilchrist.
Case 242.

Fig. 66. Jennings.
Case 418.

insufflation. The remainder showed definite patency on insufflation, performed once in one case (Jennings, Case 418), twice in another (Buchanan, Case 318), and on six occasions in the remaining two (Brophy, Case 294 and Gilchrist, Case 242). Case 318 became pregnant one month after her second insufflation (or two months after lipiodol). There is no doubt in these cases radiographs gave erroneous evidence of tubal blockage: they are reproduced in Figs. 62-66. In each instance radiographs taken twenty-four hours after lipiodol injection showed no evidence of lipiodol "spill" through the tubes.

Best picture in preceding preg: shows enlarged edges! [illegible] pregnancy

Further critical evaluation of hysterosalpingography is obtained from a study of a group of cases in which this mode of investigation of the tubal status was repeated subsequently in the same patient. It has already been mentioned that the test was done twice in fifteen patients and thrice in one. Of these sixteen cases, in one, both results were quite unsatisfactory and in another sufficiently poor to render their accurate assessment impossible. In the remaining fourteen cases, seven showed a notable discrepancy in the appearances of the respective radiographs: these are illustrated in Figs. 67-81. In two of the others (Buchanan, Case 318 and Ross, Case 278) the second/

REPETITION OF LIPIODOL.

Fig. 67. Bell.
Case 274. 24/5/38.

Fig. 68. Bell.
Case 274. 16/8/38.

Fig. 69. Brandon.
Case 311. 9/8/38.

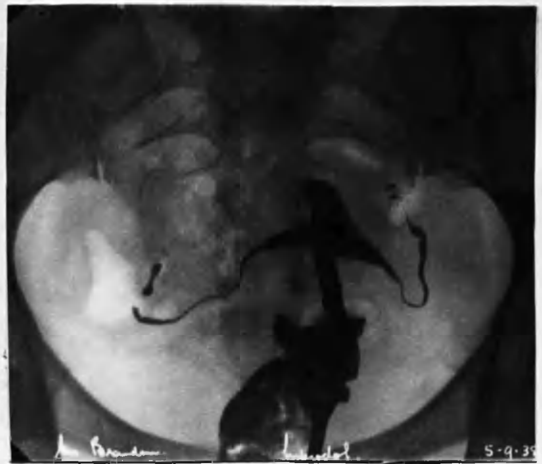


Fig. 70. Brandon.
Case 311. 5/9/38.

Fig. 71. Edmund.
Case 337. 20/12/38.

Fig. 72. Edmund.
Case 337. 24/1/39.

REPETITION OF LIPIODOL.

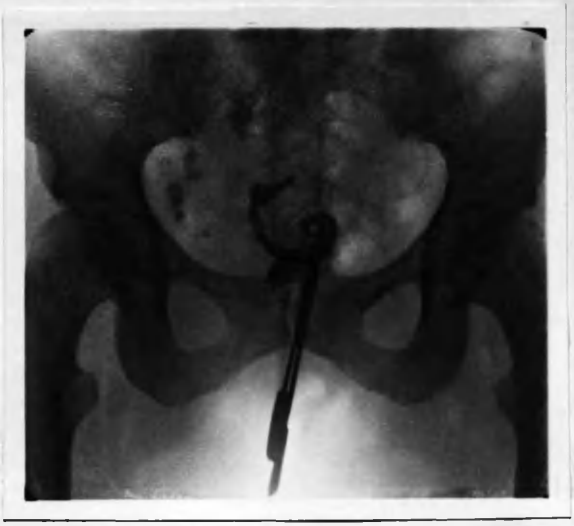


Fig. 73. Graham.
Case 111. 3/11/37.

Fig. 74. Graham.
Case 111. 5/7/38.

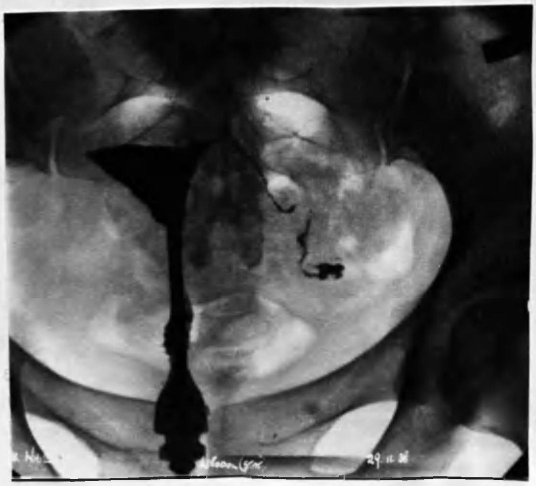


Fig. 75. White.
Case 323. 29/11/38.

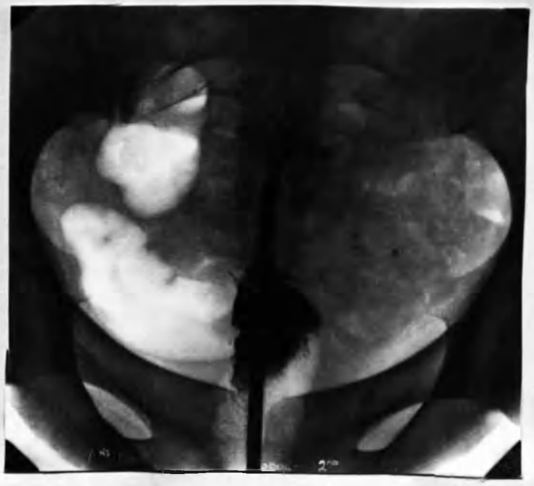


Fig. 76. White.
Case 323. 11/4/39.

Fig. 77. Brownlie.
Case 260. 24/5/38.

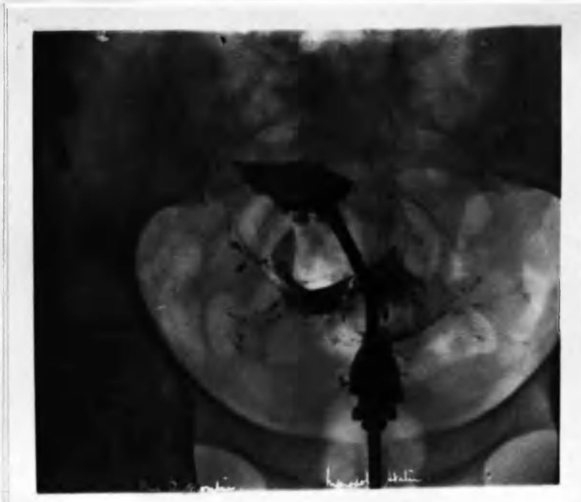


Fig. 78. Brownlie.
Case 260. 22/6/38.

REPETITION OF LIPIODOL.

Fig. 79. Kelly. Case 289. 14/6/38.

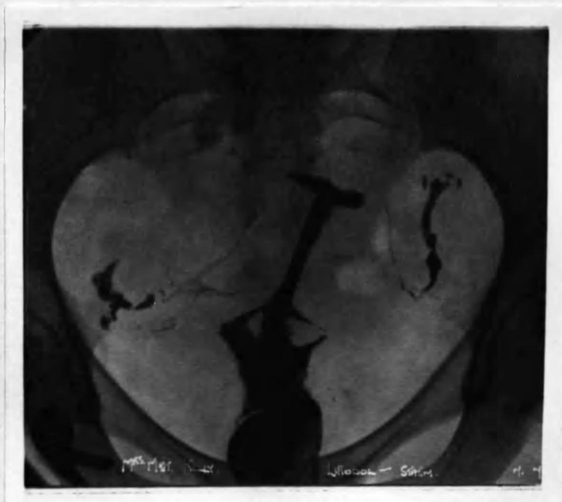


Fig. 80. Kelly. Case 289. 7/7/38.

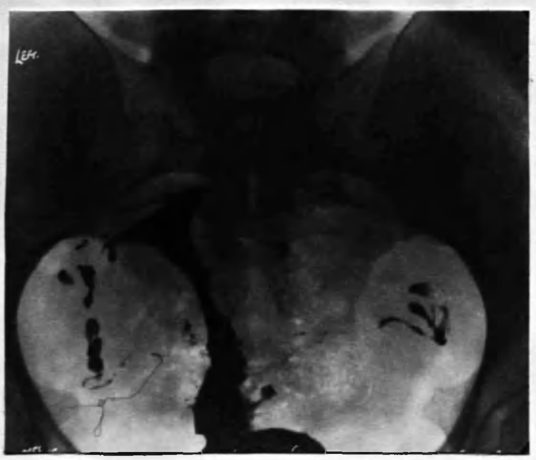


Fig. 81. Kelly. Case 289. 8/11/38.
(Note: This photograph is reversed from the ones above).

TUBAL PATENCY - PRIOR TO AND DURING PREGNANCY.

Fig. 82. Ross.
Case 278. 10/5/38.

Fig. 83. Ross.
Case 278. 14/6/38.
(Early pregnancy - note photograph is reversed from Fig. 82).

BEFORE AND AFTER RIGHT SALPINGOSTOMY.

Fig. 84. Muir.
Case 126. 18/3/37.

Fig. 85. Muir.
Case 126. 2/3/38.

(Laparotomy - left tube bound down by adhesions and twisted on itself: right tube free and bulbous, closed at fimbriated end).

UNILATERAL TUBAL PATENCY.

Fig. 86. Boyd.
Case 203.

Fig. 87. Carlow.
Case 199.

Fig. 88. Corbett.
Case 361.

Fig. 89. C. Craig.
Case 246.

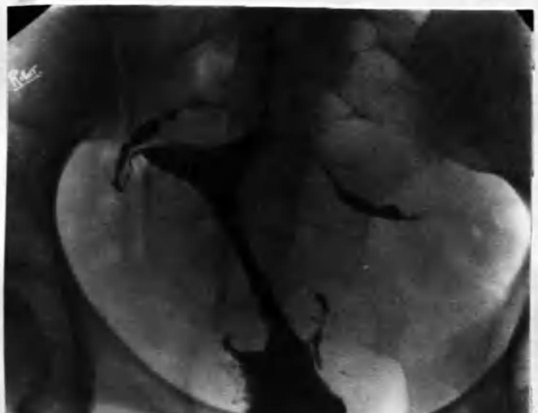
Fig. 90. Worby.
Case 395.

Fig.

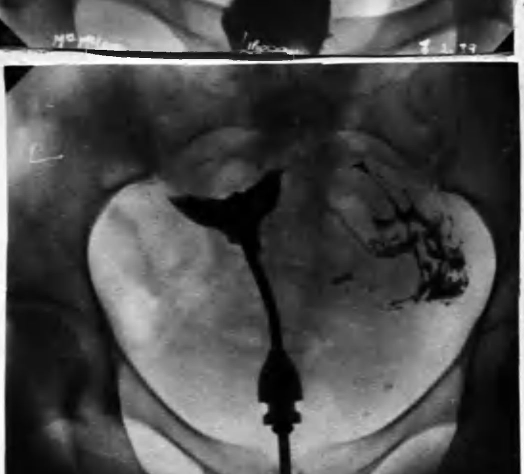
REPETITION OF LIPIODOL.

Figs. 91
& 92.
Lynch.
Case 191.
5/7/38 &
30/8/38.

Figs. 93
& 94.
McFarlane.
Case 202.
20/10/37
&
14/6/38.



Figs. 95
& 96.
McLeod.
Case 358.
7/2/39
&
28/2/39.



Figs. 97
& 98.
Scott.
Case 263.
8/3/38
&
22/6/38.

second lipiodol injection was inadvertently made while the patient was in the first few weeks of pregnancy, i.e. before she had missed a 'period,' fortunately without disturbance to gestation: in one of them both radiographs showed tubal patency and in the other both showed bilateral isthmial blockage (Figs. 83 and 64). In one case, radiographs were taken before and after salpingostomy, (Figs. 84 and 85). Four cases are illustrated in Figs. 91-98, where repetition of lipiodol injection at varying intervals showed variations in the appearances obtained although the diagnosis of patency or non-patency was corroborated.

From the above considerations one important conclusion may be drawn, namely, that accurate interpretation of a hysterosalpingograph may often be difficult. Thus, it may show blockage where none exists or its interpretation may be so difficult that an accurate conclusion cannot be reached. But it may show definite patency when insufflation has indicated blockage and in non-patent tubes it will reveal the precise site of blockage.

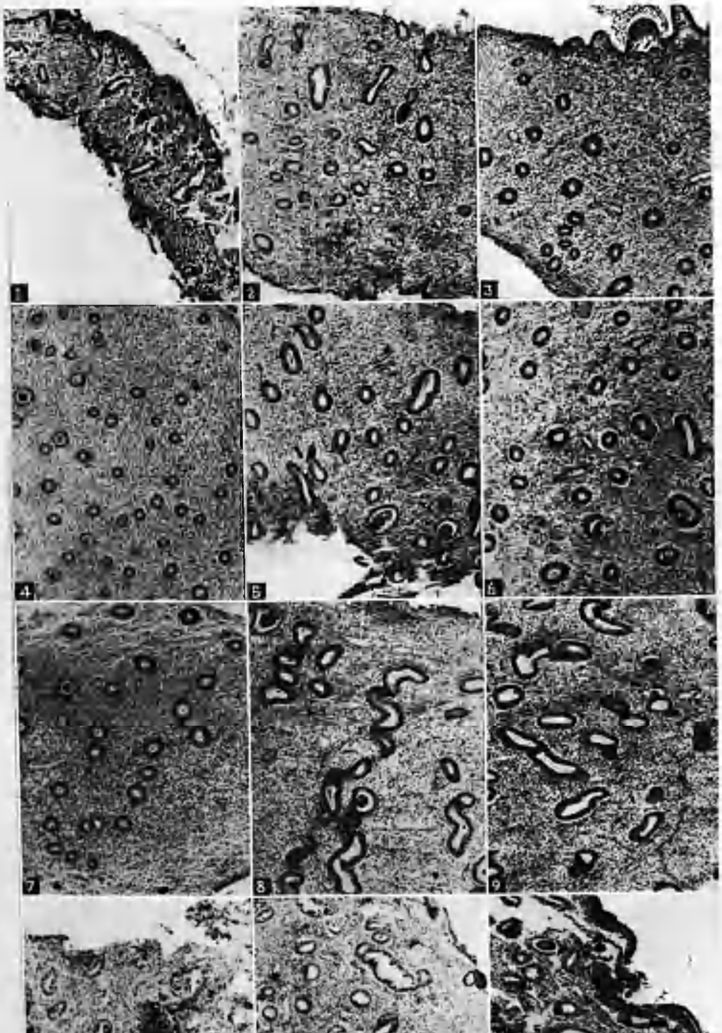
Endometrial Biopsy.

The value of endometrial biopsy in gauging the/

the functional state of the ovary has already been discussed in Part I of this thesis and in particular on pages 62 and 63. It is generally agreed that the presence of secretory changes is the criterion of corpus luteum activity and is presumptive evidence of ovulation. Novak (1940) declares, "For the present it still seems justified to assume that ovulation has occurred if the endometrium just before menstruation reveals a full-blown progestational type of endometrium and that the finding of a purely proliferative endometrium or one showing slight or uncertain evidences of secretory activity at a chronologically premenstrual phase, is justifiable presumptive evidence that ovulation has not occurred."

Eight hundred and fifty endometrial biopsies were performed, by far the larger percentage of which, by means of Sharman and Sheehan's biopsy curette in the unanaesthetized patient. In the remainder, either curettage under anaesthesia or suction (in early cases of series) without anaesthesia was employed. Endometrium was removed and examined in 392 cases of the five hundred comprising the series. Unfortunately, not all of them had endometrium removed at the premenstrual phase of the cycle, mainly because, in the early cases, the significance of biopsy, at this specific phase, in relation to ovulation was not/

PLATE XVI.



PLATES XVI and XVII.

Complete endometrail cycle represented by twenty-four specimens collected by means of a biopsy curette.

The patient, aged 20, had been married for five years. There had been no children or miscarriages. She had a regular twenty-eight-day cycle with a flow that lasted on the average four days. Specimen No. 1 was obtained the day after a period had ended. Specimen No. 24 was obtained an hour before the beginning of the next period. The numbers refer to the days of the intermenstrual interval. The actual day of the cycle on which the specimens were collected can be obtained by adding four to each number.

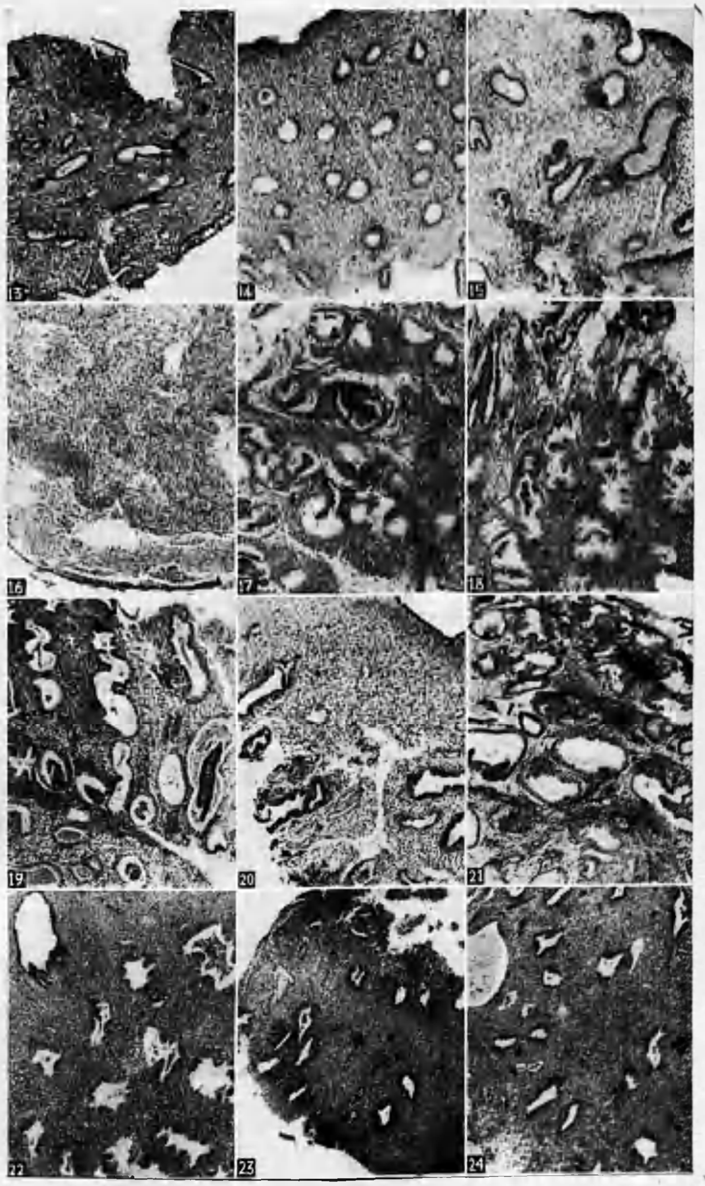
Specimens 1 to 7. These show the characteristic appearances of the post-menstrual or early proliferative phase. The glands are small and circular on transverse section. The stroma is dense and proliferating. Active mitosis is proceeding in the glandular epithelium and stroma.

Specimens 8 to 13. The glands are dilated and slightly tortuous. The stroma is still dense.

Specimens 14 to 24. Varying stages of differentiation are now evident. The glands have become coiled and large in size. The stroma has become looser and oedematous. Section 18 is highly characteristic of the premenstrual or late differentiative phase. (Specimen 16 is very poor, showing no glands, but organization with red cells, leucocytes and fibrinous material. It is probably the result of curetting an area which had been curetted some days previously. It is included solely for the purpose of preserving the continuity of the series.)

An endeavour was made to collect each specimen from an intact area by inserting the curette at a different angle each day, proceeding clockwise. Specimens were fixed in formol saline embedded in paraffin and stained with haematoxylin-eosin.

PLATE XVII.



not adequately appreciated or because of difficulty in timing biopsy in those with irregular menses, or because of the patient's failure to report after tubal insufflation, or because she could not be traced. However, in 358 cases endometrium was removed in the premenstrual phase of the cycle. Of these, 335 showed the normal characteristic, secretory or differentiative features of this phase; 11 showed absence of these features at this phase on one or more occasion, but not on all; and 12 showed their absence on every occasion on which biopsy was performed.

It is not proposed to discusss further these 335 cases which showed the normal endometrial appearances of the premenstrual (or postovulatory) stage because the general appearances have already been described and their significance discussed in the account of the Menstrual Cycle in Part I. Plates XVI and XVII illustrate these appearances throughout a complete cycle in one patient from whom a specimen was taken each day by means of the biopsy curette.

The group of twenty-three cases which showed anovulatory cycles is of much interest and importance and will receive detailed consideration.

Attention/

TO ILLUSTRATE IMPORTANCE OF KNOWING DATE OF SUCCEEDING PERIOD.

Fig. 99. Dixon.
Case 362. 16/2/39.

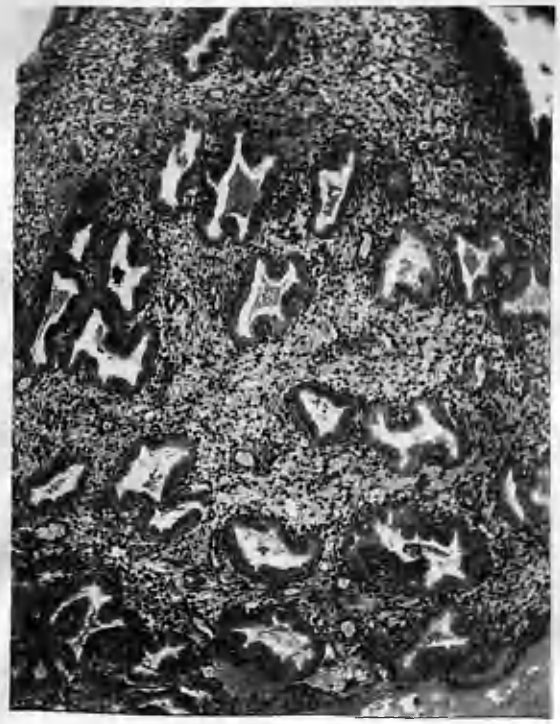


Fig. 100. Dixon.
Case 362. 20/2/39.
(Menstruation commenced 4 days later).

Attention has already been drawn to the fact that an erroneous diagnosis of an anovular cycle may be made if reliance is wholly placed on the date of the preceding menstruation and biopsy is performed only on the presumptive premenstrual phase. The date of menstruation <u>after</u> biopsy must be ascertained. In my earlier cases this mistake often occurred until it was arranged that every patient was asked to report one week after biopsy. If menstruation had not occurred a further biopsy was done. Failure to make certain that endometrium is actually 'premenstrual' in terms of the cycle is bound to give a much higher (and erroneous) incidence of anovulatory cycles. A case in point is Dixon, Case No. 362: age 25, married four years, menstrual cycle 4/28, regular and painless; biopsy 16.2.39 - menstruation due about 17.2.39 (L.M.P. 17.1.39 to 21.1.39) - endometrial findings do not correspond; biopsy repeated four days later showed definite differentiative features; menstruation two days later: both sections are illustrated in Figs. 99 and 100. In the following three cases, Nos. 237, 297 and 332, biopsy was performed within three days of expected menstruation and showed complete absence of the differentiative phase: it was performed respectively/

respectively on the twenty-ninth day of the cycle, the twenty-fourth and the twenty-sixth: these patients failed to communicate the date of menstruation or report as requested: the first was untraced but the second and third, in answer to a questionnaire three years later, replied that they had not become pregnant and did not wish further investigation or treatment. Although these cases cannot be included in this 'anovulatory' group, it is, of course, possible that any or all of them might have been in this category had further information or investigation been available.

One further type of case which may appropriately be discussed now is that in which repeated attempts at biopsy in the premenstrual phase fail to remove any endometrium. There were four cases in the series, viz., (1) Ross, Case No. 278; three biopsies, (a) 19.4.38, (b) 19.5.38 and (c) 17.6.38: (2) Sharpe, Case No. 279; five biopsies at intervals between 18.3.40 and 31.10.40: (3) Adams, Case No. 442; two biopsies during October, 1941, one without and the other with anaesthesia: (4) Shepherd, Case No. 449; four biopsies (a) 9.12.40, (b) 23.10.41, (c) 24.11.41 and (d) 16.4.42. In each of these cases there seemed no doubt that the curette was within the uterine/

PERIODICALLY ANOVULAR.

Beveridge. Case 183.

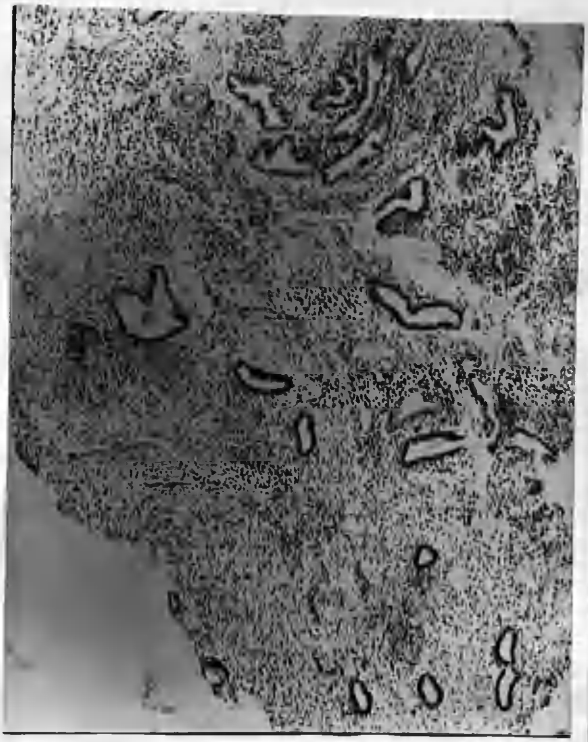


Fig. 101. 20/4/37.

Fig. 102. 7/3/38.

Fig. 103. 11/4/38.

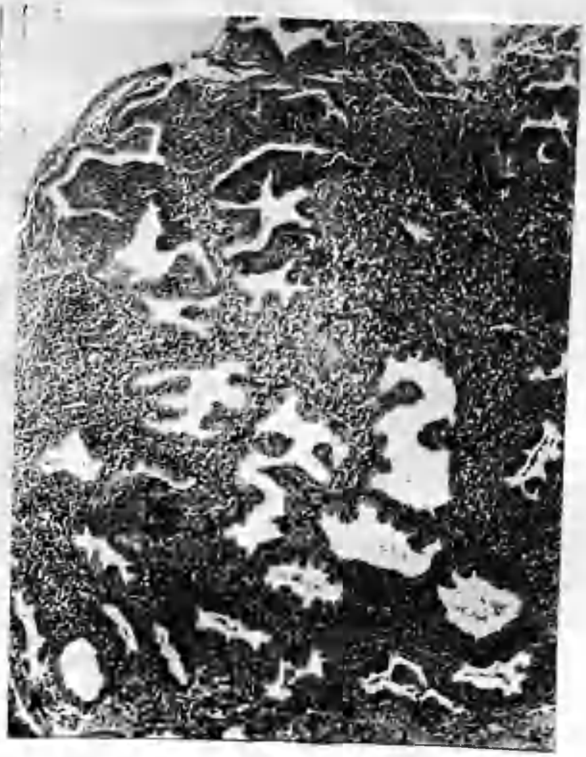


Fig. 104. 11/5/38.

uterine cavity and that failure to remove endometrium was not due (as it was on some occasions) to the fact that the instrument could not be passed through the internal cervical os. Although severe endometrial dysfunction, probably either failure to proliferate and differentiate or atrophy, may be presumed in these cases, the absence of endometrium makes it impossible to describe them as showing anovulatory cycles.

Indeed Cases 278 and 449 had normal full-time pregnancies. It may be noted here that one of the "anovular cases" (Case No. 111) had five premenstrual biopsies performed, of which only the first yielded endometrium: despite repeated efforts, subsequent attempts were fruitless.

Detailed consideration may now be given to the group of 23 cases exhibiting definitely anovular cycles in the series of 358, i.e. 6.4%. (If the very doubtful cases described in the preceding two paragraphs are added, the incidence of abnormality of the cycle is raised to 8.2 per cent.). It is proposed to describe them in two sections; A., those exhibiting both 'anovulatory' and 'secretory' cycles in the same patient - to be described as the "periodically anovular series" and B., "constantly anovular series."

It/

PERIODICALLY ANOVULAR.

Ferguson. Case 313.

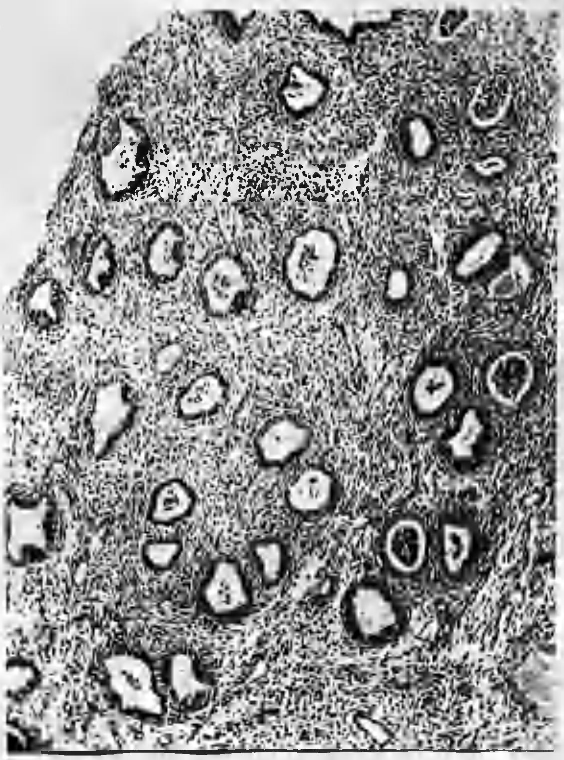


Fig. 105. 8/9/38.

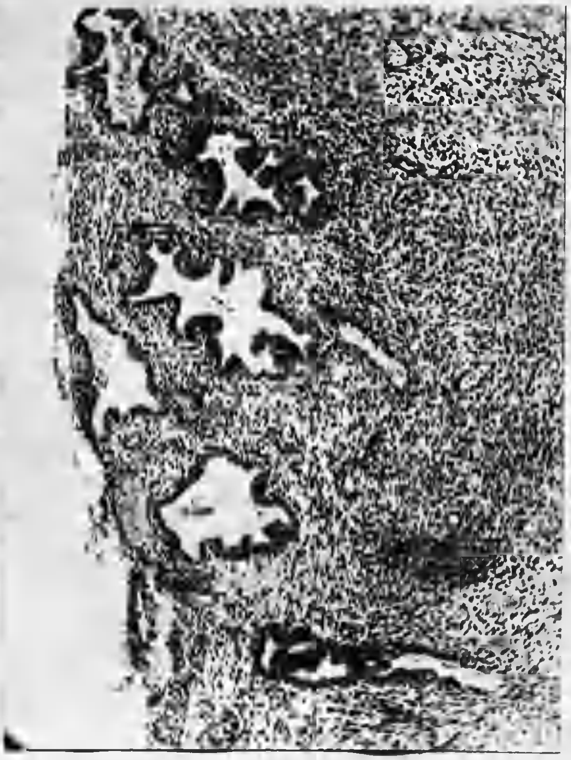


Fig. 106. 7/11/38.

Fig. 107. 7/12/38.

Fig. 108. 8/3/39.

It must be appreciated that these titles are being used descriptively and as a matter of convenience and cannot be expected to refer to more than the relatively small period of time during which the patients were studied. The two series therefore are not mutually exclusive since cases in section A. might at any future time show, during a certain period of observation, features of section B. and, alternatively, cases in section B. might possibly at one examination or another show 'secretory' endometrium. Moreover, many of the series of 335 patients already described as showing normal secretory characters, might, if the duration of their study were prolonged, show at one time or another apparently anovular cycles.

A. Periodically Anovular Series. (11 Cases).

Beveridge, Case No. 183. (Figs. 101-104).

1.	20.4.37	anovular	3 days premenstrual.
2.	7.3.38	anovular	5 " "
3.	11.4.38	secretory	1 day "
4.	11.5.38	secretory	4 days "

Ferguson, Case No. 313. (Figs. 105-108).

1.	8. 9.38	anovular	2 days premenstrual.
2.	7.11.38	secretory	2 " "
3.	7.12.38	secretory	2 " "
4.	8. 3.39	anovular	1 day "

Forrest,/

PERIODICALLY ANOVULAR.

Forrest. Case 338.

Fig. 109. 30/11/38.

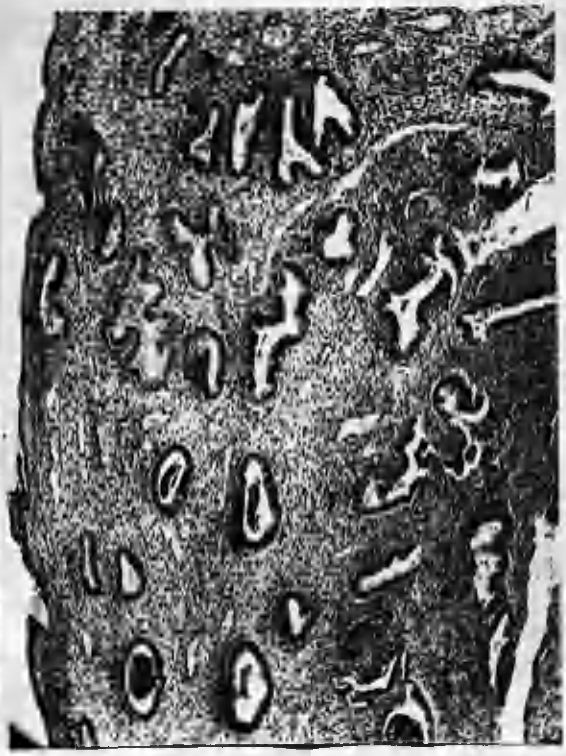


Fig. 110. 25/1/39.

Fig. 111. 27/3/39.

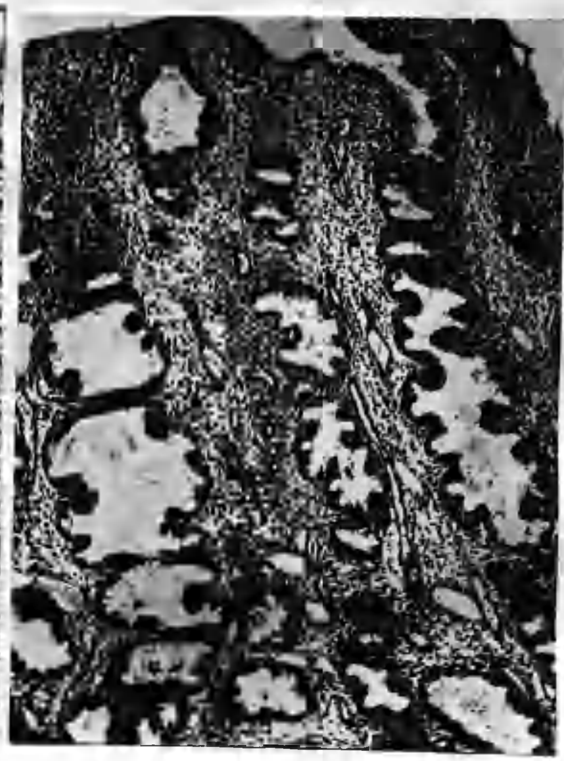


Fig. 112. 25/5/39.

Forrest, Case No. 338. (Figs. 109-112).

1. 30.11.38 - anovular - 1 day premenstrual.
2. 25. 1.39 - anovular - 6 days "
3. 27. 3.39 - secretory - 4 " "
4. 25. 5.39 - secretory - 8 " "

In the last of the above instances menstruation was six days later than expected.

Garth, Case No. 324. (Figs. 113-116).

1. 21.11.38 - anovular - 2 days premenstrual.
2. 11. 5.39 - secretory - 1 day "
3. 11. 5.39 - secretory - 2 days "
4. 10. 2.41 - secretory - 2 " "

Karnouskie, Case No. 364. (Figs. 117-121).

1. 13. 3.39 - anovular - 1 day premenstrual.
2. 12. 4.39 - secretory - 4 days "
3. 12. 5.39 - anovular - 8 " "
4. 19. 6.39 - secretory - 3 " "
5. 30.11.39 - secretory - 5 " "

The significance of No. 3 in this case might be questioned, since menstruation occurred eight days after biopsy, although due in four days, but the appearances do not correspond with the date in the cycle.

Kennedy, Case No. 445. (Figs. 122-123).

1. 20.11.39 - secretory - 2 days premenstrual.
2. 27. 4.40 - anovular - 4 " "

Martin, Case No. 132. (Figs. 124-126).

1. 5.5.39 - secretory - 3 days premenstrual.
2. 6.6.39 - anovular - same day as menstruation.
3. 3.7.39 - secretory - 3 days premenstrual.

McCabe,/

PERIODICALLY ANOVULAR.

Garth. Case 324.

Fig. 113. 21/11/38.

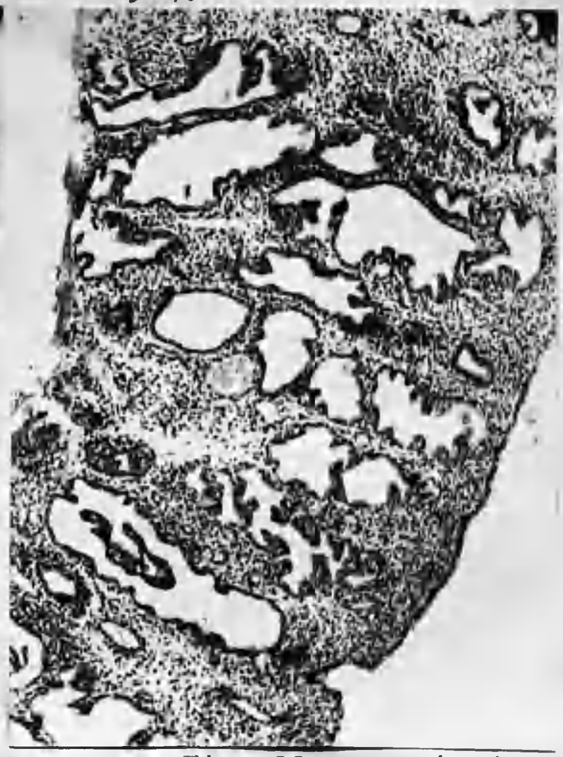


Fig. 114. 20/12/38.

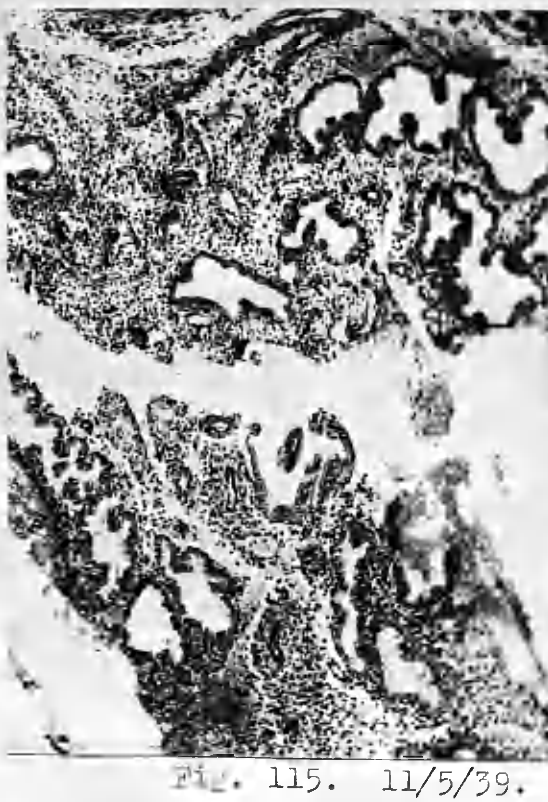


Fig. 115. 11/5/39.

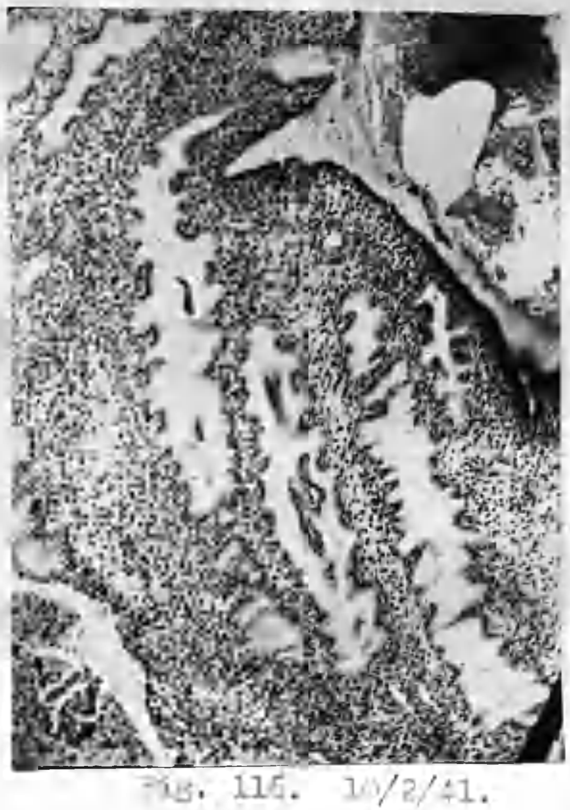


Fig. 116. 10/2/41.

PERIODICALLY ANOVULAR.

Karnouskie. Case 364.

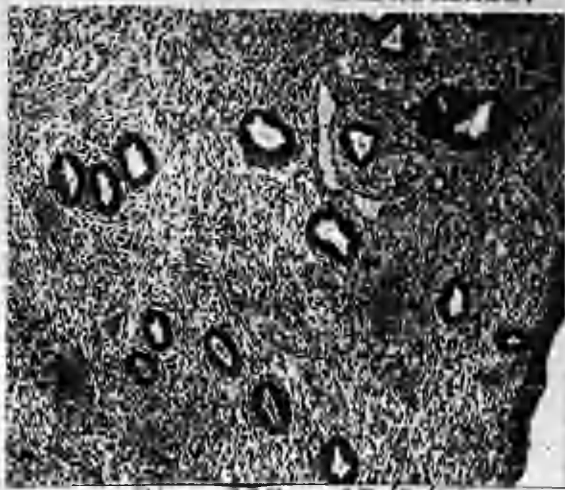


Fig. 117. 15/3/39.

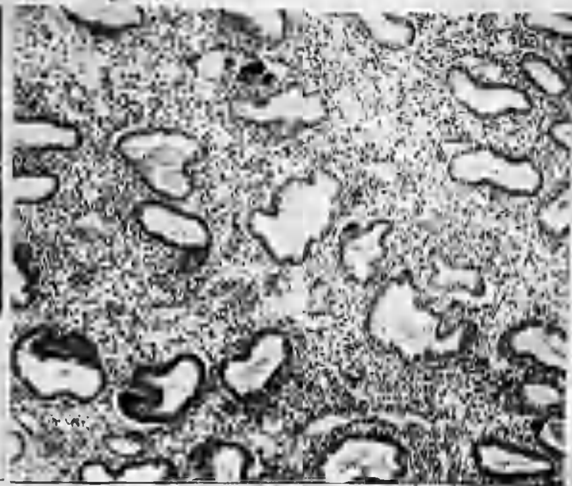


Fig. 118. 12/4/39.

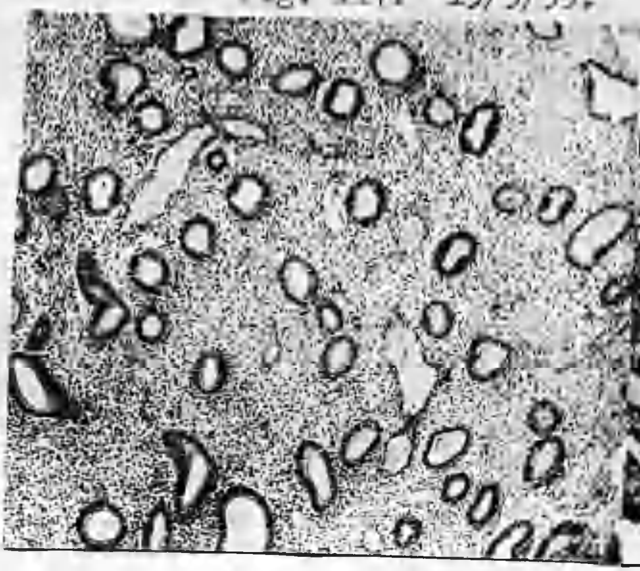


Fig. 119. 12/5/39.

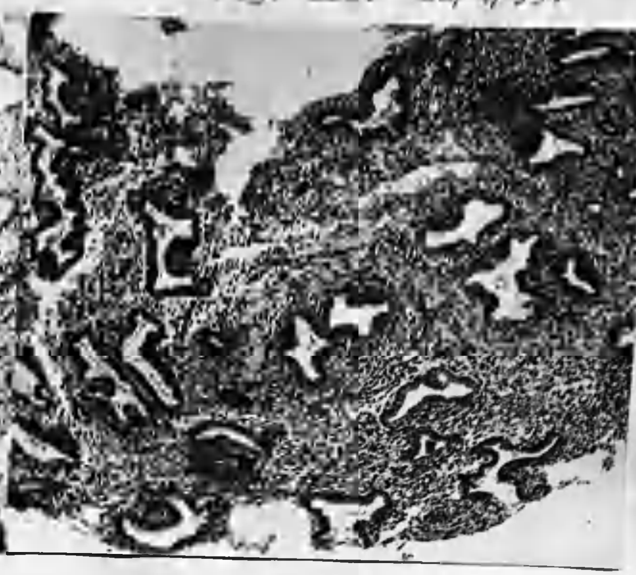


Fig. 120. 19/6/39.

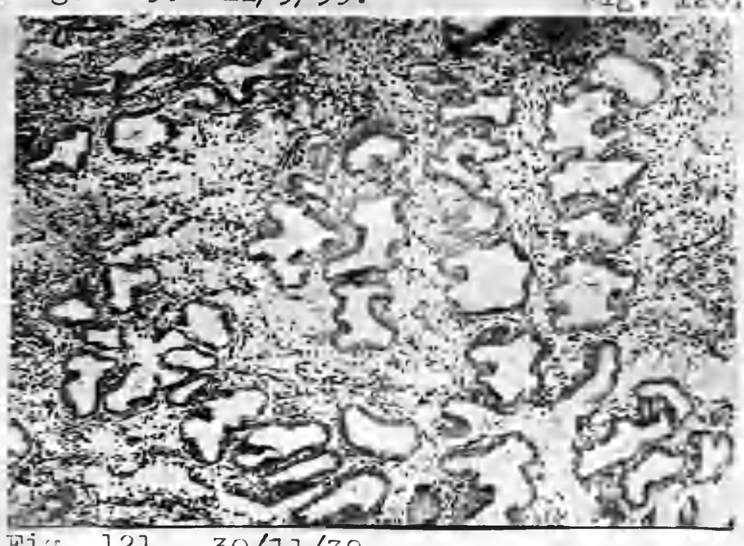


Fig. 121. 30/11/39.

PERIODICALLY ANOVULAR.

Kennedy. Case 445.

Fig. 122. 20/11/39.

Fig. 123. 27/4/40.

PERIODICALLY ANOVULAR.

Martin. Case 132.

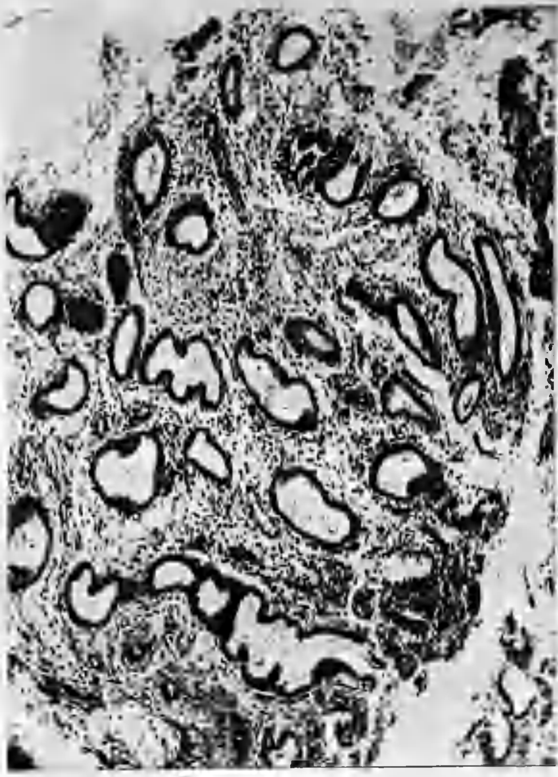


Fig. 124. 5/5/39.

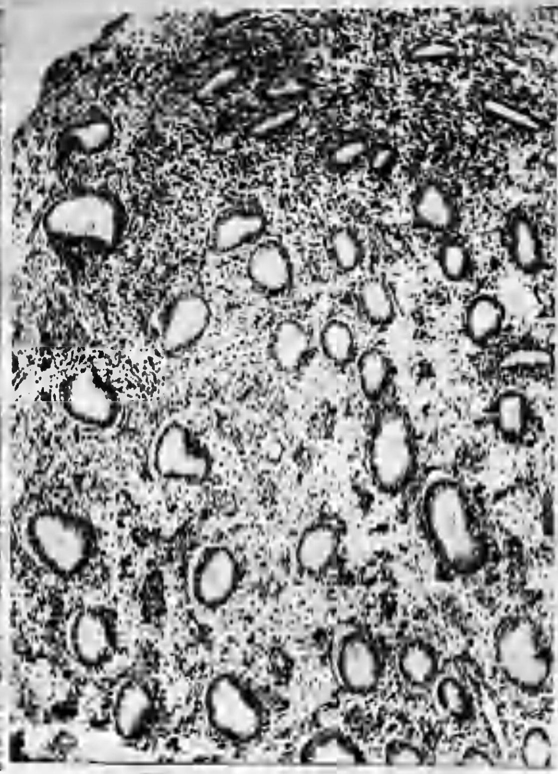


Fig. 125. 6/6/39.

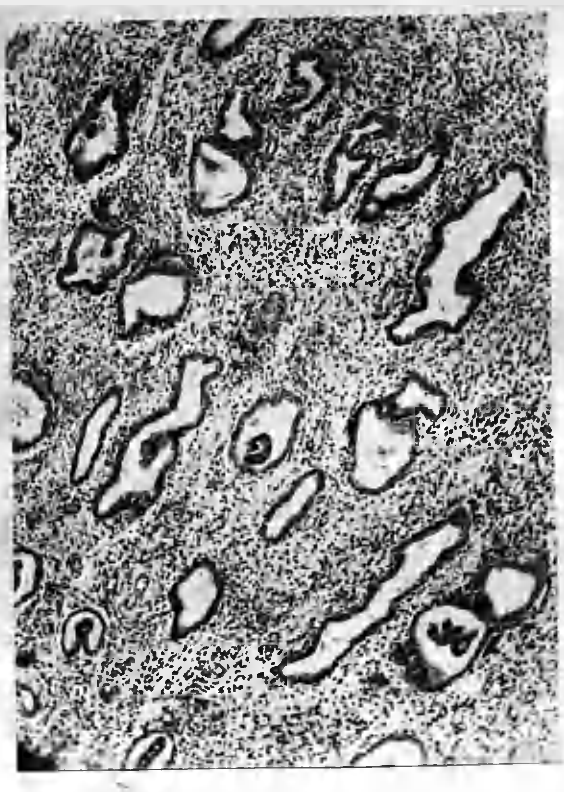


Fig. 126. 3/7/39.

PERIODICALLY ANOVULAR.

McCabe. Case 339.

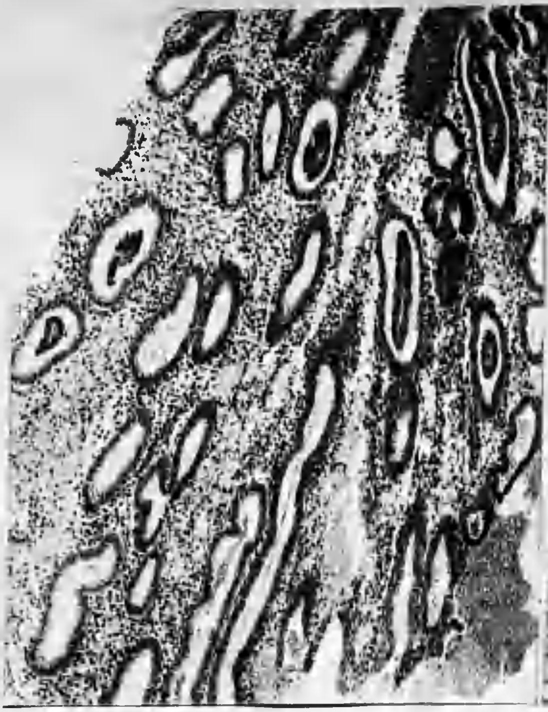


Fig. 127. 26/10/38.

Fig. 128. 13/1/39.

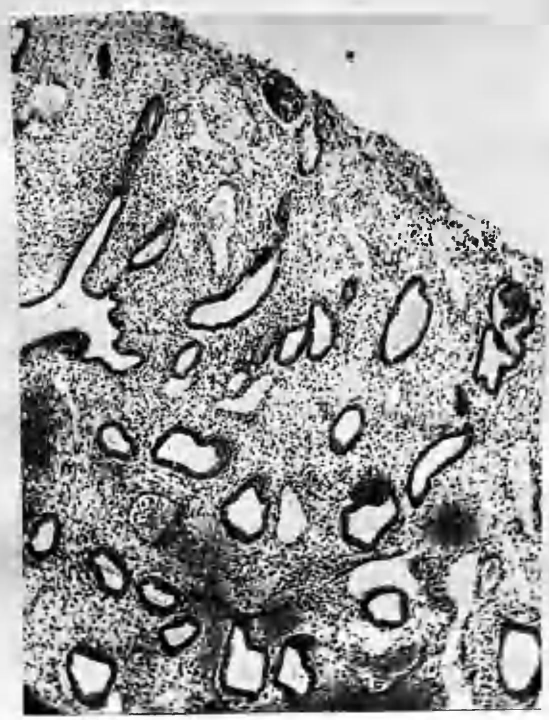


Fig. 129. 13/2/39.

PERIODICALLY ANOVULAR.

McInnes. Case 325.

Fig. 130. 26/10/38.

Fig. 131. 28/11/38.

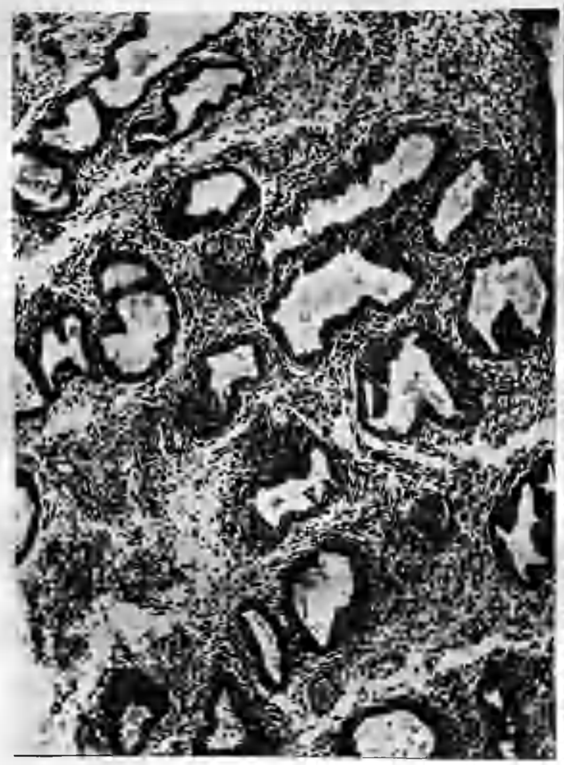


Fig. 132. 30/1/39.

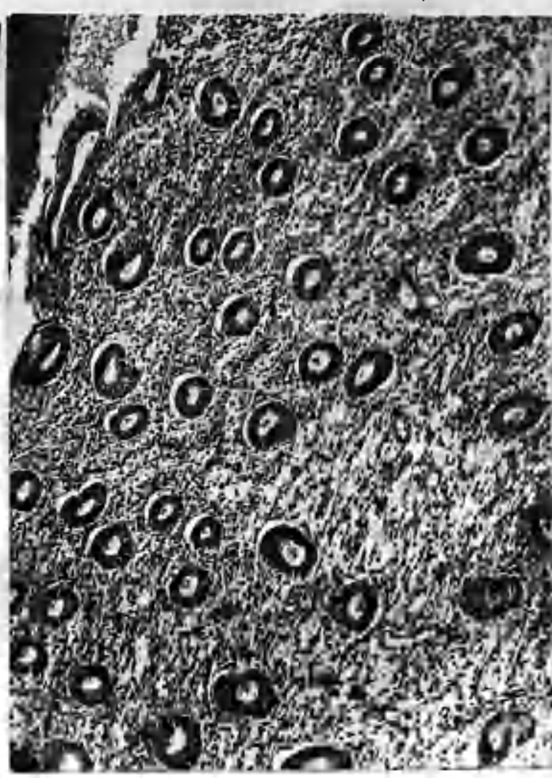


Fig. 133. 7/6/39.

PERIODICALLY ANOVULAR.

McInnes. Case 325.

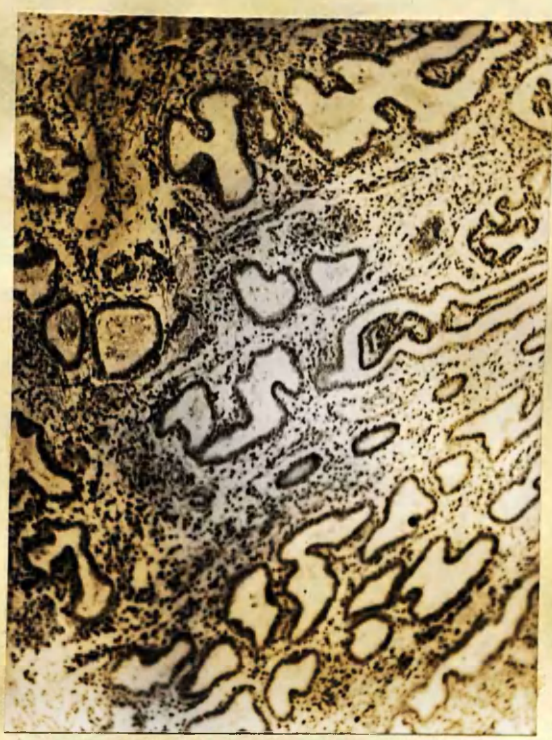


Fig. 133A. 16/11/42.

PERIODICALLY ANOVULAR.

Simpson. Case 271.

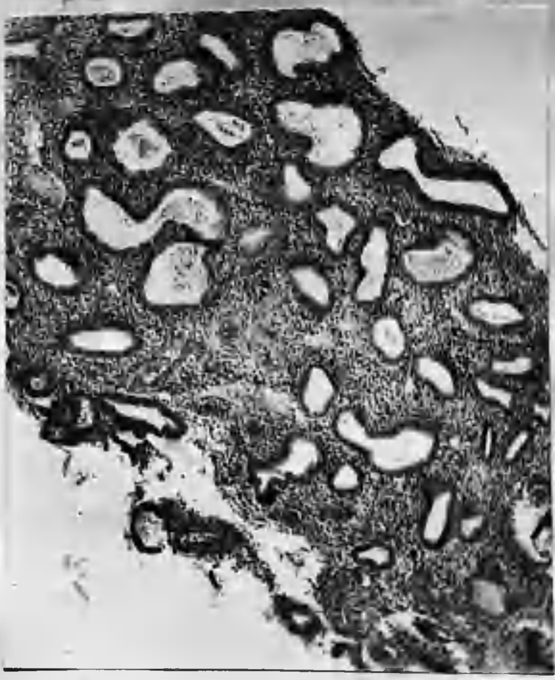


Fig. 134. 4/3/38.

Fig. 135. 25/4/38.

Fig. 136. 20/5/38.

PERIODICALLY ANOVULAR.

White. Case 323.

Fig. 137. 10/11/38.

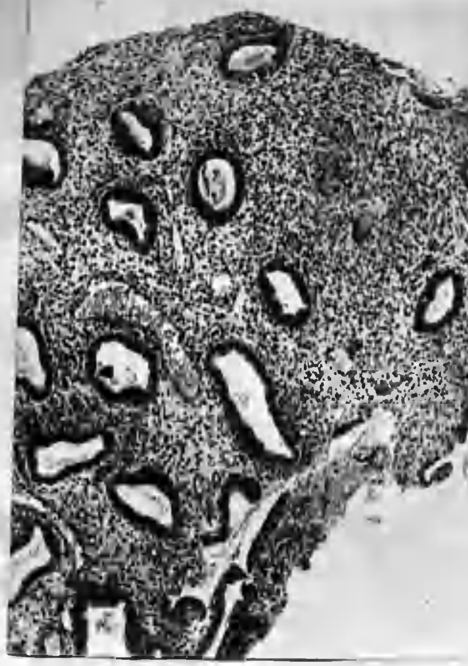


Fig. 138. 5/12/38.

Fig. 139. 21/6/39.

McCabe, Case No. 339. (Figs. 127-129).

1. 26.10.38 - anovular - 5 days premenstrual.
2. 13. 1.39 - secretory - 6 " "
3. 13. 2.39 - anovular - 3 " "

McInnes, Case No. 325. (Figs. 130-133A).

1. 26.10.38 - secretory - 2 days premenstrual.
2. 28.11.38 - anovular(?) - 8 " "
3. 30. 1.39 - secretory - 4 " "
4. 7. 6.39 - anovular - 6 " "
5. 16.11.42 - secretory - 3 " "

In No. 2 menstruation was two days overdue.

Simpson, Case No. 271. (Figs. 134-136).

1. 4.3.38 - anovular - 4 days premenstrual.
2. 25.4.38 - secretory - 3 " "
3. 20.5.38 - anovular - 3 " "

White, Case No. 323. (Figs. 137-139).

1. 10.11.38 - secretory - 1 day premenstrual.
2. 5.12.38 - anovular - 2 days "
3. 21. 6.39 - anovular - 3 " "

B. "Constantly" Anovular Series. (12 Cases).

In three of the following cases, biopsy was not repeated and so, although the endometrium was of the anovular type, the term 'constantly' is not strictly appropriate.

Carlin, Case No. 186. (Figs. 140-142).

1. 26.3.37 - anovular - 3 days premenstrual.
2. 1.7.38 - anovular - 4 " "
3. 31.7.41 - anovular - 2 " "

Craig, Case No. 227. (Fig. 143).

1. 20.11.37 - anovular - 2 days premenstrual.

Graham,/

ANOVULAR.
Carlin. Case 186.

Fig. 140.
26/3/37.

Fig. 141.
1/7/38.

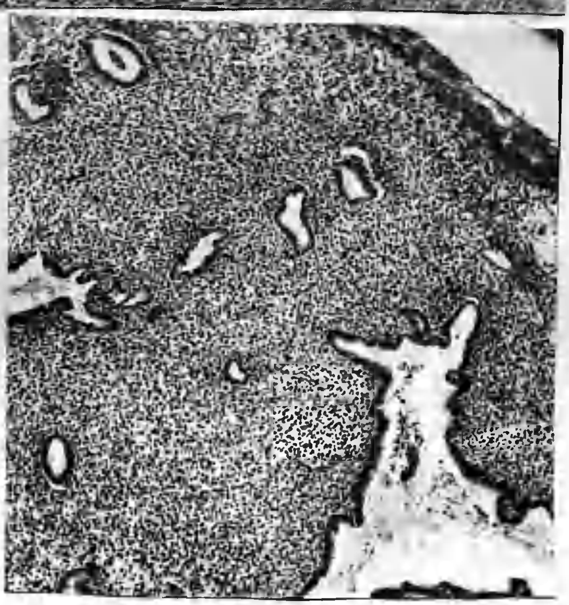


Fig. 142.
31/7/41.

<u>Graham, Case No. 111</u>. (Fig. 144).

1. 30.1.36 - anovular - 1 day premenstrual.

Four subsequent premenstrual biopsies were attempted on the following dates (1) 21.10.37, (2) 18.11.37, (3) 1.9.38, and (4) 4.11.41. In none of them was any endometrium obtained - only mucoid material and amorphous debris.

<u>Hirstfield, Case No. 179</u>. (Figs. 145-147).

1. 21.4.37 - anovular - 3 days premenstrual.
2. 18.5.37 - anovular - 3 " "
3. 29.9.37 - anovular - 7 " "

<u>Logan, Case No. 125</u>. (Figs. 148-153).

1. 23. 4.36 - anovular - 1 day premenstrual.
2. 25. 5.36 - anovular - 6 days "
3. 23.11.36 - anovular - 5 " "
4. 23. 2.37 - anovular - 1 day "
5. 27. 3.37 - anovular - same day as menstruation.
6. 22. 4.37 - anovular - 2 days premenstrual.

<u>Lyttle, Case No. 459</u>. (Figs. 154-156).

1. 21.12.39 - anovular - 3 days premenstrual.
2. 4. 3.40 - anovular - 1 day "
3. 28. 3.40 - anovular - 3 days "

<u>Maloney, Case No. 261</u>. (Figs. 157-159).

1. 9.11.38 - anovular - 3 days premenstrual.
2. 7.12.38 - anovular - 2 " "
3. 1. 2.39 - anovular - 2 " "

<u>McKenzie, Case No. 268</u>. (Figs. 160 and 161).

1. 4.4.38 - anovular - 2 days premenstrual.
2. 24.6.38 - anovular - 1 day "

<u>McVean,</u>/

ANOVULAR.

Craig. Case 227.

Fig. 143. 20/11/37.

Graham. Case 111.

Fig. 144. 30/1/36.

<u>McVean, Case No. 372</u>. (Figs. 162-165).

1. 22.3.39 - anovular - 3 days premenstrual.
2. 10.2.41 - anovular - 2 " "
3. 3.3.41 - anovular - 3 " "
4. 15.5.41 - anovular - 1 day "

<u>Sherlock, Case No. 454</u>. (Fig. 166).

1. 23.9.41 - anovular - 2 days premenstrual.

<u>Sim, Case No. 363</u>. (Fig. 167).

1. 2.3.39 - anovular - 2 days premenstrual.

<u>Stronach, Case No. 387</u>. (Figs. 168-171).

1. 22. 6.39 - anovular - 2 days premenstrual.
2. 23.10.41 - anovular - 1 day "
3. 27.11.41 - anovular - 4 days "
4. 26. 1.42 - anovular - 2 days "

Two observations of importance must be made in considering the above findings; (1) although it is a simple matter to distinguish an early proliferative from a late differentiative (secretory) endometrium, it is very difficult in some cases to decide whether an endometrium is in the late proliferative or early secretory phase, since the one merges into the other (see Martin, Case 132, Fig. 124), and (2) there is a potential source of error on occasion, since one is dependent very frequently on the patient's correctly noting or accurately remembering the date of menstruation.

It/

ANOVULAR.
Hirstfield. Case 179.

Fig. 145. 21/4/37.

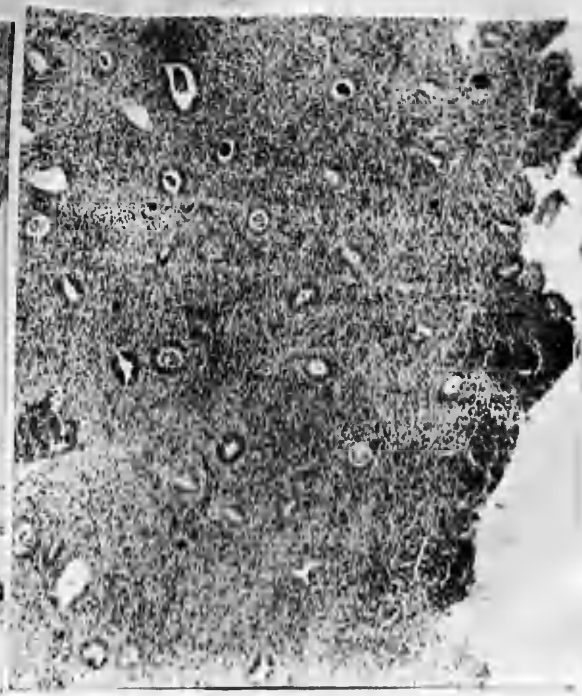


Fig. 146. 18/5/37.

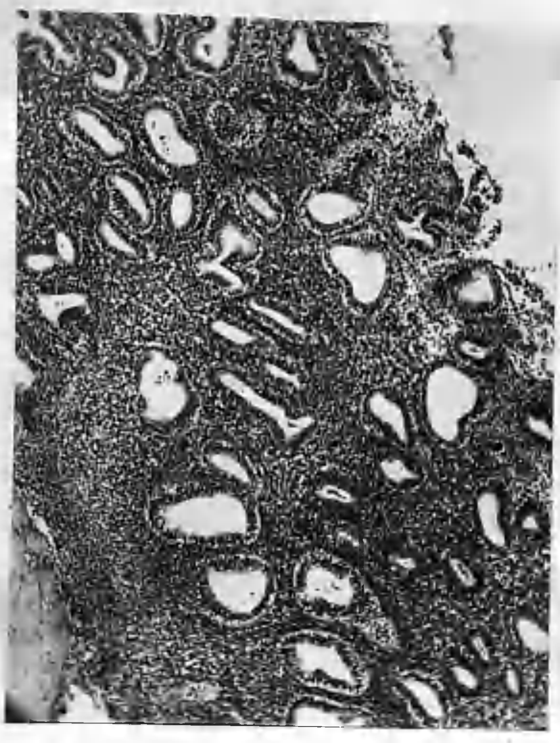


Fig. 147. 29/3/37.

It may be observed at this point that, in the combined series of 'periodically anovular' and 'constantly anovular' cases, none of the 23 became pregnant during study and observation (although one did after treatment), and that five of them showed tuberculosis of the endometrium. These findings will be discussed more fully in the appropriate sections. Likewise the effects of treatment of the above cases will be discussed later and the resultant endometrial reactions illustrated by microphotographs. Six of the series showed chronic endometritis (not tubercular).

A survey of the results of insufflation in these cases shows that the tubes were patent in eleven and not patent in twelve, i.e., an incidence of 52 per cent. non-patency, compared with 38 per cent. in the whole series of 480 patients. No special significance need be attached to this finding, since all five which showed also tubercular endometritis had non-patent tubes. Kymographic tracings in the patency cases showed no features of note, i.e., other than have been already described in the general series. Indeed, active and frequent peristaltic contractions were observed at potential ovulation-time (e.g. McCabe, Case No. 339 - fourteenth day of cycle and McInnes, Case No. 325 - twelfth day). Thus, presumed absence of/

ANOVULAR.
Logan. Case 125.

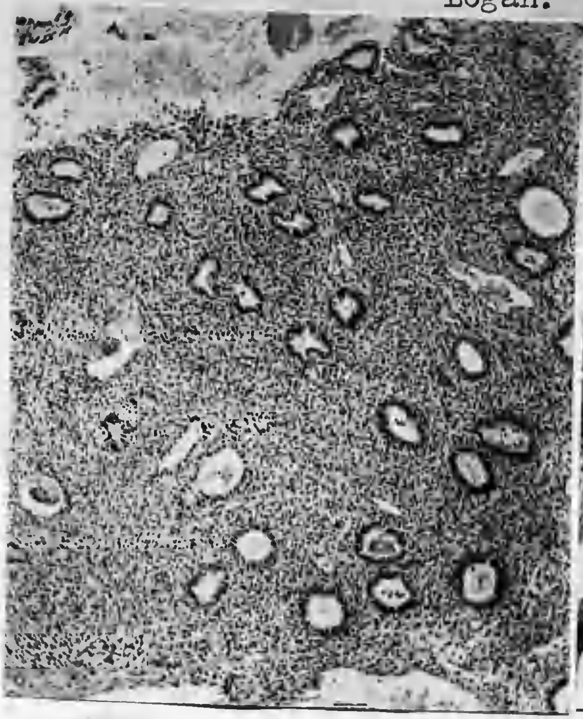


Fig. 148. 23/4/36.

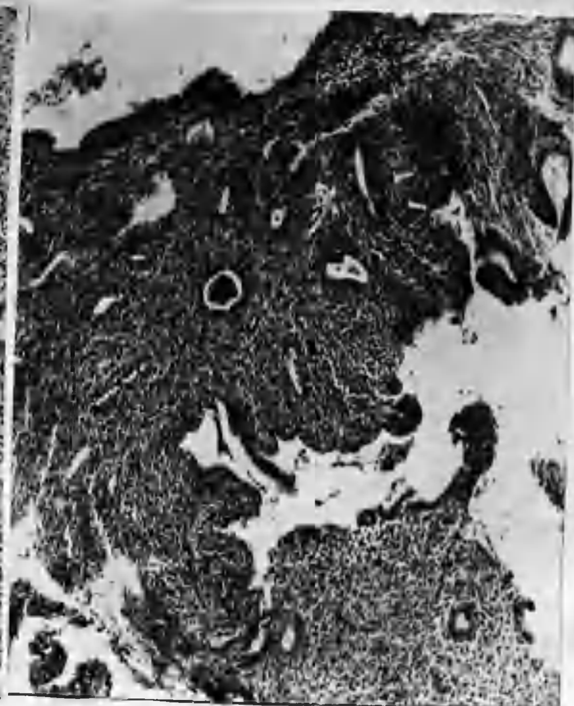


Fig. 149. 25/5/36.

Fig. 150. 23/11/36.

of ovulation did not seem to influence tubal peristalsis.

In concluding this study of the group of twenty-three cases exhibiting anovular cycles, attention may again be drawn to its incidence, namely, 6.4 per cent. in a series of 358 patients. Although this figure is relatively low, it is of much importance since there is no doubt that the presence of anovular cycles is a major infertility factor.

The frequency of 'anovulation' during reproductive life in cases other than those of sterility has not received so much attention, Novak (1940) in fact stating that it would be unsafe to hazard any estimate of its frequency. I, therefore, decided to review a series of 250 consecutive patients - in hospital during 1934-1937 - in whom endometrium had been removed 'premenstrually,' in order that a basis for comparison might be established. Only those patients with regular menstrual cycles were included, but of course it must be admitted that these were not strictly normal cases, otherwise they would not have been curetted in a gynaecological hospital. They merely represent the nearest approach to a normal series which I could obtain. A total of fifteen showed absence of 'secretory' or late differentiative/

ANOVULAR.

Logan. Case 125.

Fig. 151. 23/2/37.

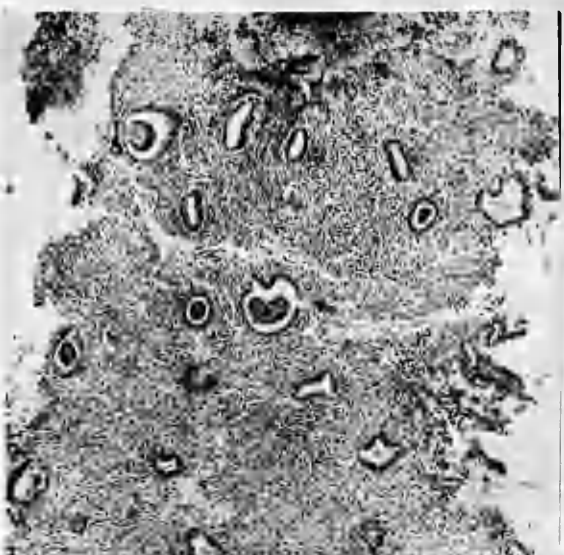


Fig. 152. 27/3/37.

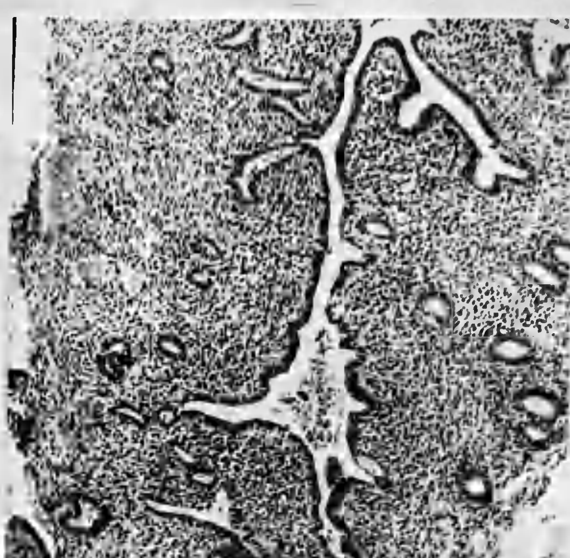


Fig. 153. 22/4/37.

ANOVULAR.

Lyttle. Case 459.

Fig. 154. 21/12/39.

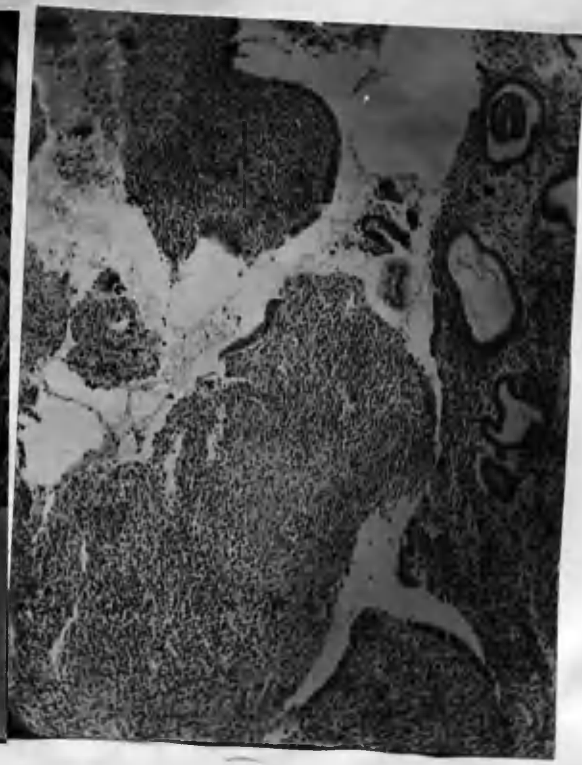


Fig. 155. 4/3/40.

Fig. 156. 28/3/40.

ANOVULAR.

Maloney. Case 261.

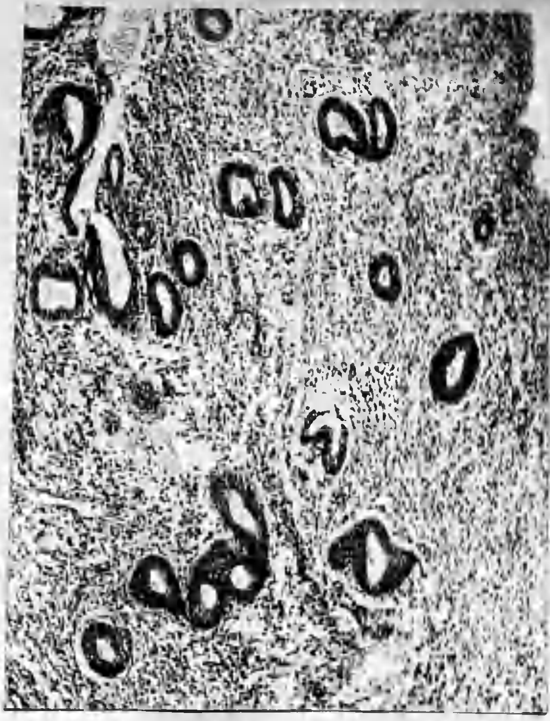


Fig. 157. 9/11/38.

Fig. 158. 7/12/38.

Fig. 159. 1/2/39.

ANOVULAR.
McKenzie. Case 268.

Fig. 160. 4/4/38.

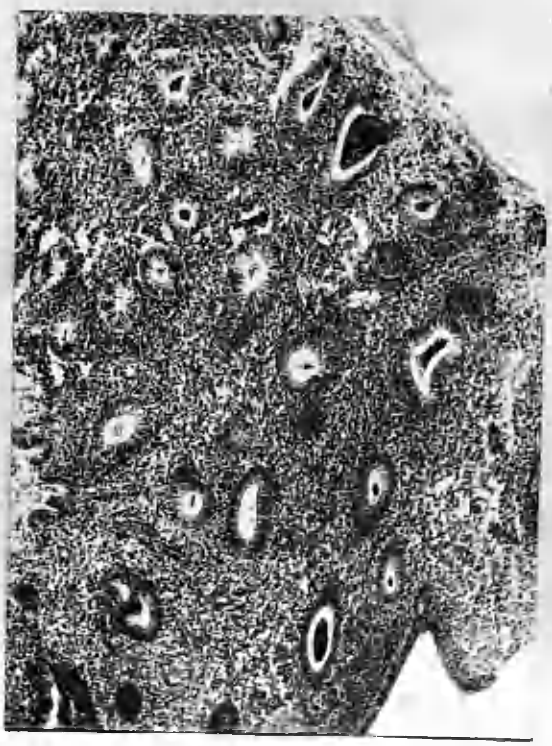


Fig. 161. 24/6/38.

ANOVULAR.

McVean. Case 372.

Fig. 162. 22/3/39.

Fig. 163. 10/2/41.

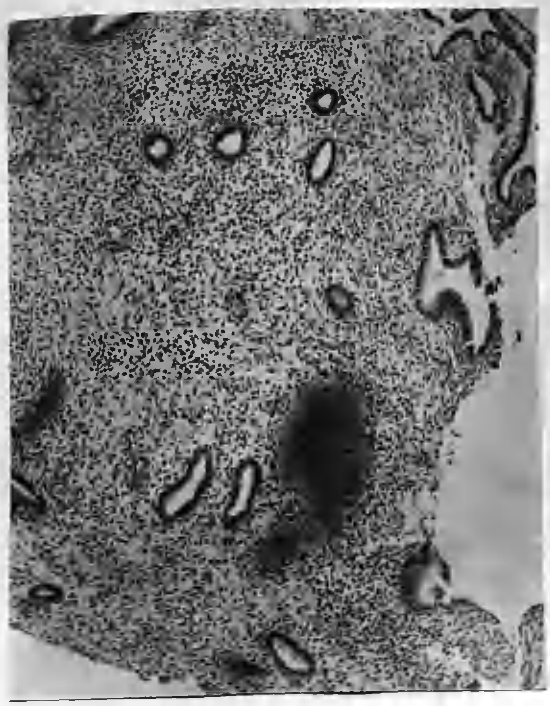


Fig. 164. 3/3/41.

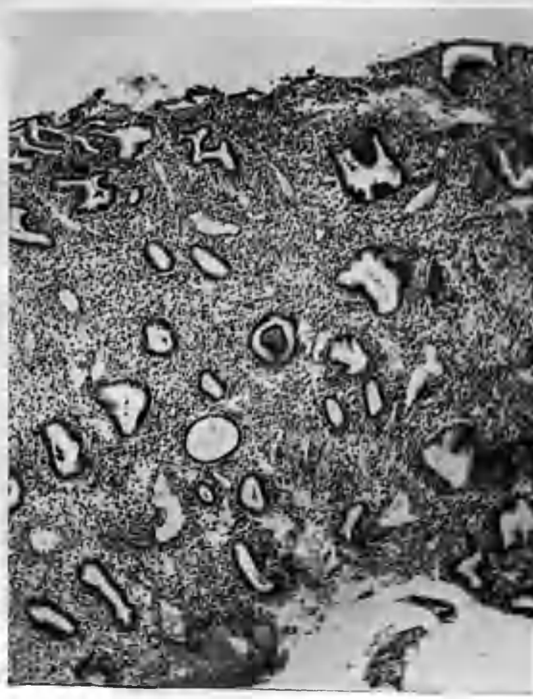


Fig. 165. 15/5/41.

ANOVULAR.

Sherlock. Case 454.

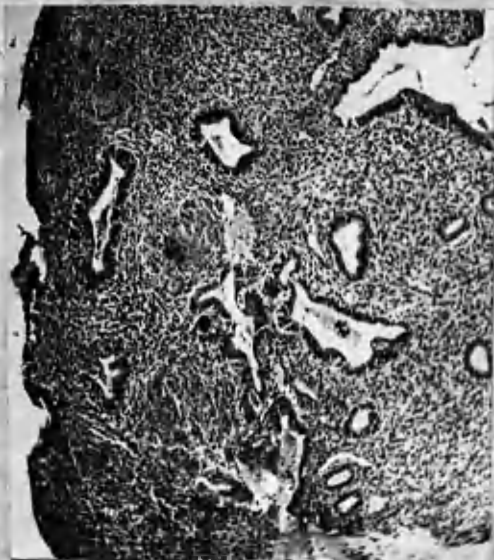


Fig. 166. 23/9/41.

Sim. Case 363.

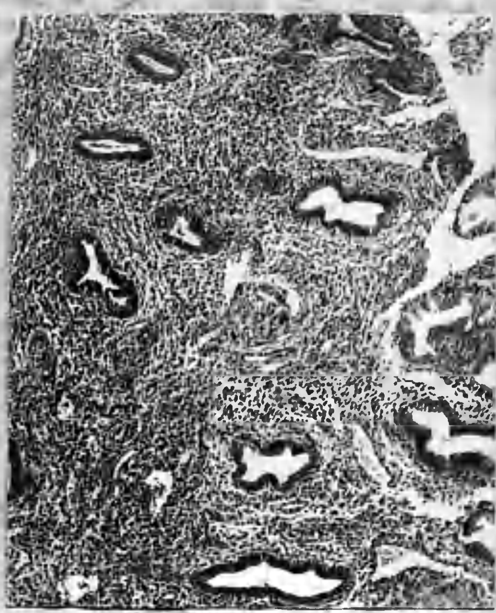


Fig. 167. 2/3/39.

ANOVULAR.

Stronach. Case 387.

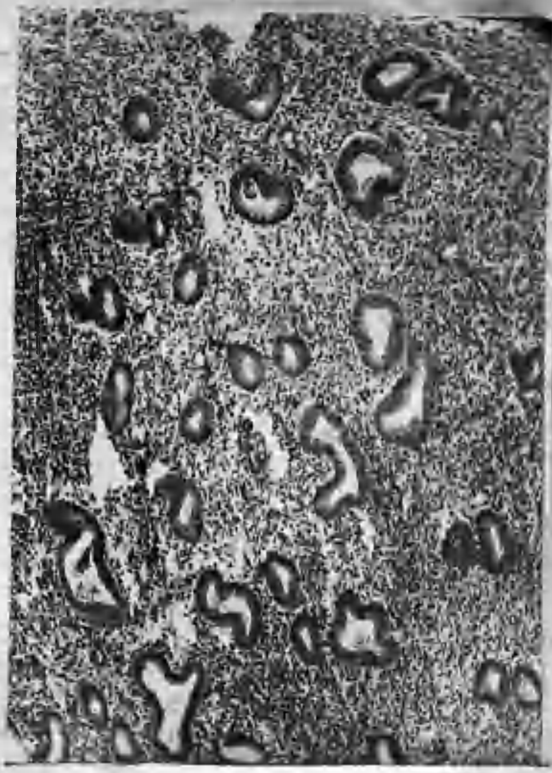


Fig. 168. 22/6/39.

Fig. 169. 23/10/41.

Fig. 170. 27/11/41.

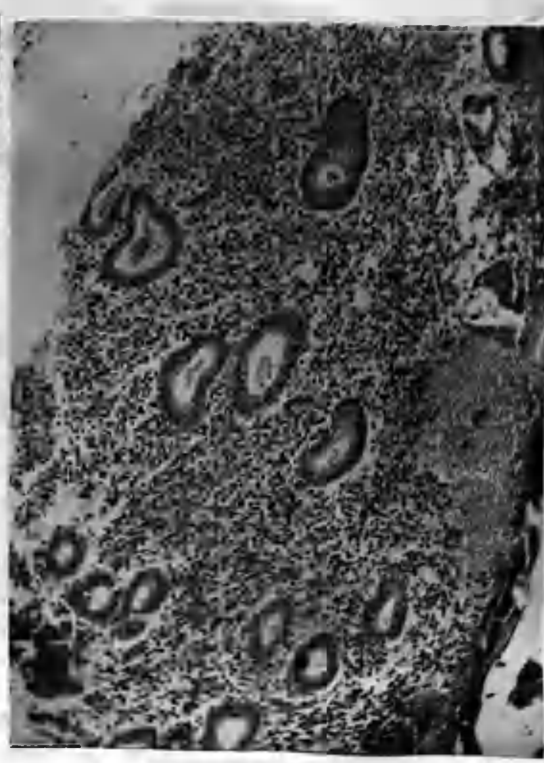


Fig. 171. 26/1/42.

differentiative features and, of these, six were 'sterility cases.' Thus, the general incidence of the condition was 6 per cent., (15 in 250), but in other than sterility cases it was 3.7 per cent (9 in 244). It is to be noted that in these patients the date of onset of menstruation succeeding biopsy is not recorded in the case-histories and therefore the potential source of error, already referred to, must enter into consideration. Accordingly, the incidence figure of 3.7 per cent. must be regarded as a maximum one.

TUBERCULOSIS OF THE ENDOMETRIUM*.

At the beginning of the section on endometrial biopsy it was stated that endometrium was removed and examined in 392 cases. Twenty of these (5.1 per cent.) showed chronic tubercular endometritis, the essential lesion being the presence of an occasional tubercle follicle or cluster of tubercles with the characteristic epitheloid and giant cells. In many of the cases, marked chronic/

*I am indebted to Professor J.W.S. Blacklock, Notman Professor of Pathology, Glasgow University, for examination and confirmatory diagnosis in all the sections of tubercular and suspected tubercular endometria, and to Dr. A.M. Sutherland, Pathologist, Royal Samaritan Hospital for Women, for guinea-pig inoculations, cultures & co-operation in diagnosis and follow-up.

Fig. 172. Adamson.
Case 97. 23/2/39.

Fig. 173. Barlow.
Case 437. 2/8/39.

Fig. 174. Barlow.
Case 437. 29/1/42.

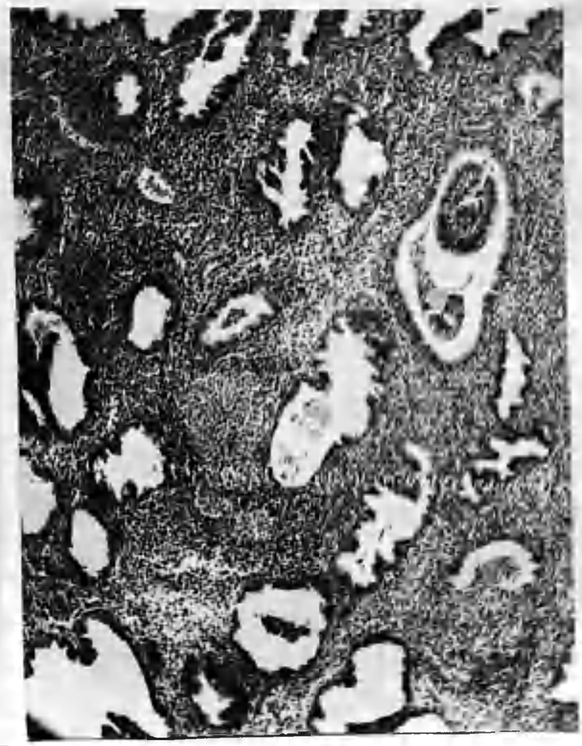


Fig. 175. Bolton.
Case 146. 22/8/36.

chronic inflammatory infiltration with plasma and round cells was also present. (It may be mentioned here that with the exception of six cases in the anovular groups, no other sections showed chronic endometritis in any of the entire sterility series). Some of the sections showed caseation to a greater or lesser degree and some showed almost complete destruction of the endometrial glandular structure. In these twenty patients, fifty-two endometria were removed and examined: in thirteen of the patients endometrium was removed premenstrually, eight showing normal differentiative characters and five showing their absence [already included in the 'periodically anovular' group (two cases) and 'constantly anovular' group (three cases)]; in the remaining seven patients endometrium was not removed at the premenstrual phase. A full account of the biopsies and findings in each case now follows:

<u>Adamson, Case No. 97</u>.

1. 12.12.35 - tubercle negative.
2. 23. 2.39 - " positive.

Tubes not patent: radiograph pelvis negative: follow-up, six years.

<u>Barlow, Case No. 437</u>.

1. 2.8.39 - tubercle positive.
2. 29.1.42 - " "

Tubes not tested: radiograph chest negative: follow-up two years.

Bolton,/

Fig. 176. Bolton.
Case 146. 2/12/37.

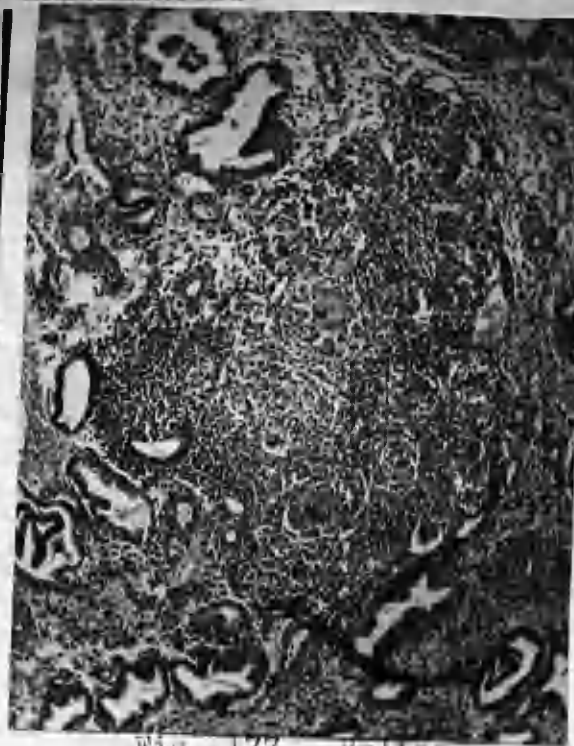


Fig. 177. Bolton.
Case 146. 25/8/41.

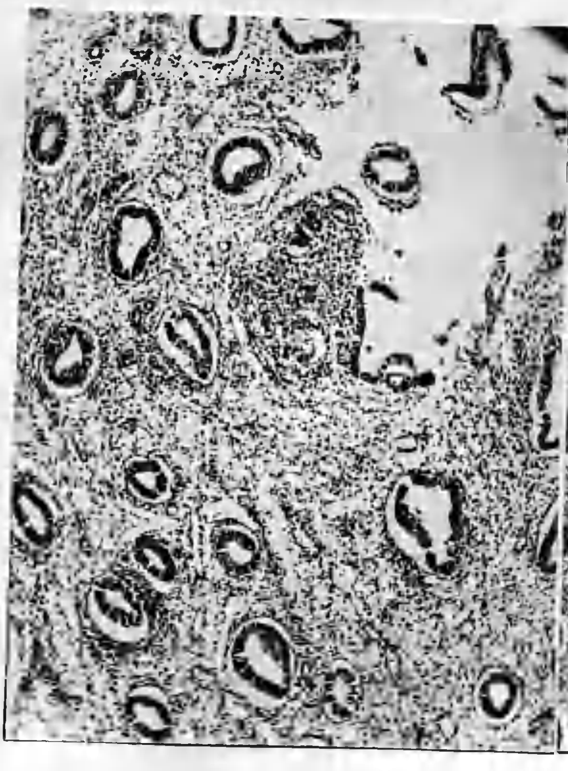


Fig. 178. Burns.
Case 96. 18/11/35.

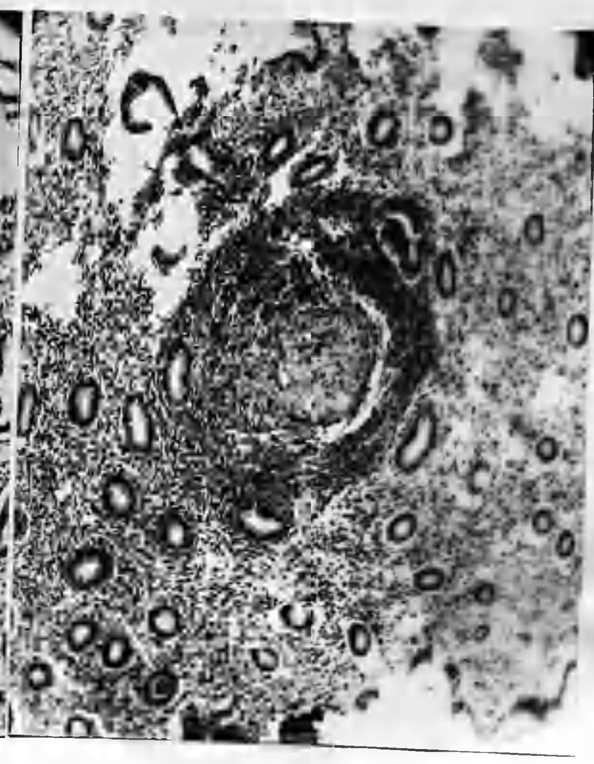


Fig. 179. Burrell.
Case 106. 2[illegible]/2/36.

Bolton, Case No. 146.

1. 22. 8.36 - tubercle positive.
2. 2.12.37 - " "
3. 25. 8.41 - " "

Tubes not patent: radiograph chest negative: follow-up, five years.

Burns, Case No. 96.

1. 18.11.35 - tubercle positive.

Tubes not patent: no radiographs: no follow-up.

Burrell, Case No. 106.

1. 20.2.36 - tubercle positive.

Tubes not patent: no radiographs: no follow-up.

Caul, Case No. 452.

1. 26.10.39 - tubercle positive.
2. 18.12.39 - " negative.
3. 24. 2.42 - " positive.

Tubes patent: radiograph chest negative: follow-up, two years.

Craig, Case No. 227.

1. 20.11.37 - tubercle positive.

Tubes not patent: radiograph pelvis negative: follow-up, four years.

Forrest, Case No. 338.

1. 30.11.38 - tubercle positive.
2. 25. 1.39 - " negative.
3. 27. 3.39 - " "
4. 25. 5.39 - " "

Tubes not patent: radiograph pelvis negative: follow-up three years.

Haig, Case No. 347.

1. 18.4.40 - tubercle positive.
2. 24.2.42 - " "

Tubes not tested: radiograph chest negative: follow-up four years.

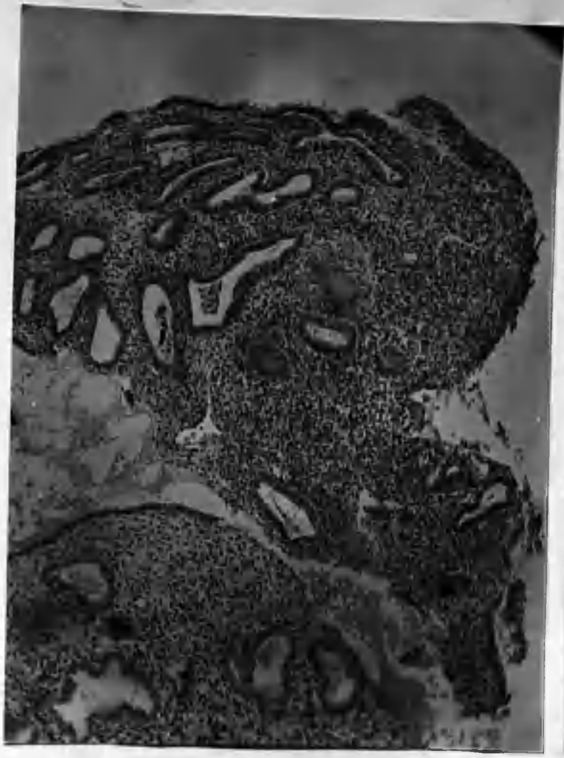


Fig. 180. Caul.
Case 452. 26/10/39.

Fig. 181. Craig.
Case 227. 20/11/37.

Fig. 182. Forrest.
Case 338. 30/11/38.

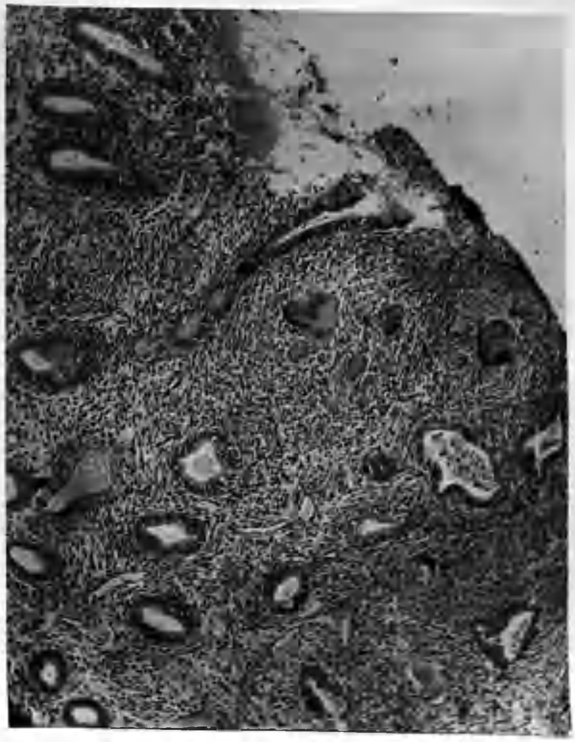


Fig. 183. [illegible]ig.
Case 347. 18/4/4[illegible].

Lyttle, Case No. 459.

1. 21.12.39 - tubercle negative.
2. 4. 3.40 - " positive.
3. 28. 3.40 - " "
4. 17. 2.42 - " negative.

Tubes not patent: radiograph chest negative: follow-up two and a half years.

Moss, Case No. 394.

1. 25.5.39 - tubercle positive.
2. 17.8.39 - " negative.
3. 29.1.42 - " "

Tubes patent: no radiographs: follow-up, two and a half years.

McPherson, Case No. 393.

1. 11. 5.39 - tubercle positive.
2. 19. 5.39 - " "
3. 3.11.41 - " "

Tubes not patent: radiographs chest and abdomen negative: follow-up, two and a half years.

Quinn, Case No. 21.

1. 10.9.35 - tubercle positive.
2. 28.6.38 - " "

Tubes not patent: radiograph chest positive: follow-up, two and a half years.

Sherlock, Case No. 454.

1. 23. 9.41 - tubercle positive.
2. 8.12.41 - " "

Tubes not patent: radiographs chest and abdomen negative: follow-up, two years.

Shields, Case No. 84.

1. 14. 3.35 - tubercle positive.
2. 25.11.41 - " negative.

Tubes not patent: radiographs chest and abdomen negative: follow-up, seven years.

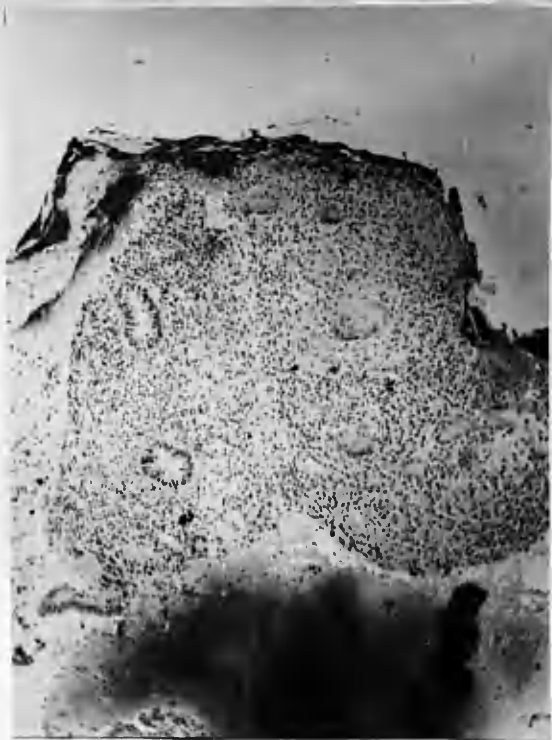


Fig. 184. Haig.
Case 347. 24/2/42.

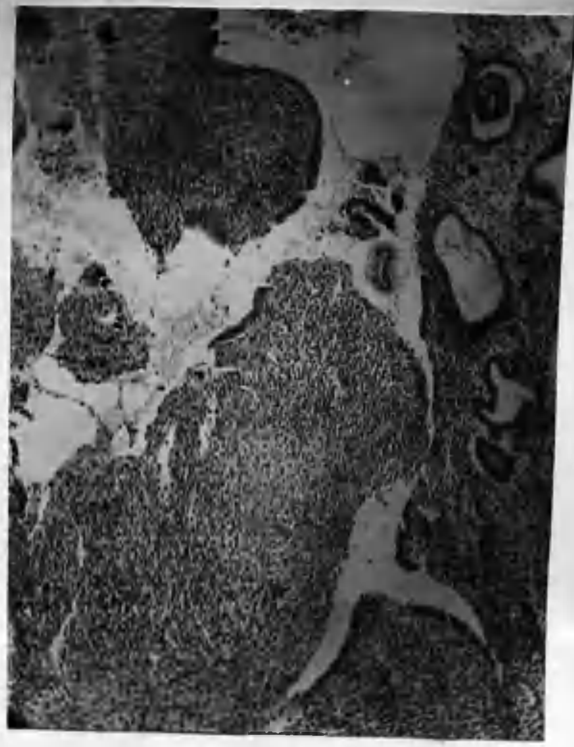


Fig. 185. Lyttle.
Case 459. 4/3/40.

Fig. 186. Lyttle.
Case 459. 28/3/40.

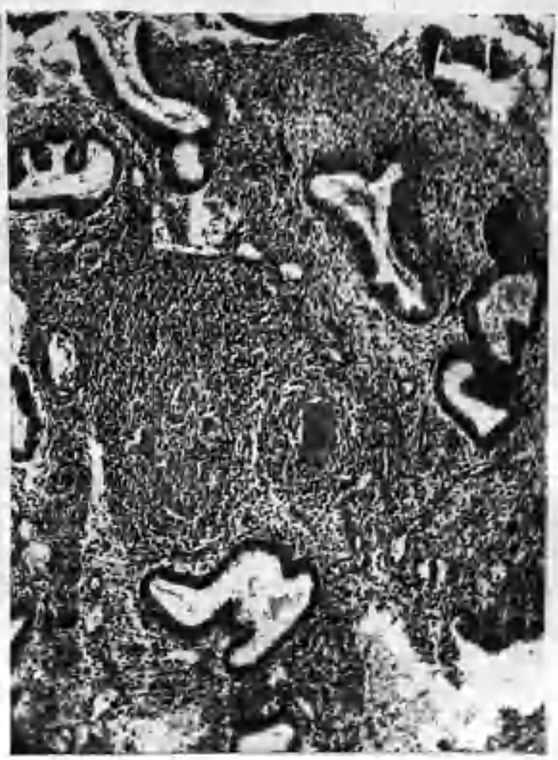


Fig. 187. Ross.
Case 394. 25/5/39.

E. Smith, Case No. 98.

1. 26.11.35 - tubercle negative.
2. 26. 5.37 - " "
3. 22.12.37 - " positive.
4. 26.10.39 - " negative.

Tubes patent: radiographs chest and spine positive, abdomen negative: follow-up, six years: died 18.1.42 - "spinal abscess."

H. Smith, Case No. 469.

1. 15.4.40 - tubercle positive.
2. 31.7.41 - " negative.
3. 7.8.41 - " "
4. 27.8.41 - " "

Tubes not patent: radiograph chest positive: follow-up, two years.

Thomson, Case No. 76.

1. 20. 6.35 - tubercle negative.
2. 9.11.37 - " "
3. 16.11.37 - " positive.
4. 23.11.37 - " negative.

Tubes not patent: no radiographs: follow-up, two and a half years.

White, Case No. 323.

1. 10.11.38 - tubercle positive.
2. 5.12.38 - " "
3. 21. 6.39 - " "

Tubes not patent: radiograph pelvis negative: follow-up, three years.

Whitelaw, Case No. 353.

1. 22.10.41 - tubercle positive.
2. 28.10.41 - " "

Tubes patent, no radiographs: follow-up, two years.

Fig. 188. McPherson.
Case 393. 11/5/39.

Fig. 189. McPherson.
Case 393. 3/11/41.

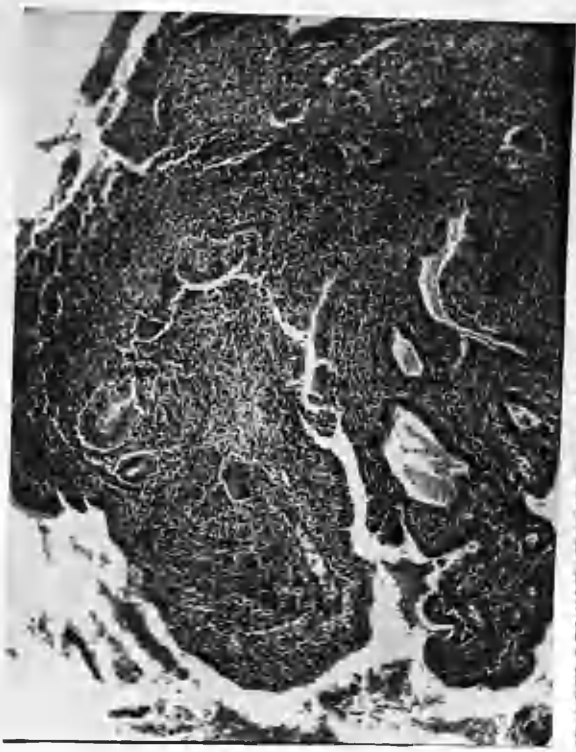


Fig. 190. Quinn.
Case 21. 10/9/35.

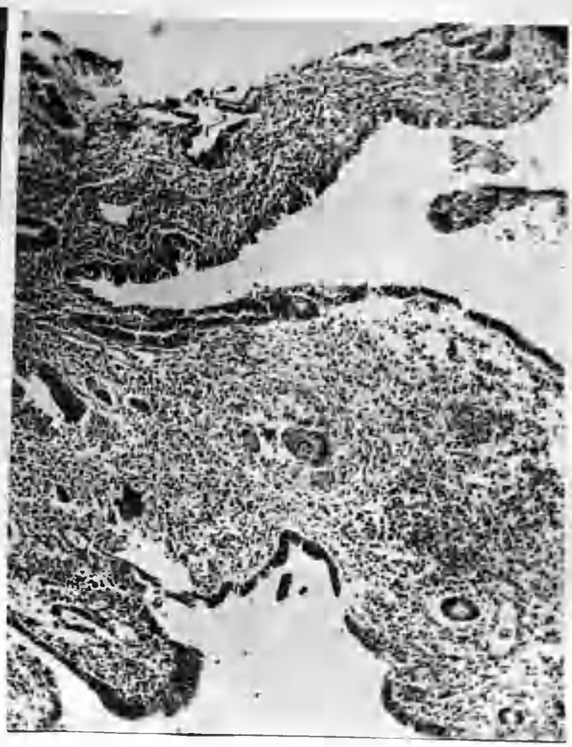


Fig. 191. Quinn.
Case 21. 28/6/35.

All of these sections which showed tubercle (thirty-three) are illustrated in Figs. 172-203 (except two which reproduced poorly on account of scantiness of endometrium or ill-formed follicle, viz., Caul, 24.2.42 and McPherson, 3.11.41).

Review of the above findings gives the following results:

1. One biopsy was performed in three cases;
   two biopsies were " " seven " ;
   three " " " " five " ;
   four " " " " five " ;

2. When biopsy was performed only once, on each occasion, of course, it was tubercle positive: when performed twice, it was tubercle positive on both occasions in five patients and once positive and once negative in two patients: when performed either three or four times in the remaining patients, on eighteen occasions it was tubercle positive and on seventeen, tubercle negative.

3. Endometrial tuberculosis was found to be still evidenced after the following lengthy periods of time: (a) two and a half years, Barlow; (b) five years, Bolton; (c) two and a third years, Caul; (d) two years, Haig; (e) two and a half years, McPherson; (f) two and three quarter years, Quinn.

4. In five cases, (Lyttle, Moss, Shields, E. Smith and H. Smith), no evidence of tuberculosis was seen after the following lengthy intervals of time respectively had elapsed since a positive finding; two/

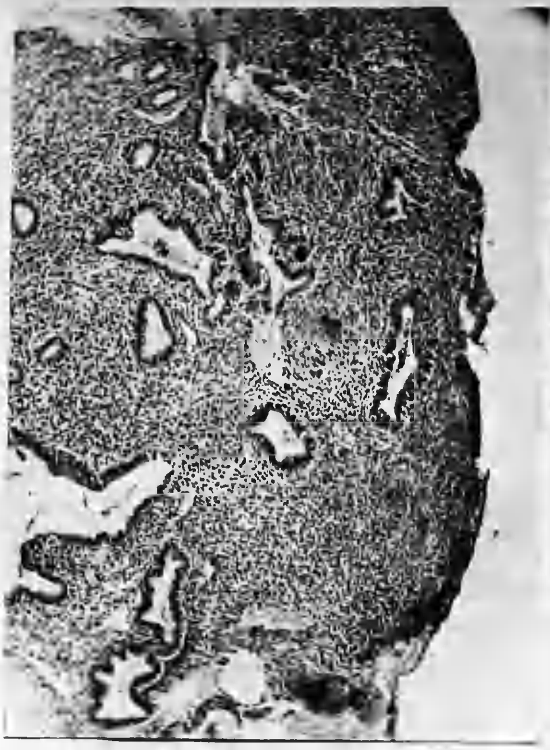
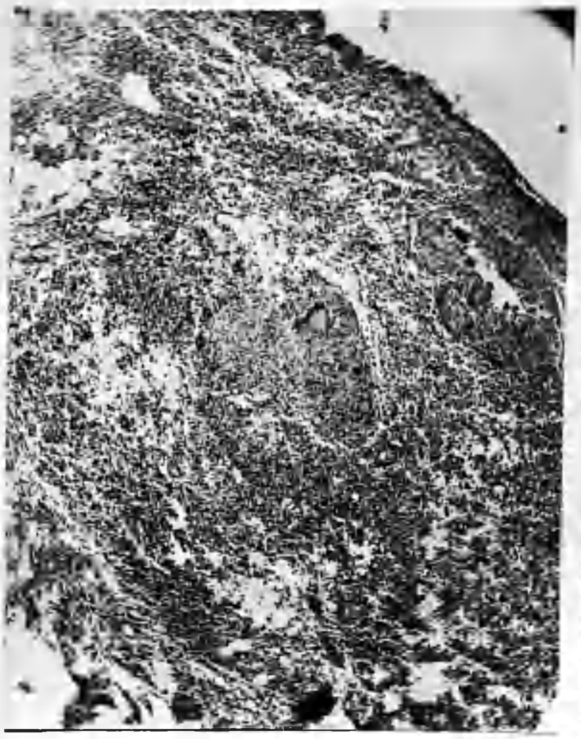


Fig. 192. Sherlock.
Case 454. 23/9/41.

Fig. 193. Sherlock.
Case 454. 8/12/41.



(Two sections from same 'block'.)

Fig. 194. Shields.
Case 84. 14/3/35.

Fig. 195. Shields.
Case. 84. 14/3/35.

two years, two and a half years, six and a half years, two years and one and a half years. This finding must not be taken to mean that the disease was no longer present: it simply means that the particular sections examined did not show it - this will be referred to presently.

5. Tubal insufflation, performed in eighteen of the twenty cases, showed non-patency in fourteen and patency in four: hysterosalpingography in four cases confirmed non-patency.

6. Radiographs of the chest in ten cases showed no evidence of pulmonary tuberculosis in seven, but two showed apical tuberculosis of both lungs (Quinn, Case No. 21 and H. Smith, Case No. 469) and the other calcified plaques at both apices (E. Smith, Case No. 98) - in the latter, radiograph of the spine showed Pott's disease: no calcified glands were seen in abdominal radiographs (four cases) or in pelvic ones (four cases, after lipiodol).

7. Two patients had no follow-up and could not be traced: the period of follow-up in the others was:- two to three years in ten, three years in two, four years in two, five years in one, six years in two and seven years in one.

None of the above group became pregnant, but this cannot be ascribed wholly to the presence of tubercular endometritis since, as has been mentioned, fourteen of the patients had blocked tubes. It must be emphasized, however, that in no instance at the time of insufflation was any tubal mass palpable or

blockage/

TUBERCULOUS ENDOMETRITIS.

Fig. 196. E. Smith.
Case 98. 22/12/37.

Fig. 197. H. Smith.
Case 469. 15/4/40.

Fig. 198. Thomson.
Case 76. 16/11/37.

Fig. 199. White.
Case 323. 10/11/38.

blockage suspected (fourteen of the patients had pelvic examination under anaesthesia). In addition, in none of these cases was pelvic tuberculosis diagnosed or suspected when endometrial biopsy was performed. Indeed, all were noted as enjoying good health and, with the exception of three cases, there was no history suggestive of tuberculosis in childhood or adolescence; the three exceptions were, (1) Caul, Case No. 452, aged 28 years, "pleurisy and gastroenteritis" at age of 17 years, (2) Sherlock, Case No. 454, aged 29 years, "T.B. gland of neck" at age of 5 years, and (3) Thomson, Case No. 76, aged 24 years, "tabes mesenterica" at age of 14 years (nine months in sanatorium).

In this connection it may be mentioned that in the whole series of five hundred cases, seven had a definite tubercular history (excluding the three cases just described), viz. (1) "abdominal tuberculosis in childhood," (2) dactylitis, (3) abdomino-pelvic, (4) abdomino-pelvic, (5) abdomino-pelvic, (6) pelvic and (7) thoracic and pelvic - in one of these cases the diagnosis was made on laparotomy before marriage, but in four the diagnosis was made on laparotomy during the course of these studies. All had endometrial biopsy performed but none showed tuberculosis.

Examination/

Examination of the husbands by Dr. W.S. Mack was performed in five cases: none showed genital tuberculosis: in four, sperm morphology and count were normal and in one very deficient.

Guinea-pigs were inoculated with biopsied endometrium in twelve cases:* eight gave positive results and four negative: in one of the latter, insufficient endometrium was obtained for histological study, but in the others tubercle follicles were not seen in the sections examined. All but one of the positive cases, examined histologically, showed tubercle follicles in the endometrium removed for inoculation. From five of the positive guinea-pigs, cultures of the tubercle bacillus were made. Growth was obtained in three and each was identified by animal inoculation as being of the human type.

The occasional absence of evidence of tubercular follicles on several occasions prompted further study of the endometria concerned. The paraffin blocks were re-imbedded and re-orientated so that further sections might be taken from the other end of the biopsy material. This was done in twelve blocks from six patients. Numerous sections were examined, but there was no evidence of tuberculosis in any of them. Further light in this connection/

* The inoculation technique was as follows: the tissue was placed in 2-3 ccs. normal saline, transferred to a mortar cut into very small portions and finely macerated by a pestle: subcutaneous inoculation of the "mixture" was made into a guinea-pig. After two months the animal was killed. All material used was, of course, sterile. In the positive guinea-pigs, Lowenstein's medium was inoculated from the splenic lesions: in those in which culture was positive a moderate growth was usually obtained in four weeks.

 Duplicate

Examination of the husbands by Dr. W.S. Mack was performed in five cases: none showed genital tuberculosis: in four, sperm morphology and count were normal and in one very deficient.

Guinea-pigs were inoculated with biopsied endometrium in six cases: four gave positive results and two negative: in one of the latter (Bolton, Case No. 146) insufficient endometrium was obtained for histological study, but in the other (Shields, Case No. 84, 25.11.41) tubercle follicles were not seen in the sections examined. All four positive cases showed tubercle follicles histologically in the endometrium removed for inoculation.*

The occasional absence of evidence of tubercular follicles on several occasions prompted further study of the endometria concerned. The paraffin blocks were re-imbedded and re-orientated so that further sections might be taken from the other end of the biopsy material. This was done in twelve blocks from six patients. Numerous sections were examined, but there was no evidence of tuberculosis in any of them. Further light in this connection/

* The inoculation technique was as follows: the tissue was placed in 2-3 ccs. normal saline, transferred to a mortar, cut into very small portions and finely macerated by a pestle: subcutaneous inoculation of the "mixture" was made into a guinea-pig. After two months the animal was killed. All material used was, of course, sterile.

Fig. 200. White.
Case 323. 5/12/38.

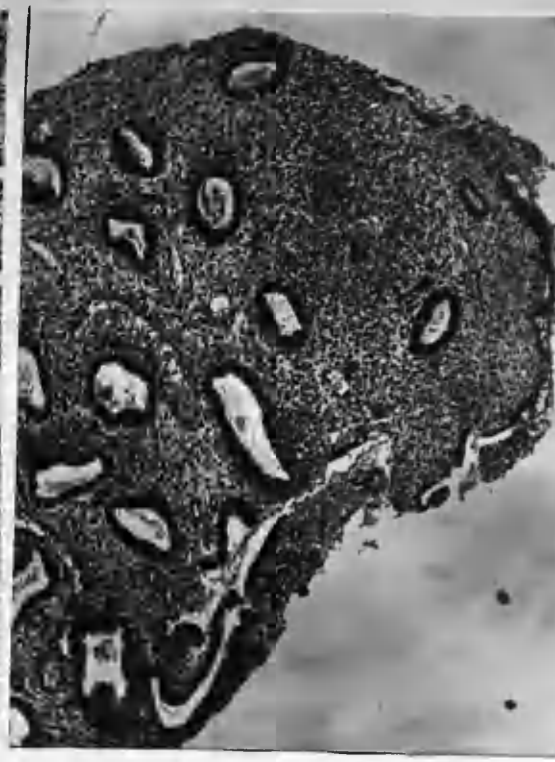


Fig. 201. White.
Case 323. 21/6/39.

Fig. 202. Whitelaw.
Case 353. 22/10/41.

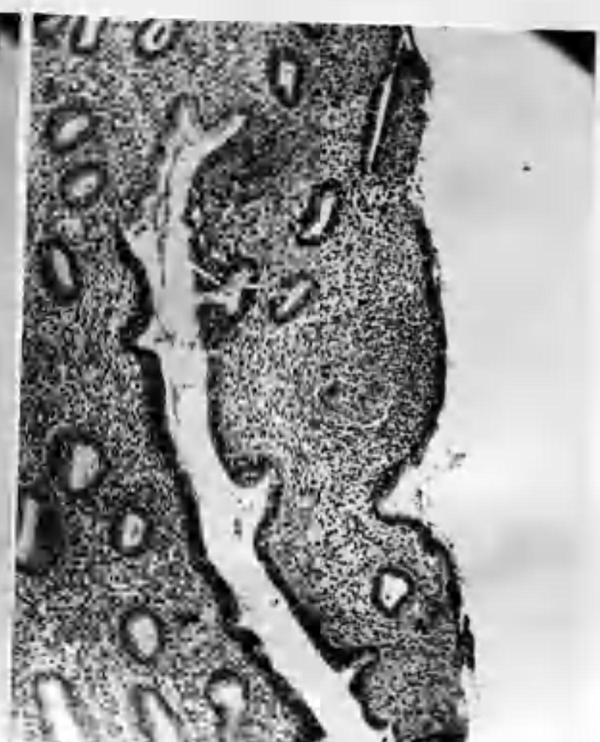


Fig. 203. Whitelaw.
Case 353. 28/10/41.

connection was thrown by the examination of additional sections of the definitely positive biopsies: in several of the cases, sections showed no evidence of tubercle follicles. It may be concluded, therefore, that absence of signs of tubercular endometritis in any given biopsy is not evidence that the disease is not present and that the incidence figure of 5.1 per cent. in my series of 392 cases is an absolutely minimal one. There is no doubt that the frequency of endometrial tuberculosis in cases of sterility (and unsuspected of tuberculosis), is not sufficiently appreciated by gynaecologists. It would follow, therefore, that endometrial biopsy should be performed in all cases, with a view to excluding the possibility of tubercular endometritis, and that, to obtain a high degree of diagnostic accuracy, it should be repeated, when negative, in those showing evidence of anovular cycles or of chronic endometritis.

Examination of the Husband.

Examination of the husbands was performed by Dr. W.S. Mack in 114 cases of the total series of 500. The proportion is, unfortunately, small and, in view of the findings about to be described, unsatisfactory. But a study of the 114 cases, entirely unselected, ought to give information which may be regarded as representative/

tive of the larger series. The main reasons for the relatively small number of husbands examined were, (1) in the earlier cases of the series the importance of this aspect of the subject was not sufficiently emphasized, (b) disinclination and often complete refusal of the male partner, on various grounds and (c) since September, 1939, war has made it extremely difficult to get more than an exceptional case to attend.

Examination was particularly directed to general health, previous history, sexual life, genitalia and seminal fluid, but I do not propose to describe these findings in detail. However, fuller consideration will be given to those cases in which the results of seminal examination could be correlated to the findings in the partners and to the results of follow-up.

Seminal Examination.

Specimens were examined in 114 cases: 78 were normal (68.4 per cent.), 15 were markedly deficient (13.2 per cent.) and 21 showed complete absence of sperms - azoospermia (18.4 per cent.). The arbitrary figure of thirty million sperms per ccm. was used as the basic distinguishing line between normality and marked deficiency, keeping close in mind, however, the fact that sperm morphology is as important if not more important/

important than the mere count. However, it was found that in the "normal group" (over 30 million per ccm.) only in one case were the morphological characters abnormal.

The essential features of each of these groups are as follows:

A. Normal - 78 cases (68.4 per cent.).

1. All showed a sperm count of over thirty million per ccm., most being between 100 and 160 million.

2. Sperm morphology was normal in all except Sim, Case No. 263, showing "an undue percentage of rounded heads; count 60 million."

3. Two cases showed numerous crystals, (a) Oliver, Case No. 451, (on each of three tests) and (b) McDonnell, Case No. 419 (on one test, count being 70 million).

4. In three (Garth, Case No. 324; Hamilton, Case No. 331; and Stewart, Case No. 322), a large left varicocele was present. (The wives of the two latter had normal full-time pregnancies).

5. Results of follow-up of wives:

Untraced 6
Pregnancy 17

(All pregnancies went to normal full-time, except one that miscarried at three months and one that had to be terminated at four months for hyperemesis).

No pregnancy .. 55.

(Twenty/

(Twenty had non-patent tubes and of the remaining thirty-seven with patent tubes, four had anovular cycles and one had tubercular endometritis).

B. Markedly Deficient - 15 cases (13.2 per cent.).

1. All showed a sperm count of under thirty million, several of them being below four million.
2. Sperm morphology was normal in six but the others showed various abnormalities, e.g., aberrant, immature forms and head irregularities.
3. The test was done once in five patients, twice in six patients, thrice in three patients and on four occasions in one. Repetition of the test (within six months) invariably gave the same result.
4. One patient had a history of malaria, but none of the others presented features of note either in their medical history or on physical examination.
5. Results of follow-up of wives:

   Untraced 1
   Pregnant 3

   (One miscarried at one month, one miscarried at two months and one went on to full-time. In the last case, although the seminal specimen showed "many crystals, count of 28 million [repeated], many of which with rounded heads," pregnancy ensued within two months of the test).

   No pregnancy 11

   (Only one had non-patent tubes: all the others had patent tubes, but one of them had anovular cycles/

cycles and one had tuberculous endometritis. One patient [Burt, Case No. 464] had curettage performed "on several occasions" in different hospitals for sterility - her husband had not been examined: the present investigation showed on two occasions a sperm count of under twenty million and poor morphology: another patient [Moss, Case No. 394] had curettage performed eighteen months previously - here, also, the husband's semen had not been examined.)

C. <u>Azoospermia</u> - <u>21 cases (18.4 per cent.)</u>.

1. Seminal examination was performed once only in nine patients, twice in eleven and four times in one. In all cases, sperms were entirely absent.

2. Four patients showed abundant crystals but no other deposits in the semen.

3. In seven nothing abnormal was found either in the medical history or on physical examination: in six, one or both testicles were small and soft: one had been operated upon for undescended testicles: two had a testicle removed on account of tuberculosis: one had an atrophic left testicle: one had bilateral gonococcal epididymitis nine years previously and one had had uncomplicated gonococcal urethritis.

4. Results of follow-up of wives:

   <u>Untraced</u> .... nil.
   <u>Pregnant</u> ....nil.

   (Fifteen had patent tubes, four non-patent and in/

in two tubal patency was not tested: one of the "patency-group" showed anovular cycles. Six had previously had a dilatation and curettage performed for sterility by other surgeons, without the male being referred for examination; indeed one of them had been curetted twice.)

Treatment.

The methods of treatment employed - some of them are also diagnostic measures and have already been discussed - were as follows:

1. Tubal insufflation.
2. Pelvic diathermy with repeated insufflation.
3. Hystero-salpingography.
4. Hormone therapy for (a) blocked tubes, (b) anovular cycles and (c) no endometrium.
5. Surgical methods.
   (a) dilatation and curettage:
   (b) perineoplasty - for dyspareunia:
   (c) salpingostomy.
6. Treatment of the male partner.
7. Artificial insemination.

1. Tubal insufflation.

This has already been described.

2./

2. Pelvic diathermy with repeated insufflation*.

Nineteen patients with blocked tubes had a course of pelvic diathermy: all but one had repeated insufflations, either before or during the treatment. Non-patency was confirmed in seventeen cases by hysterosalpingography. Laparotomy in two patients (in one prior to treatment and in the other subsequently with a view to salpingostomy) revealed tuberculous salpingitis: lipiodol showed hydrosalpinx in another case.

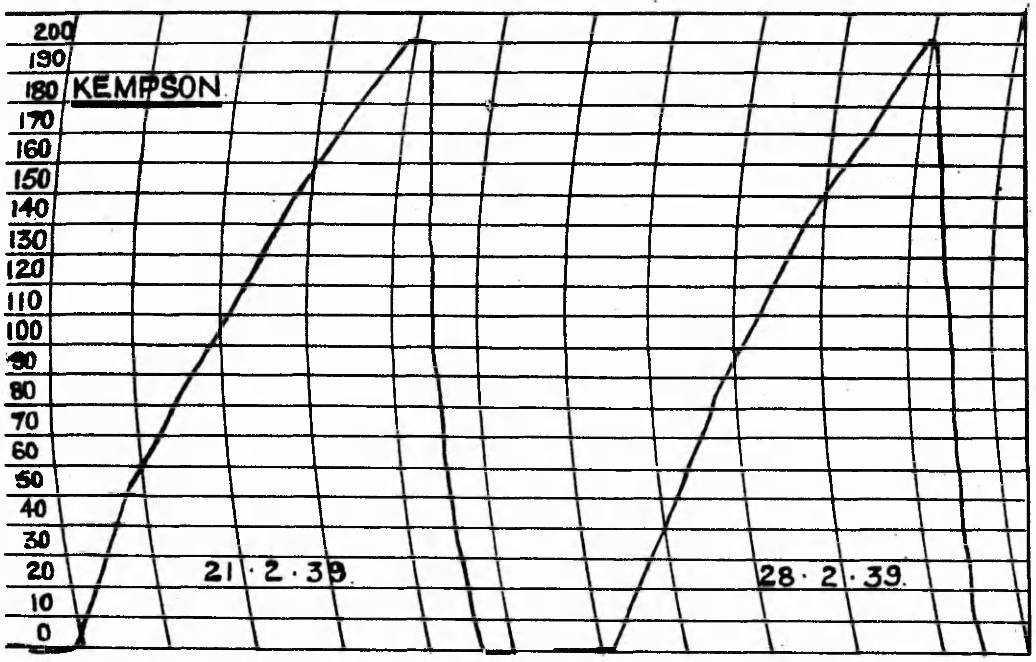
One patient failed to report after treatment and could not be traced: twelve of the remainder had kymographic insufflation repeated and eleven of them still showed complete tubal blockage: in the remaining one (Kempson, Case No. 427), normal tubal patency appeared to have been established and she became pregnant/

*Pelvic Diathermy. The patient is placed on a couch in the supine position. A lead belt electrode is placed round the abdomen just above the iliac crests so that the whole belt is in contact with the skin. This belt is then connected to one pole of the Diathermy apparatus.

A solid cylindrical vaginal electrode is lubricated and inserted. When this is in position, the blunt metal end of the vaginal electrode is in contact with the cervix. This electrode is connected to the other pole of the Diathermy apparatus. The temperature of the vaginal electrode is about 108°F.

The current is increased from the lowest reading on the scale of the meter to 1,000 milliamperes. The treatment is continued at this level for thirty minutes, five or six daily treatments being given each week. The course consists of twenty treatments.

PLATE XIV.


KEMPSON
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
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10
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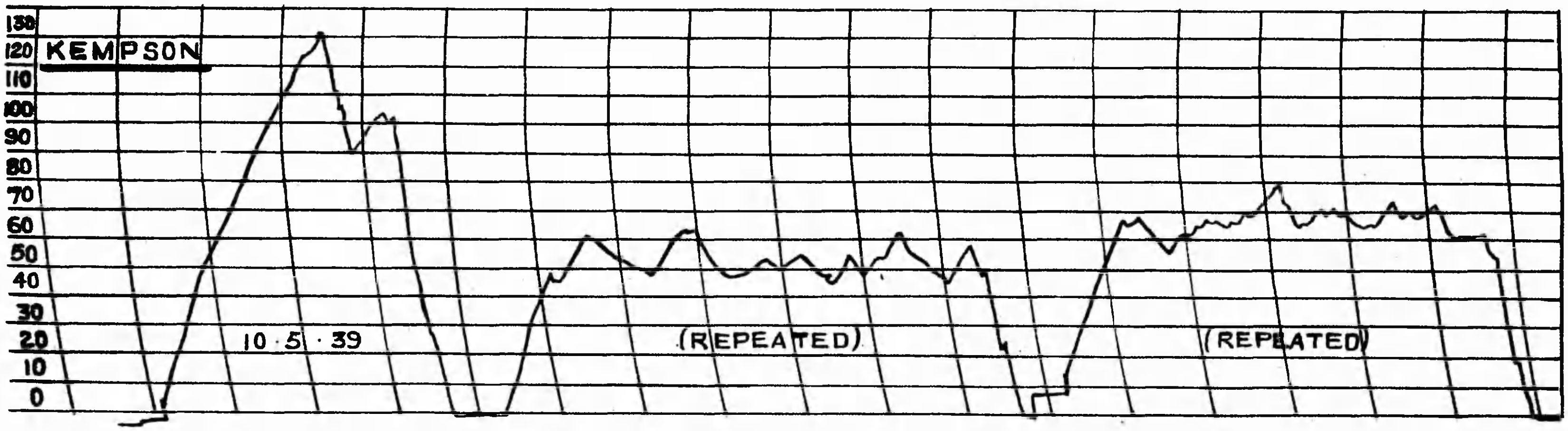
21 · 2 · 39.
28 · 2 · 39.


KEMPSON
130
120
110
100
90
80
70
60
50
40
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20
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0
10 · 5 · 39
(REPEATED)
(REPEATED)


KEMPSON
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
16 · 5 · 39.
(REPEATED)
(REPEATED)

pregnant one month after completion of diathermy (Plate XIV). A normal full-time child was born. In eighteen patients traced no pregnancy ensued (two husbands had azoospermia).

3. Hystero-salpingography.

This has already been described.

4. Hormone therapy.

(a) Blocked tubes (6 cases):

Logan, Case No. 125: three insufflations (without kymograph) showed non-patency on the following dates, 23.4.36, 23.11.36 and 19.2.37: four months later she had twenty injections of antuitrin S. - P.D. & Co. - (1 cc. daily for ten days before each of two 'periods') in an endeavour to promote ovulation: eight months later she had six daily injections of pregnant mare serum (Serogan - B.D.H. - 200 Rat units each); it was not until three years later that insufflation was repeated but on this occasion the kymograph showed normal patency and function: no claim, of course, can be substantiated in this case that establishment of patency was due to hormone administration.

Sharpe, Case No. 279: a course of pelvic diathermy failed to restore tubal patency; five injections of Dimenformon (Organon: 50,000 international units each benzoate) at five day intervals also failed; two months

later/

later. she was given two injections of Dimenformon (50,000 units) at weekly intervals during the first half of a menstrual cycle and two injections of Progestin (Organon - 5 international units each) during the second half; one year later insufflation still showed non-patency: a further course of oestrogenic hormone (Ovocyclin P - Ciba - 50,000 dipropionate units each) was then given, as above, during the next three months, three insufflations were performed, all showing tubal blockage.

Wallace, Case No. 285: insufflation and lipiodol injection in 1938 showed bilateral blockage at fimbriated ends: three years later kymographic insufflation confirmed blockage: five injections of Ovocyclin (50,000 units each) were given at five-day intervals: two further insufflations at a short space of time showed no tubal patency.

Simons, Case No. 288: several insufflations showed non-patency: lipiodol failed to pass into tubes: six injections of pregnant mare serum (Serogan) were unsuccessful; a course of pelvic diathermy had no effect: stilboestrol (1 mgm. t.i.d.) tablets were prescribed; on two occasions subsequently kymographic insufflation still showed non-patency (on each of these occasions the pressure of gas was raised to 230 mm. Hg., but without avail).

McVean, Case No. 372: three insufflations showed tubal blockage: seven injections of Progynon (10,000 units each) were given at two-day intervals; two months later, insufflation showed non-patency.

Kennedy, Case No. 445: two insufflations: course of diathermy: insufflation repeated still showed tubal blockage: five injections of Benzo-gynoestrol (Roussel) at/

ANOVULAR CASE AFTER TREATMENT.

(Compare with Figs. 148-153).

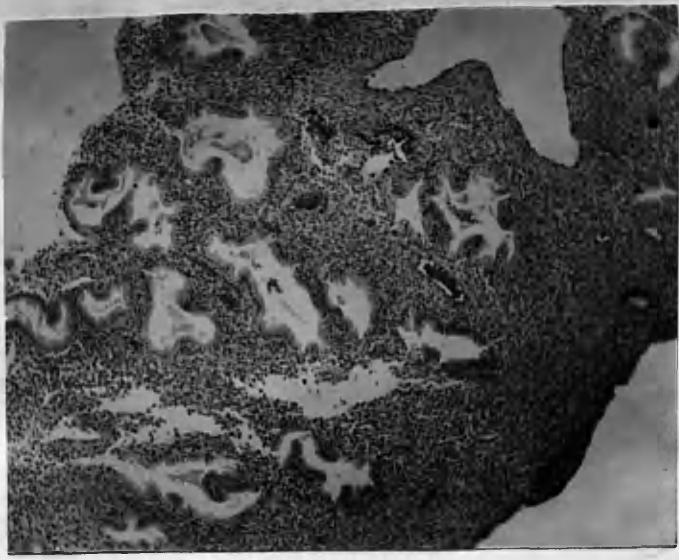


Fig. 204. Logan.
Case 125. 10/2/38.
(See page 262).

Fig. 205. Logan.
Case 125. 10/3/38.
(See page 262).

at five-day intervals, 50,000 unit doses, were unsuccessful, gas failing to pass in either of two tests at a two-month interval; one year later a similar course of Dimenformon was administered but without success.

(b) <u>Anovular Cycles (5 cases)</u>:

<u>Logan, Case No. 109</u>: six constantly anovular sections are illustrated in Figs. 148-153. After twenty injections of Antuitrin S, biopsy was performed on 10.2.38: the section obtained is illustrated in Fig. 204: menstruation occurred two days later. On 22.2.38 she received the first of six daily intramuscular injections of pregnant mare serum: biopsy was performed on 10.3.38, eight days before menstruation commenced: the section is shown in Fig. 205.

Both sections are seen to be quite different from those before hormonal treatment, secretory features being apparent: no pregnancy ensued.

<u>Hirstfield, Case No. 179:</u> three constantly anovular sections are illustrated in Figs. 145-147. On 8.3.38 she received the first of six daily injections of pregnant mare serum intramuscularly. Biopsy was performed on 31.3.38, menstruation commenced later on the same date: the section is shown in Fig. 206: late differentiative features are present.

No pregnancy has resulted.

<u>McKenzie</u>,/

ANOVULAR CASES AFTER TREATMENT.

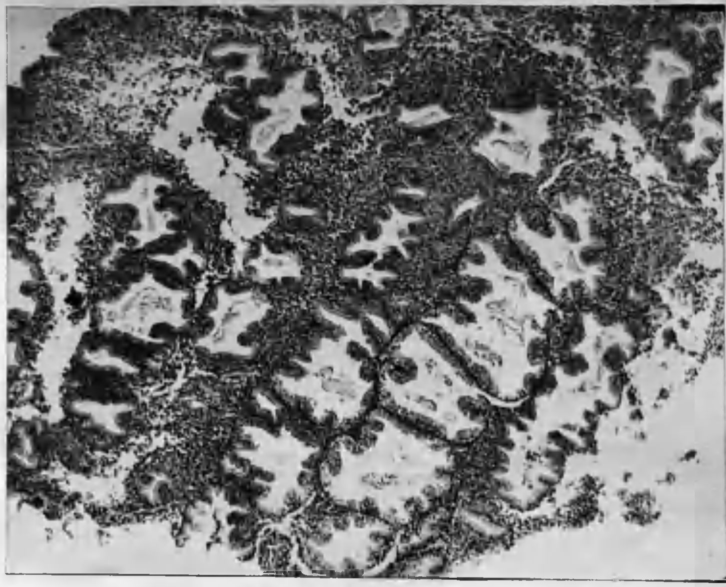


Fig. 206. Hirstfield.
Case 179. 31/3/38.
cf. Figs. 145-147.

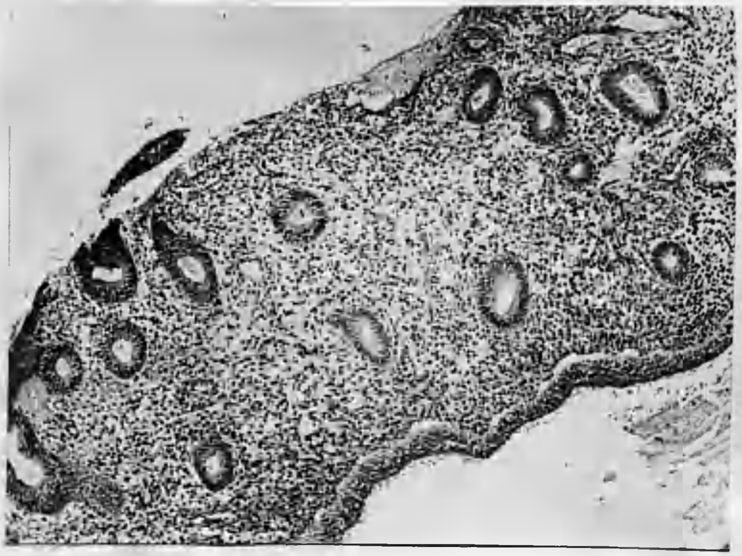


Fig. 207. Kennedy.
Case 445. 16/9/41.
cf. Figs. 122-123.

ANOVULAR CASE AFTER TREATMENT.
cf. Figs. 160-161.

Fig. 208. McKenzie.
Case268. 23/2/39.

Fig. 209. McKenzie.
Case 268. 30/3/39.

McKenzie, Case No. 268: two anovular sections are illustrated in Figs. 160 and 161. Commencing on 3.8.38 she was given 1 c.c. Progynon (10,000 units) twice weekly for six weeks (until 12.9.38). After a rest of one month, she was given a further course as above (until 1.12.38). Biopsy performed on 23.2.39 (six days before menstruation) and 30.3.39 (six days before menstration) showed early differentiative features on both occasions: the sections are illustrated in Figs. 208 and 209. Subsequently she had small doses of Stilboestrol at intervals.

Just under a year after the above biopsies, she became pregnant. A normal full-time infant was born on 7.11.40.

Stronach, Case No. 387: four constantly anovular sections are seen in Figs. 168-171. On 22.12.41 (twenty-first day of cycle) she received a single intramuscular injection of 100,000 international units of Glandubolin (Richter) - "oestrone shock therapy of Clauberg." Biopsy was performed on 26.12.41, a section of endometrium being illustrated in Fig. 210. Menstruation commenced two days later. On 9.2.42 (twelfth day of cycle) the above injection was repeated: biopsy was done on 26.2.42: (Fig. 211) menstruation commenced two days later. On the second day of menstruation biopsy was again done: the section is illustrated in Fig. 212. On the twelfth day of this cycle an intramuscular injection of pregnant mare serum (Luteoantin - Richter - 400 rat units) was given: twelve days later, biopsy was performed: the section is shown in Fig. 213. On no occasion were differentiative features present.

Kennedy,

ANOVULAR CASE AFTER TREATMENT.

(Stronach, Case 387).
See page 263.

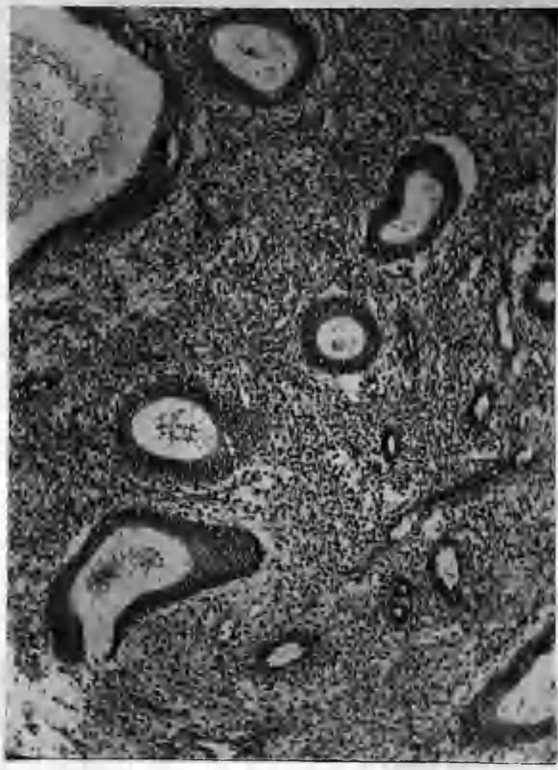


Fig. 210. 26/12/41.

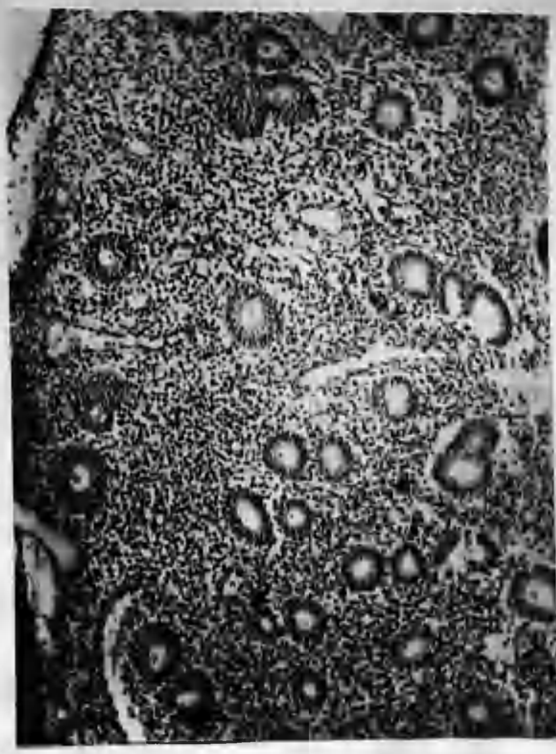


Fig. 211. 26/2/42.

Fig. 212. 2/3/42.
(During menstruation).

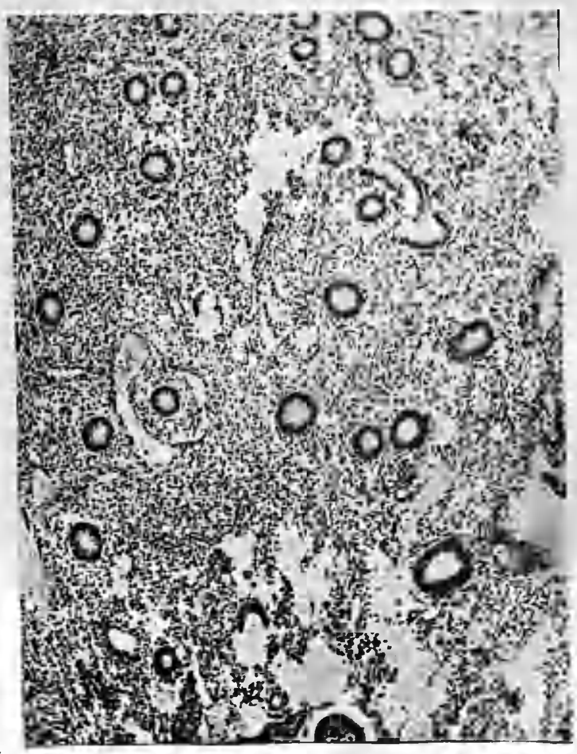


Fig. 213. 24/3/42.

Kennedy, Case No. 445: two sections are shown in Figs. 122 and 123.
The first shows differentiative characters but the second does not, although menstruation occurred four days later. Sixteen months later an attempt was made to restore tubal patency by five injections of 50,000 units, Dimenformon daily, commencing on the sixth day of a cycle. Biopsy was performed on the twenty-sixth day of the same cycle: although menstruation was due two days later it did not occur until twelve days later. The section, illustrated in Fig. 207 shows no evidence of differentiation.

(c) No endometrium (2 cases):

Of the four cases in which no endometrium was obtained premenstrually after many attempts (already described in the section on "Endometrial biopsy"), two were treated by hormone injections. In one, courses of large doses of oestrogenic hormone in the first half of two cycles failed to produce endometrium and in the other treatment by oestrogenic hormone followed by progesterone was equally unsuccessful.

5. Surgical Methods.

(a) Dilatation and curettage:

This operation was used in many of the earlier cases of the series in the course of investigation, but not as a therapeutic procedure exclusively. During the last five years it has been very largely abandoned.
As/

As already stated, only twenty of the entire series of five hundred cases did not have tubal insufflation: fourteen had dilatation and curettage and six had endometrial biopsy only: nine curetted patients were traced, one of whom had become pregnant, and all six biopsy cases were traced, four of whom had become pregnant. These pregnancies will be referred to again in the results of "follow-up."

(b) Perineoplasty:

This was performed in nine patients complaining of dyspareunia, but in no instance without curettage or insufflation. Its contribution to the successful treatment of sterility was undoubted in some cases, almost impossible to assess in a few others, but in at least one case it was valueless since the patient affirmed that coitus remained impossible, although examination showed that the anatomical result was satisfactory.

(c) Salpingostomy:

New openings were made in the Fallopian tubes in five cases. The diagnosis of non-patency was confirmed by lipiodol in four of them. In one patient (Wilson, Case No. 44), insufflation performed three years after salpingostomy showed tubal patency. One patient was untraced, but the remainder did not become pregnant. Hysterographs, taken before and after salpingostomy are shown in Figs. 84 and 85.

6. Treatment of the Male Partner.

Dr. W.S. Mack treated a number of husbands in the "azoospermia" and "markedly deficient" groups with various preparations and dosages of gonadotropic hormone. Great difficulty was experienced in obtaining systematic attendance and co-operation and, since the outbreak of war, treatment of the males has become almost impossible. In no case has azoospermia been benefitted, but occasionally the quality of a deficient semen has improved.

7. Artificial Insemination.

In one case (Phillips, Case No. 385), the husband having azoospermia, semen from a donor was injected on one occasion into the vagina and external cervical os about presumptive ovulation time. No pregnancy resulted.

Results of Follow-up.

Of the 500 cases, 409 were traced following at varying intervals from one to eight years after investigation or treatment. None are included without one full year's observation: indeed, in more than 50 per cent. of patients the follow-up extended to three years or more. Failure to trace the remaining 91 patients is very largely due/

due to war circumstances, e.g. evacuation, absence from home on service or war work, being "bombed-out," etc. Loss of desire to become pregnant is a frequent cause of patients failing to report or even to reply to a follow-up letter.

Of the 409 cases traced, 115 became pregnant, i.e. 28.1 per cent. Their main features are summarised as follows:

1. Eighty-two were under 30 years of age and thirty-three were 30 years or older when first under observation.

2. The oldest was 40 years old (married four years) - she miscarried at three months.

3. Forty-nine were married three years or more; seventeen were married five years or more: one was married ten years (aged 32): (no patient married longer than this became pregnant).

4. Tubal insufflation was performed in 110: patency had been diagnosed in 81 and non-patency in 29 - of the latter, 23 had been insufflated under anaesthesia and 6 without it: in one of the 29 cases which showed apparent tubal blockage two insufflations had been performed, and, in another, five insufflations during a course of pelvic diathermy, but in all the others only one: hysterosalpingography was done in four of the twenty-nine, but showed tubal patency: the fallacy of a single finding of non-patency on insufflation is apparent from these figures, but the possibility of the therapeutic effect of insufflation/

insufflation must not be overlooked.

5. Pregnancy terminated in miscarriage in eighteen of the 115 i.e. 16 per cent., but four subsequently had a full-time child: one further case had pregnancy terminated (in another hospital) for hyperemesis gravidarum: and another for pre-eclamptic toxaemia at seven months: thus, 101 or 88 per cent. bore a child (two cases had twins): one patient had three miscarriages and another two - neither have since gone to term. Endometrium, removed premenstrually, in fifteen of these cases showed normal features in all. Semen was examined in four husbands: it was markedly deficient in two.

6. The sex incidence of the infants was approximately 46 per cent. male and 54 per cent. female.

7. <u>Time elapsing between insufflation and conception</u>.

15	pregnancies	occurred	within	1	month	after	insufflation.
11	"	"	"	2	months	"	"
14	"	"	"	3	"	"	"
2	"	"	"	4	"	"	"
6	"	"	"	5	"	"	"
7	"	"	"	6	"	"	"
55							

Thus, forty of 110 pregnancies (36 per cent.) occurred within three months of insufflation and fifty-five (50 per cent.) within six months. During the following six months twenty-four became pregnant. It must not be overlooked, however, that in 36 per cent. of the group of 110 cases more than one insufflation was performed; the data given above refer to the latest insufflation.

In/

In view of the fact that repeated kymographic studies were made in many of the cases, it was almost inevitable that insufflation would be performed inadvertently in the first week or two of pregnancy. This happened in three patients, viz.:

1. Haswell, Case No. 92: Twenty-second day of cycle, biopsy and insufflated (no kymograph); gas passed at 120 mm. Hg.; normal full-time pregnancy.
2. McLean, Case No. 164: Twenty-eighth day of cycle: biopsy and insufflated (no kymograph): gas passed at 80 mm. Hg.: normal full-time pregnancy.
3. Jack, Case No. 326: Eighteenth day of cycle, kymographic insufflation; gas passed at 90 mm. Hg. with normal tubal contractions: normal full-time pregnancy.

8. In five patients who became pregnant neither insufflation nor lipiodol injection was performed: in one, dilatation and curettage and perineoplasty was done and, in the others, only endometrial biopsy: the time elapsing between the procedure and conception was twenty-eight months, twenty months, one month, eleven months and twelve months respectively.

Similarly, as with the kymographic tests, the nature of these studies - especially in the investigation of premenstrual endometrium - made it inevitable that biopsy would inadvertently be performed in the first week or two of pregnancy. This occurred in six cases: the endometria,/

endometria, of course, showed secretory changes; a definite decidual reaction in the stroma was noted in one, only. One patient miscarried at three months but the other five had normal full-time pregnancies. (Two, as already mentioned, had insufflation at the same time as biopsy). All but one had only one biopsy performed, the exception having three biopsies, viz., twenty-eighth day of cycle, thirty-fourth and forty-first; it was thought that the risk of miscarriage would be great in this case and so she was given three intramuscular injections of Progestin during a period of six weeks following the last biopsy: the remainder of her pregnancy was uneventful. One further case had biopsy attempted, when it was not known that she was at a very early stage of pregnancy, but no endometrium was obtained. (This case was mentioned in the discussion of unsuccessful attempts at biopsy - Ross, Case No. 278).

9. Of the 114 patients who had hysterosalpingography, thirty became pregnant. Lipiodol showed bilateral tubal patency in twenty-five, unilateral fimbrial blockage in three, unilateral isthmial blockage in one, and one result was unsatisfactory. All had insufflation performed at least once prior to lipiodol injection and many of them also subsequently. It is, therefore, impossible in these cases to apportion to these/

these procedures possible therapeutic responsibility. However, in fourteen of the thirty the interval between lipiodol injection and conception was sufficiently long (or subsequent insufflation was followed very quickly by pregnancy) to make it seem unlikely that hysterosalpingography was immediately or directly responsible for the sequel.

In concluding this account of the results of follow-up, consideration must be given to the "unsuccessful" cases. Of the 409 patients traced, 294 did not become pregnant, i.e. 72.0 per cent. Factors preventing pregnancy were present as follows:

Tubal blockage 112
Azoospermia 17
(Four remaining "azoospermia cases" are included in the total of "tubal blockage," since both conditions were present).

Thus of the 294 who did not become pregnant this event may be regarded as impossible in 129. In addition, the occurrence of anovular cycles, endometrial tuberculosis, and the finding of markedly deficient semen are obviously "major infertility factors;" these together account for twenty-one cases. Two husbands died within two years of their wives' first attendance at hospital.

Summing/

Summing these cases gives a total of 152 in which pregnancy was either impossible or very unlikely. This leaves 142 cases in which, as far as investigation went, no reason was discovered for the infertility of marriage. Thus, although only 28.1 per cent. of the 409 patients traced became pregnant, pregnancy occurred in 115 of 257 or 44.8 per cent. of patients in whom no barrier to pregnancy was found. One further point, however, must be borne in mind, namely, that the incidence of azoospermia, anovular cycles and endometrial tuberculosis, already described, makes it reasonably certain that a further number of cases would have come into the group where pregnancy was impossible or improbable if more cases had been appropriately examined. Further, one patient had a hysterectomy performed for fibroids (three years after insufflation - tubes patent), one was divorced three years after insufflation and one died after the same interval of time. Finally, in reviewing and analysing those cases in which pregnancy did not occur, the effect of war, mainly in respect of frequently separating partners in a hitherto sterile marriage but also in other directions, raises a totally incalculable factor.

Summary.

1. Five hundred cases of "primary sterility" were studied and followed-up during the course of almost ten years.

2. Tubal insufflation was performed in four hundred and eighty patients, the total number of insufflations amounting to one thousand and three.

3. Normal tubal patency was present in 58.9 per cent. of cases, spasm-normal patency in 2.5 per cent., stenosis in 0.6 per cent. and non-patency in 38.0 per cent.

4. The injection of lipiodol into the uterus and tubes (hysterosalpingography) was performed in one hundred and fourteen cases. Tubal patency was shown in 62.3 per cent. and non-patency in 37.7 per cent.

5. Endometrial biopsy was performed on eight hundred and fifty occasions in three hundred and ninety-two patients.

6. Of three hundred and fifty eight patients in whom biopsy was performed premenstrually, 6.4 per cent. exhibited anovular cycles.

7. Of three hundred and ninety two patients in whom biopsy was performed, 5.1 per cent. showed chronic tubercular endometritis.

8. Seminal examination in 114 husbands revealed normal characteristics in 68.4 per cent., marked deficiency in 13.2 per cent. and azoospermia in 18.4 per cent.

9. Lines of treatment employed include tubal insufflation, hysterosalpingography, pelvic diathermy, hormones and surgical methods.

10. Of four hundred and nine cases traced, one hundred and fifteen, i.e., 28.1 per cent. became pregnant.

11. Pregnancy did not occur when anovular cycles or endometrial tuberculosis or azoospermia were present (with the exception of one case of anovular cycles after treatment).

12. Of two hundred and ninety four sterile marriages, in one hundred and fifty-two, i.e. 51.7 per cent., infertility factors were found such as to render pregnancy impossible or very unlikely. If a greater number of cases had had endometrial biopsy and seminal examination performed, there is little doubt that infertility factors of anovular cycles, tubercular endometritis and azoospermia would have appreciably reduced the figure of one hundred and forty-two cases in which, as far as investigation went, no reason was discovered for the infertility of the marriage.

13. Important conclusions are:
    (a) Tubal insufflation is an essential diagnostic and a valuable therapeutic measure: the addition of a kymograph not only provides a permanent record but is most informative in illustrating tubal function and indicating such deviations as spasm and stenosis.

(b)/

(b) A single insufflation finding of non-patency is not reliable. For diagnostic accuracy, it should be repeated at a later date: two such findings of non-patency render the diagnosis of tubal blockage almost certain.

(c) Hysterosalpingography is a very useful adjunct to insufflation and may be of therapeutic importance. The correct interpretation of the films may be difficult and may be erroneous.

(d) Premenstrual endometrial biopsy must be regarded as a very important procedure in the scientific investigation of a case, in view of the importance of anovular cycles as a major infertility factor.

(e) Endometrial tuberculosis is much more common and of more significance in cases of sterility than has been generally recognised. In every case, therefore, with this fact in mind, endometrium should be examined histologically.

(f) The incidence of azoospermia (and gross seminal deficiency) is sufficiently high to render seminal examination essential in a sterile marriage.

(g) Treatment should be based on the results of diagnostic investigations: in some cases these results will indicate that every line of treatment will almost certainly be unavailing, in others that expectation of success will depend upon improvement or removal of a specific infertility factor but in many others that any or all therapeutic procedures should be used, either simultaneously of successively, which will raise the "fertility-sterility level above the threshold of conception."

APPENDIX.

In the course of the studies described in Part II, it became evident that more detailed research was desirable into certain aspects of the problem. It was decided to investigate more fully (1) the normal and "anovular" endometrial cycles, (2) the effect of curettage on endometrial tuberculosis, (3) (A) the accuracy of tubal insufflation as a diagnostic test and (B) certain possible causes of tubal occlusion and (4) the relationship of tubal peristalsis to phases of the menstrual cycle and to presumptive "ovulation time."

(1) The Normal and Anovular Cycles.

A complete normal endometrial cycle, represented by twenty-four specimens collected by means of a biopsy curette, has already been illustrated in Plates XVI and XVII. As this was the first occasion, as far as could be ascertained, on which daily biopsy had ever been performed, it was thought advisable to repeat the procedure in two other cases for purposes of comparison.

In one patient, twenty-two daily specimens were taken, beginning on the day after menstruation and concluding on the day after which it next occurred. Two of the sections proved to be quite useless, showing nothing but blood clot and necrotic, structureless debris, infiltrated in places with polymorphonuclear leucocytes.

All/

All the other sections were satisfactory and showed in series the progressive gradations from the postmenstrual proliferative phase to the premenstrual differentiative one. The last biopsy, indeed, was performed after menstruation had started and showed a typical menstruating endometrium of the normal secretory type. The series as a whole showed a close general correspondence to the one already illustrated in the text. Secretory changes first appeared on the eighteenth day of the cycle. In the other patient, there were twenty daily biopsies, of which three were unsatisfactory, showing no glands. The normal cycle, as far as the early differentiative phase, was well demonstrated by the remaining sections, but the later ones showed scanty endometrium with imperfect differentiative or secretory features.

Daily endometrial biopsy was also undertaken in two patients who were known (by previous premenstrual biopsies) to have anovular cycles. In each case twelve satisfactory endometrial sections were obtained (out of nineteen specimens in one patient, and twenty-five in the other). The sections in each of these cases are illustrated in Plates XVIII and XIX and reveal the essential features of "anovular cycles" (cf. Plates XVI and XVII). In the relatively high number of instances where biopsy was unsatisfactory, the reason was either that no tissue was/

was obtained or that it proved to be little more than amorphous debris. The endometrium shown in the last photograph of each series was actually removed a few hours after menstruation had commenced and demonstrates the histological character of pseudo-menstruation. This has already been illustrated in a non-serial biopsy in Fig. 212, which is that of endometrium removed during the second day of menstruation.

The writer would like to make it absolutely clear that he does not regard daily biopsy either as a necessary or a justifiable procedure in any case of sterility. These special investigations were undertaken to establish the facts regarding anovulatory cycles - once this has been done the process need not be repeated.

Plate XVIII.

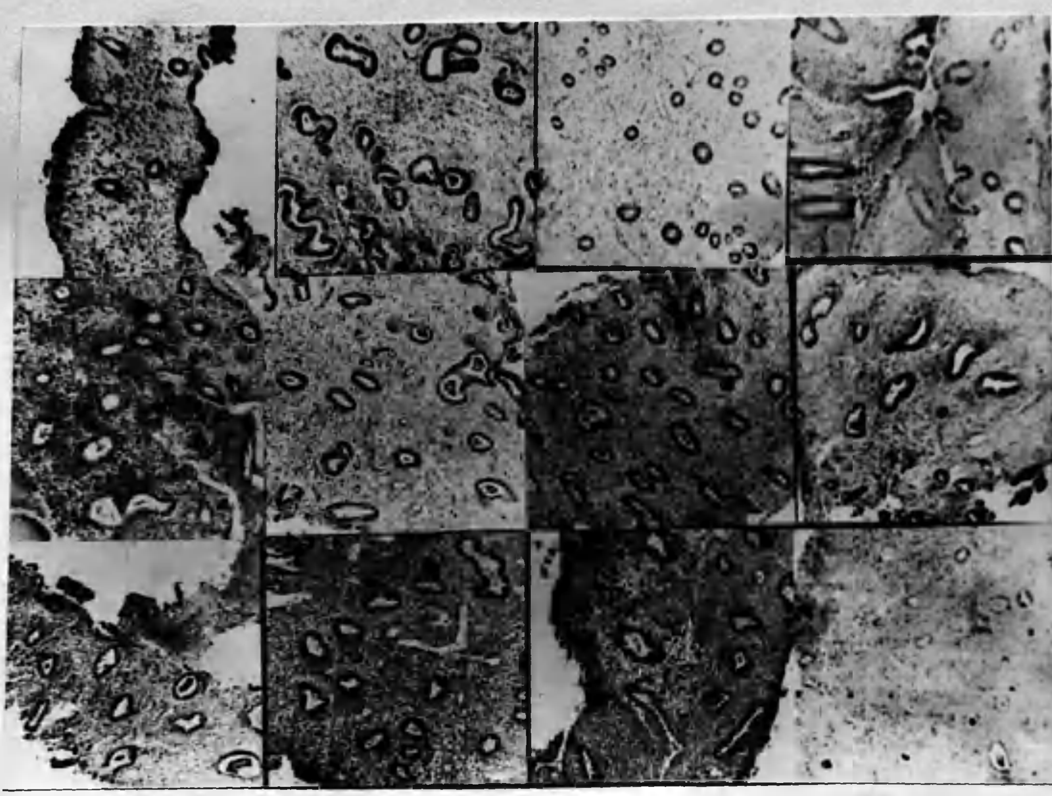
Anovular Endometrial Cycle Represented by twelve specimens collected by means of a biopsy curette. (x 75).

The patient, aged 26, had been married for six years. She had a regular twenty-eight day cycle with a flow that lasted three to six days. Specimen No. I (top row, left) was obtained the day after a period had ended.

Specimen No 12 (bottom row, right) was obtained a few hours after the next period commenced.

The days of the cycle shown are - reading from left to right - :

Top row:	7th, 8th, 9th, and 10th.
Middle row:	12th, 13th, 14th, and 16th.
Bottom row:	20th, 21st, 23rd, and 24th.



In none of the sections is there any evidence of secretory or differentiative changes.

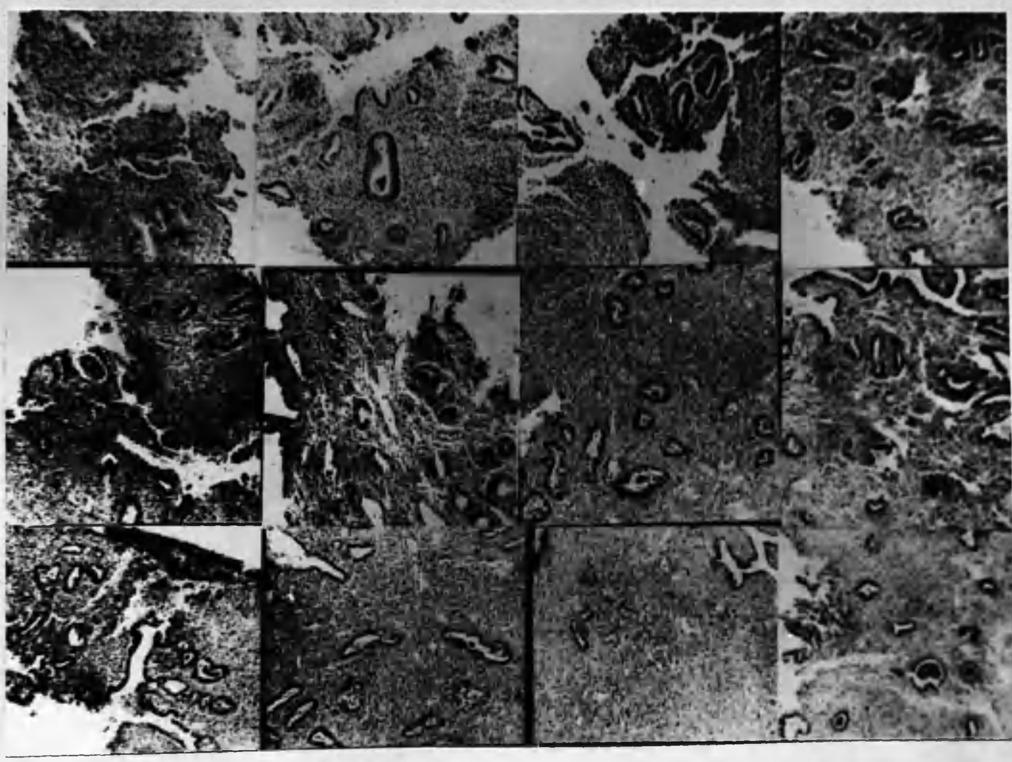
Plate XIX.

Anovular Endometrial Cycle represented by twelve specimens collected by means of a biopsy curette. (x 75).

The patient, aged 24, had been married for two years. She had a regular twenty-eight day cycle with a flow that lasted three to six days. Specimen No. 1 (top row, left) was obtained the day after a period had ended. Specimen No. 12 (bottom row, right) was obtained a few hours after the next period commenced.

The days of the cycle shown are - reading from left to right - :

Top row:	7th, 8th, 11th, and 12th.
Middle row:	18th, 19th, 20th, and 21st.
Bottom row:	22nd, 23rd, 27th, and 31st.



In none of the sections is there any evidence of secretory or differentiative changes.

The above cases exhibited regular monthly menstrual cycles, and, therefore, the time in the cycle when ovulation should have occurred and the differentiative phase of the endometrium developed was approximately known. But what of the endometrial pattern in cases with lengthy spells of amenorrhoea? Do secretory or differentiative features appear regularly or irregularly, and is the occurrence of menstruation preceded by these features? To investigate these points three cases were studied; Case I and Case II had menstrual intervals of 6-12 weeks: weekly biopsies were performed: in the one case, not one biopsy showed secretory features during an intermenstruum. In the other, the endometrium removed on the fifty-fourth day of the cycle showed the typical appearances of the premenstrual phase, but menstruation did not supervene till many days later. Case III had lengthy spells of amenorrhoea and, when the first biopsy was done, had not menstruated for eleven months. Three biopsies at monthly intervals failed to remove even the smallest fragment of endometrium. These three cases illustrate points of importance in women who are sterile and have spells of amenorrhoea, viz:-

1. Secretory changes may not occur in the endometrium: hence ovulation may be presumed to be absent. Pseudo-menstruation is present, i.e. bleeding from a proliferative mucosa.

2./

2. Secretory changes may occur, but need not necessarily be followed by menstruation: this evidence of ovulation goes far to explain those cases of pregnancy in patients with amenorrhoea. Such patients may bear normal children without ever having had a single menstrual flow. Mazer and Israel observe that this phenomenon is akin to the sexual cycle of most animal species and can be explained on the basis of the absence of the hypothetical bleeding-factor resident in the uterus.
3. Spells of amenorrhoea may be associated with complete failure of endometrial development. This is not incompatible with pregnancy, but must be a contributory infertility factor.

(2.) The Effect of Curettage on Endometrial Tuberculosis.

Although it was considered most improbable that even very thorough curettage of a tubercular endometrium would "cure" the condition, studies were carried out to observe the recurrence of the tubercle follicle and to determine its time-interval. Four sterile patients were investigated. The details are as follows:

Case I. Mrs. C., 31 years, married 5 years, menstruation regular but scanty, sole complaint sterility, no history of tuberculosis:

21.8.42. Curettage under anaesthesia - tuberculous endometritis - no tubal lesion detected - gas failed to pass on tubal insufflation.

1.9.42/

1.9.42. Menstruation.
24.9.42. Endometrial biopsy showed tuberculosis.

Case II. Mrs. F., 39 years, married 3 years, menstruation normal, sole complaint sterility, no history of tuberculosis, radiographs chest and abdomen negative:

14.9.42. Endometrial biopsy showed tuberculosis.
22.9.42. Curettage under anaesthesia - endometrium removed from anterior wall showed tubercles, but tissue removed from posterior wall, right and left sides, did not. - General curettage of the uterine cavity showed foci - gas passed, but at very high pressure on tubal insufflation.
4.10.42. Menstruation.
12.10.42. Curettage under anaesthesia - endometrium from anterior wall, posterior wall, right side and left side, each showed tubercular foci - insufflation repeated, showed as above.

Case III. Mrs. H., 21 years, married 19 months, menstruation normal, sole complaint sterility, no history of tuberculosis but is losing weight, radiographs of chest and abdomen negative:

21.7.42. Curettage under anaesthesia - tuberculous endometritis - bilateral tubo-ovarian swellings about size of hen's egg: gas failed to pass on tubal insufflation.
26.7.42. Menstruation.
6.8.42. Biopsy produced no endometrium.
3.9.42. Biopsy showed no evidence of tuberculosis.
24.9.42. Biopsy (several attempts) produced no endometrium.
25.9.42. Menstruation.
22.10.42. Biopsy showed tuberculous endometritis (numerous sections were examined, only one of which showed a focus).

Case/

Case IV. Mrs. L., 26 years, married 6 years, menstruation excessive, prolonged and irregular, complaint - menorrhagia and sterility, no history of tuberculosis.

13.10.42. Curettage under anaesthesia - tuberculous endometritis - no tubal lesion detected.
22.10.42. Curettage under anaesthesia - no evidence of tuberculosis in endometrium (many sections examined).
26.10.42. Menstruation.
2.11.42. Biopsy showed no evidence of tuberculosis.
9.11.42. Biopsy - tuberculous endometritis.

The findings in the above four cases may be summarised: tubercular endometritis was found to have recurred at the following intervals of time after thorough curettage under anaesthesia (1) 34 days (2) 20 days (3) 3 months and (4) 27 days. There seems little doubt therefore that reinfection of the endometrium rapidly recurs after curettage. In view of the well-established fact (Novak) that tuberculosis of the endometrium is, almost without exception, secondary to tuberculosis of the tube, it is most probable that so long as the tubal focus remains re-infection continues.

The findings in these cases confirm the opinion expressed on page 253 that evidence of tuberculous endometritis is frequently missed and its incidence is accordingly much higher than is generally recognised. Most tuberculosis authorities and pathologists maintain that endometrial tuberculosis is rare, e.g. Lackner, Schiller and Tulsky, who found only 1.87 per cent. of cases of isolated tuberculous endometritis in 3,000 autopsies in tubercular adult women and 1.60 per cent. in clinical cases of primary progressive pulmonary tuberculosis. The studies which we have described leave no doubt, however, that in sterile women tuberculous endometritis is present in more than five per cent. of cases.

(3.) The High Incidence of Tubal Non-patency.

Insufflation has shown an incidence of occlusion of the Fallopian tubes of sterile women which has varied considerably among different investigators, being as high as 50 per cent. and seldom lower than 30 per cent. This problem may be approached from two angles, viz. (A) the criterion for diagnosis of tubal blockage and (B) the etiology of tubal blockage.

A. The diagnosis of tubal blockage.

It has already been indicated that a single insufflation showing non-patency is not evidence of tubal blockage, because, out of 283 patients whose tubes were patent, 25 appeared to be non-patent on one occasion (page 215). Subsequent examination by lipiodol showed that insufflation had erroneously indicated blockage in 6 out of 60 cases (page 228). Moreover, of 115 patients

who/

who became pregnant, 29 had been diagnosed as having non-patent tubes as the result of a single insufflation. It would follow therefore, that in all reported series, except where two or more insufflations (and/or a hysterosalpingogram) established non-patency, the incidence figure of blocked tubes is too high. It may be concluded that a single insufflation is not an accurate criterion for the diagnosis of tubal non-patency, but falsifies the diagnosis in approximately five to ten per cent. of cases.

These findings prompted investigation into the question - what prevents the gas from passing through the tube on one occasion, while it passes freely on other occasions? This problem was studied from three aspects, (1) the effect of anaesthesia (2) the time-relationship of insufflation to the phase of the cycle, (particularly the premenstruum) and (3) the rate of flow of the gas.

(1) It seemed possible that anaesthesia might have the effect of permitting gas to pass through tubes which had shown non-patency without it, or vice-versa. But this possibility received no support from the findings described on page 215 where, of the series of twenty-five patients, a false finding of non-patency was obtained in twelve cases under anaesthesia and in thirteen without it. Nevertheless, a small group of cases (6) was investigated to note the effect of anaesthesia on tubal patency and on apparent blockage/

age as recorded by kymographic insufflation. Various anaesthetics were employed, viz., chloroform, ether, gas and oxygen, and intravenous evipan-sodium. In three of the cases, insufflation was performed firstly without and immediately afterwards with anaesthesia; in the other three it was done firstly under anaesthesia and soon afterwards when it had been discontinued. No anaesthetic had any material effect on the type of tracing obtained.

(2) It has already been pointed out that, for various reasons, insufflation should not be performed during the premenstrual phase of the cycle. The hypothetical consideration that the temporary thickening of the endometrium around the uterine end of the Fallopian tube might give an erroneous finding of blockage has not found any support in the series of nine patients showing normal tubal patency when insufflated on six or more occasions at different phases of the cycle (page 214). Again, a study of the group of twenty-five patients with patent tubes, but who showed on one insufflation apparent non-patency (page 215) revealed that the latter finding occurred irregularly in the cycle and was not related to any particular phase. Corroborative information was obtained as the result of further studies:

(a)/

(a) An additional case to the one already described (page 212) had a kymographic insufflation performed on twenty consecutive days (menstruation intervening).

No material change in the type of tracing occurred at any phase. All showed patency.

(b) In the course of investigations, four further cases were encountered in which a finding of patency was followed by one of non-patency on a subsequent date. The following are the details:

Case I. Two "patencies" followed by a "non-patency."

Case II. Two "patencies" followed by a "non-patency."

Case III. One "patency" followed three days later by a "non-patency" and four days still later by a "patency."

Case IV. One "patency" followed by a "non-patency."

Only in Case II was the "non-patency" finding at the pre-menstrual phase, in all the other instances insufflation having been performed in the first half of the cycle.

It may be concluded that a fallacious finding of non-patency may be obtained at any point of the cycle.

(3) Numerous experimental insufflations were carried out in both anaesthetised and non-anaesthetised patients to determine whether variations in the rate of flow of/

of gas into patent tubes could materially alter the appearance of a kymographic tracing, even to the extent of simulating tubal blockage. Numerous variations from 30 c.c. per minute to 120 c.cs. per minute (the latter rate is never used in clinical routine) were employed and in varying sequences; in a few instances the excessive rate of flow of the gas caused the pressure to rise considerably, but never above 150 mm. Hg.: in no case was the tracing of non-patency obtained.

To sum up, these investigations have had a negative result in that no light has been thrown on the causation of "pseudo-blockage," but they prove that the above-mentioned factors are not responsible. Assuming no blockage in the instrument employed for insufflation (which should be tested both before and after use), tubal or utero-tubal spasm, for no apparent reason, on occasion resists the pressure of gas up to 200 mm. Hg. This spasm is sometimes very apparent in hysterograms and is now and again illustrated in kymographic tracings when repetition of insufflation a few seconds later shows gas passing through tubes after initial failures.

B. The etiology of tubal blockage.

Tubal blockage due to gross pelvic lesions requires no further consideration. The problem under

consideration/

consideration at the moment is the etiology of blockage in tubes which appear normal on bimanual examination. In cases of this type, laparotomy is seldom performed and the history of the case seldom indicates any special illness to which the tubal occlusion can be attributed. The problem calls for further study, and certain investigations were made concerning the role of tuberculosis, gonorrhoea and congenital hypoplasia of uterus and tubes in this type of case.

The unexpectedly high incidence of endometrial tuberculosis (5.1 per cent.), in an unselected series of cases (392) in which pelvic symptoms and signs of the disease were absent, prompted the thought that tubal tuberculosis of a degree insufficient to be grossly recognizable, except on laparotomy, might be responsible for a much greater number of cases of tubal non-patency than is generally recognized. Since endometrial involvement is almost always secondary to tubal infection, but tubercular salpingitis very frequently exists without endometrial infection, it would follow that more - probably considerably more - than 5.1 per cent. of those patients, who had endometrium examined, had unrecognized tubercular salpingitis: presumably most would be associated with blocked tubes. Support for this view was found in the finding that in eighteen of these cases insufflated, fourteen or 78 per cent. showed non-patency. It was therefore/

therefore decided to take the first opportunity of removing portions of non-patent tubes for histological examination. Since the cases under consideration were complaining only of sterility and no gross pelvic swelling or thickening could be detected, the only reasonable excuse or justification for laparotomy could be salpingostomy. Unfortunately, only three suitable patients to-date have been found agreeable to operation, during the period of study. The diagnosis of tubal blockage was made on the results of three insufflations and a hysterogram in each of two of the cases and on four insufflations and a hysterogram in the third. In one, blockage was at the isthmi and in the others at the fimbriated ends. One case showed marked uterine hypoplasia. All three presented evidence of chronic tubercular salpingitis on histological examination. It must be emphasised that, just as in endometrial tuberculosis, some sections may show no evidence of the disease and so in certain cases many sections may require to be examined.

The role of the gonococcus in causing salpingitis is well recognized: Novak states that about 60 per cent. of cases are due to it and Mazer and Israel maintain that partial or complete tubal occlusion is usually the residium of an antecedent gonorrhoeal infection. But it is also well known that resolution of this type of infection may

result/

result in restoration of the tubes to an essentially normal condition. It is extremely difficult to estimate the proportion of cases in which this happens. However, it may be said that, whereas a tuberculous salpingitis is likely to cause permanent blockage, gonorrhoeal salpingitis does not always do so. It is not disputed that gross pelvic conditions such as pyosalpinx and tubo-ovarian abscess, resulting from acute or subacute gonococcal infection, are definite causes of tubal blockage and sterility, but there is little positive evidence that the gonococcus is often responsible for occlusion in tubes which are not palpably thickened. In fifty consecutive cases of this type with non-patent tubes careful clinical history and examination were directed to this point: not one gave a history of or suggestion of gonorrhoea and only eight showed chronic cervical infection (or erosion). This, of course, does not exclude the possibility of infection. Another approach to the problem was made with the co-operation and assistance of Dr. Nora Wattie of Glasgow Public Health Department. The records of acute gonorrhoea in women who attended the principal clinic from 1930 to 1937 were surveyed, with special reference to the incidence of pelvic involvement. There were five cases of the latter in a total of five hundred and forty patients. A follow-up of the five cases revealed that one subsequently had

three/

three pregnancies, but the others had not become pregnant. During the years 1938 to 1942 (inclusive) the total number of new cases of acute gonorrhoea over 15 years of age, attending all of the Glasgow municipal treatment centres, amounted to 912. Of these there were twenty cases of acute pelvic involvement, i.e. 2.2 per cent. On the whole, pelvic complications (recognizable clinically) are not common.

The remaining aspect to be considered is that of the etiological importance of congenital hypoplasia of the uterus and tubes as a causative factor of tubal blockage. The significance of this factor was first described and stressed by Clauberg, who maintained that, in cases of infantile uterus, the tubes often shared in the developmental deficiency and were consequently impermeable (page 160). There has been a vague general acceptance of Clauberg's theory, but the present writer is not satisfied that it is correct. The following arguments may be raised against it; (1) Clauberg's evidence was almost entirely radiological(apart from investigations on lower animals), (2) a large number of cases of uterine hypoplasia have shown normal tubal patency and function on kymographic insufflation (3) radiographs frequently show patency in tubes presenting the long, thin, tortuous features of the "congenital hypoplastic" type, (4) in a small series of cases showing <u>definite</u> tubal blockage, and treated by Clauberg's method with oestrogenic hormone, none showed patency after treatment (as claimed by him)

(5)/

(5) tubal blockage, associated with uterine hypoplasia, need not be due to tubal hypoplasia, but may be due to latent tuberculosis as found at salpingostomy (as described above). It is not disputed, of course, that follicular hormone produces proliferation of the mucous membrane and general hyperaemia of the Fallopian tubes, as Clauberg has shown, but the point at issue is whether the hypoplastic or infantile tube is essentially a non-patent structure or not. This question was approached from two angles (1) a histological study of the prepubertal tube and (2) kymographic insufflation in an unselected, consecutive series of unmarried women. (This procedure in a series of children at various ages up to puberty would have been very informative, no doubt, but has proved, so far, impracticable).

(1) The prepubertal tube.

Fallopian tubes were removed post-mortem and sectioned from cases of the following ages: (1) a seven months' foetus, (2) a foetus still-born at term, (3) a child aged two days, (4) a child aged ten weeks, (5) a child aged three months, (6) a child aged four and a half months, (7) a child aged seven months, (8) a child aged sixteen months, (9) a child aged three years, (10) a child aged four years, (11) a child

aged/

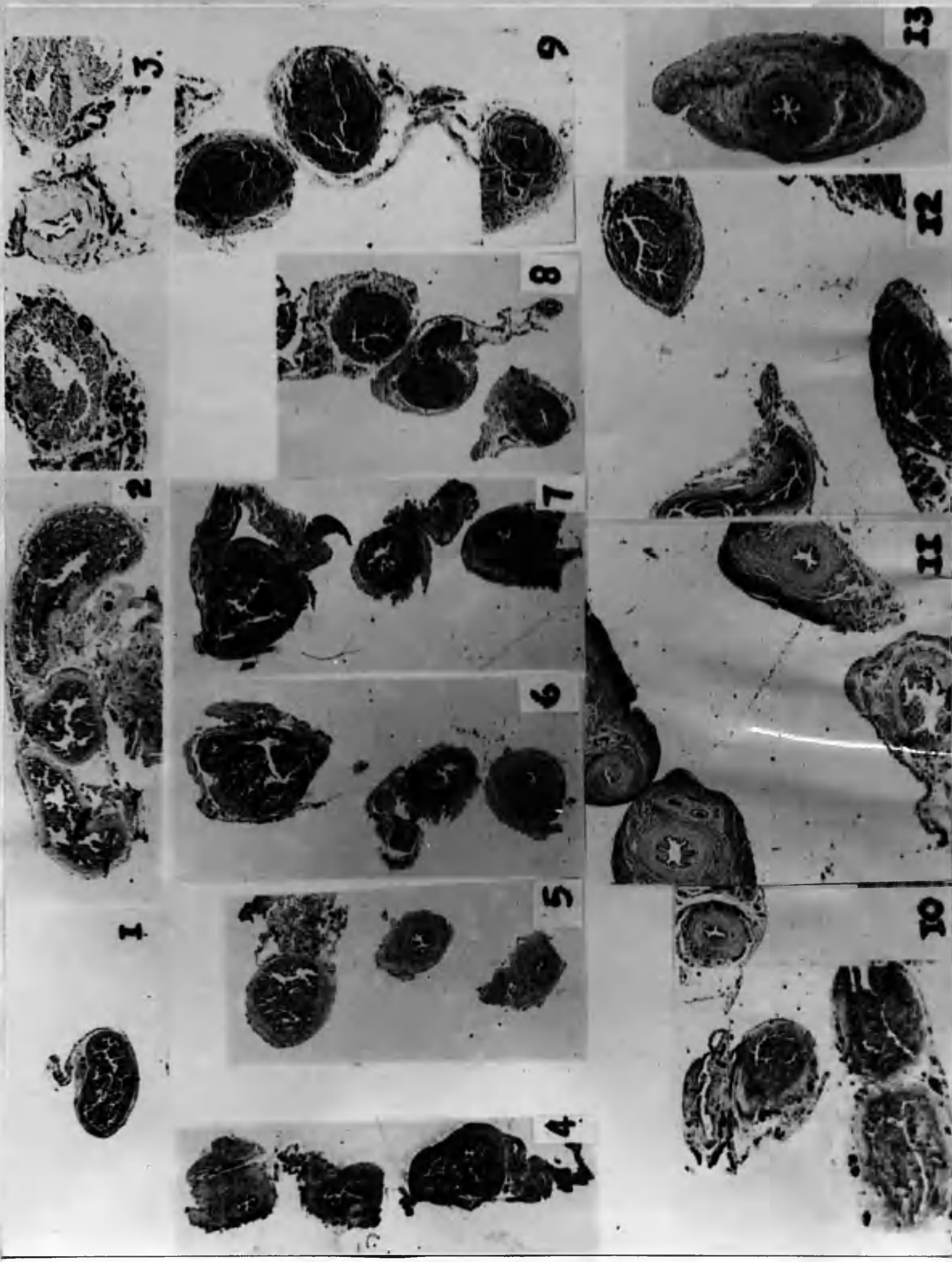
aged eight years, and (12) a child aged ten years. Sections were cut through fimbrial, ampullary and isthmial portions. All are illustrated in Plate XX. The appearances of the tube throughout the series are those of a patent structure and there is no evidence that the normal canalisation of the Mullerian ducts which occurs in the process of development is associated with impermeability in infancy or childhood. It is possible, of course, that major developmental abnormalities, either of the tubes or uterus, e.g. uterus bicornis, may be accompanied by defective tubal canalisation.

(2) Insufflation in unmarried women.

These cases were unselected and included women with a variety of complaints, the commonest being dysmenorrhoea. Fifty were studied, their ages ranging from 13 to 30 years. Two were aged 14, two aged 15 and two aged 16. It was estimated that in approximately one-third of the patients, the uterus appeared to be of the small, hypoplastic type. Kymographic insufflation showed normal tubal patency and function in all but five; the exceptions showed patency after a high degree of spasm (varying from 150 to almost 200 mm. Hg.). Despite the presence of varying degrees of uterine hypoplasia (and ? tubal), in no case were the tubes impermeable to gas.

Plate XX.

Sections of Fallopian tubes from foetal to adult life (x 12). No.13 is an adult, normal tube for comparison. The ages of the other tubes are indicated in the text.



(4) The Relationship of Tubal Peristalsis to Phases of the Menstrual Cycle and to Presumptive "Ovulation-time."

In Part II of this thesis it has already been stated that no close correspondence between the type of peristaltic wave on the kymographic tracing and the chronological phase of the cycle could be regularly established (page 214). This finding was in variance with that of prominent workers in the subject (Rubin). Further studies on additional cases were advisable. The following kymographic insufflations were made:

1. In one patient every day for twenty days, except during menstruation, which intervened for five days.
2. In one patient, who had amenorrhoea for ten months, weekly for eight weeks. Menstruation did not occur.
3. In fifty unmarried girls at varying times in the cycle.
4. In thirty patients in the course of studies primarily directed to investigating the effect of alteration in the rate of flow of the gas or the response to anaesthesia: in most of these cases menstruation was regular, but one case had amenorrhoea for over a year when the test was performed.
5. In four patients at weekly intervals.

The results were as follows:

1. In ten patients, very active and frequent peristaltic waves were present, such as are described as occurring

at/

at ovulation-time: six of these occurred between the fourteenth and nineteenth days of the cycle, two at the fifth, one at the twenty-seventh and one at the sixty-sixth (in a case of amenorrhoea).

2. In five patients, very flat and infrequent waves occurred between the thirteenth and eighteenth days of the cycle.

3. The frequency and amplitude of peristaltic waves varied little in many repeat insufflations: when more considerable variations did occur they were found more frequently around mid-cycle, but often at other times.

The more important conclusions reached in the above studies may be summarised:

1. In tuberculous endometritis - a condition much more common in sterile women than is generally accepted - curettage is followed by rapid re-infection.

2. Just as tuberculous endometritis has been found "accidentally" in routine investigations, so has tuberculous salpingitis been found as the result of examination of portions of tubes removed at salpingostomy, in unsuspected cases.

3. Since tuberculous endometritis is almost invariably secondary to tubal and the latter is often present without endometrial involvement, the actual incidence of/

of tubal infection in sterile women is more than 5.1 per cent: (this figure has already been shown to be a minimal one for endometrial tuberculosis).

4. The incidence of partial or complete tubal occlusion in these cases is high: tubal tuberculosis, hence, is a much commoner cause for non-patency than is appreciated.

5. It has already been proved that a single finding of non-patency on tubal insufflation is not dependable and cannot be accepted as a diagnostic criterion. It has also been suggested that, in this event, the test should always be repeated once or oftener and/or combined with hysterosalpingography. Failure so to confirm non-patency is responsible for its exaggerated incidence in many series.

6. The cause of a fallacious finding of non-patency is utero-tubal spasm: this is not materially influenced by anaesthesia, the rate of flow of the gas or phases of the menstrual cycle.

7. Evidence of gonorrhoea (or history) is rare in cases of blocked tubes; the incidence of pelvic involvement in acute gonorrhoea is, clinically, extremely low. In association with the observed fact that complete tubal restoration to normal is frequent, this suggests that blockage due to the gonococcus is not common.

8./

8. The opinion is expressed (and supported by studies) that impermeability of the tubes due to congenital hypoplasia is a rare condition.

9. A large number of further kymographic insufflations have confirmed the opinion, expressed on page 214, that there is no evidence that there is any constant, close correspondence between the type of tracing obtained and the endometrial cycle or ovarian-hormone influence or presumptive ovulation-time.

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