dysfunction, but, with increasing age, the frequency with which other factors operate may make the eliminative diagnosis more difficult. As the bulk of the cases fall between the ages of 40 and 50, when cancer and fibroids compete so largely, the need for an immediate and complete investigation in such patients is specially urgent, and the same applies to bleeding beginning for the first time after the menopause when malignancy, usually in the cervix, more rarely in the uterine body or ovary, is the most frequent single factor present.

Where physical examination fails to reveal the presence of an adequate explanation of the bleeding, such as fibromyoma, cervical cancer, a polypus projecting from the cervix, or an inflammatory mass in the tubo-ovarian region, it may be laid down as a rule that curettage is the first step in the diagnosis. Bleeding in the teens is the only exception to this rule, and in such cases treatment may usually be commenced forthwith on a clinical diagnosis.

We have seen that a considerable number of cases of ovarian dysfunctional bleeding may have a preceding period of amenorrhoea, and in such the exclusion of the pregnancy factor is often possible only after curettage and the discovery of the cystic endometrial changes so characteristically found in this class of case.

TREATMENT

Until we have arrived at a more precise understanding of the ovarian factors, it is inevitable that our treatment of such dysfunctional bleeding must be largely symptomatic. It is true that therapeutic claims are advanced on behalf of many of the commercial ovarian preparations, but these claims have little foundation in science and, for the most part, equally little sanction in practice. In 23 intractable cases of excessive and irregular bleeding in my department the effect of a concentrated dosage of some of the commercial ovarian products of proved activity—and of these sistomensin has been chiefly employed—has been carefully studied by Dr. W. P. Kennedy. Cure of the symptoms is reported in 5 and marked improvement in 5—a total positive result of 10 in 23—and it is interesting to note that in 7 of these cases an associated dysmenorrhoea for which, in fact, the treatment was initiated, has simultaneously responded to the measure.

There is a steadily increasing literature in regard to the results of the treatment of dysfunctional uterine bleeding with ovarian or placental extracts. Thus, Campbell and Collip¹⁸ have recently recorded success in the treatment of metrorrhagia with the anterior-pituitary-like principle of the placenta. Many, however, of these records deal with the use of experimental material prepared in the worker's own laboratory.

A finding of considerable moment in regard to the treatment of these cases is the relief, both immediate and permanent, which may follow the diagnostic curettage. Thus, out of the 86 cases specially studied for this paper, in all of which curettage was done, the notes record "cure" of the bleeding in 11 (menorrhagia 3, polymenorrhoea 5 and continuous bleeding and metrorrhagia 2). It is true that cauterization of a chronically infected cervix was carried out at the same time in 4 of the cases.

In the case of intractable bleeding which fails to respond to the above conservative measures, we are constrained to adopt more drastic methods, and, of these, the choice lies between hysterectomy and radium or x -rays sterilization. These measures are frequently called for, especially in the intractable dysfunctional bleeding of women between 40 and 50. It is now my practice in such cases to induce an artificial menopause by introducing radium into the uterus or by exposing the ovarian region to three successive doses of x rays. In the present series hysterectomy was carried out 4 times, radium was employed 14, and x rays 5 times.

SUMMARY

1. Except after a recent childbed infection or gonorrhoea inflammation of the endometrium or myometrium is a rare cause of irregular and excessive uterine bleeding.

2. There is evidence that in a large majority of such cases the uterine pathology—the endometrial proliferation and congestion and the myohyperplasia—and the symptoms are dependent upon aberration in the ovarian function. The most common recognizable causes of this aberration are childbirth and general organic disease.

3. The terms chronic endometritis, chronic metritis, fibrosis uteri, and subinvolution applied to the pathology found in irregular and excessive uterine bleeding are, therefore, inappropriate.

4. The diagnosis in such cases rests upon an absence of a gross pathology—tumours, placental remains, tubo-ovarian inflammatory masses, etc.—and the appearances found in the endometrium after curettage.

5. The treatment consists of curettage, ovarian therapy or, in intractable cases, of the use of sterilizing doses of radium or x rays.

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PHYSIOLOGICAL ASPECTS OF MENSTRUATION*

BY

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In opening this discussion on menorrhagias not due to uterine disease I am very conscious of the fact that my own knowledge does not extend to the clinical aspect of the problems involved. I would wish, therefore, to take up the standpoint of the experimental physiologist, and to discuss some facts which may be of assistance in analysing the human menstrual cycle, and therefore of assistance in considering disorders caused by physiological deficiency or excess.

In an endeavour to homologize the menstrual cycle of primates with the oestrous cycle of lower mammals, we may first consider certain of the fundamental processes involved in the latter. In lower mammals the ovarian cycle consists essentially of two phases—first, the phase in which the Graafian follicle undergoes maturation and finally ovulates, and secondly, the phase in which the corpus luteum develops from the shell of the ruptured follicle. In most species only minor changes take place in the uterus during the first of these ovarian phases, the so-called oestrous phase; more obvious changes occur in the vagina, changes that facilitate copulation, which is restricted to this period. In the second ovarian phase—the so-called luteal phase—marked changes take place in the uterus. These changes vary in degree and kind in

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different species, but the end-result is the same—namely, the uterus is prepared by an increase in its physiological sensitivity, with or without proliferation of the endometrium, for the reception of the fertilized ovum. In the mouse and rat the development of the corpus luteum required to produce the characteristic pre-gestational changes in the uterus is only attained after copulation, while in such animals as the rabbit and ferret copulation is necessary to cause ovulation.

From our present point of view the most interesting feature of this pre-gestational development of the endometrium is its behaviour when the animal fails to become pregnant—in other words, when the prepared endometrium is found to be unnecessary. In all animals so far known, retrogressive changes take place in the prepared endometrium when pregnancy fails to supervene, and the degenerate mucosa returns after a period of time to normal. The severity of the process of destruction of the developed endometrium varies in different species, and does not appear to depend upon the extent of the previous endometrial development.

In the rat and mouse, following sterile copulation, the morphological changes in the uterus are slight compared with those found in some other species, and the subsequent process of destruction is comparatively mild. In extreme cases a certain amount of intercellular haemorrhage is found which may lead to the appearance of small haematomata under the epithelium, but haemorrhage into the lumen rarely occurs. In the guinea-pig during the luteal phase the morphological change in the uterus is again slight. In the rabbit a very considerable degree of pre-gestational proliferation occurs after ovulation. In this species the development consists very largely of glandular proliferation, and at the end of ten days after ovulation the uterine endometrium is honeycombed with large glands opening out into the lumen. The destruction of this development in the rabbit is carried out by a process of retrogression of the glands and sloughing of the epithelium. Thus, 18-20 days after ovulation, the lumen is found to contain large multi-nucleate giant cells formed by the conglomeration of debris from the epithelium. In the rabbit, however, this extensive process of destruction is associated with little or no haemorrhage, and red blood corpuscles are rarely found in the lumen. A similar, though more prolonged, period of pseudopregnancy is also found in the ferret. In the dog, pseudopregnancy lasts 6-7 weeks, and is followed by uterine retrogression resulting in a variable degree of haemorrhage into the stroma. In various other animals, post-ovulation development and retrogression of the uterus have also been studied.

It may be said, therefore, that in known species of lower mammals the uterus exhibits a tendency to undergo breakdown of the endometrium at a certain definite phase of the cycle, namely, at the end of the phase of development carried out in preparation for the reception of the fertilized ovum. There is, however, one other phase of the cycle in which certain animals, at any rate, appear to undergo some destruction of the endometrium. In the dog haemorrhage into the uterine lumen is found in the immediate pre-ovulation phase, and in this case the actual haemorrhage is more pronounced than that found at the end of the subsequent pseudopregnant period. Thus, external bleeding may continue for as much as ten days in the pro-oestrous dog. A similar, though less extensive pre-ovulation destruction of the uterus may also occur in such animals as the cow.

In attempting to interpret the human menstrual cycle in the light of these facts relating to lower mammals, it is necessary to consider the one salient point which occurs in the human, namely, the period of menstruation. Taken

in conjunction with what is known of lower mammals, two alternative theories could be evolved: (a) that menstruation is a pre-ovulation phenomenon similar to that occurring in the dog but more intense, or (b) that human menstruation is an exaggerated homologue of the pseudopregnant breakdown found in many of the lower mammals.

Regarding menstruation as a pro-oestrous phenomenon, the haemorrhage would precede the ovulation of the same cycle, and therefore at puberty the first menstruation would precede the first ovulation. Regarding it as an end-of-pseudopregnancy phenomenon, menstruation would follow ovulation of the same cycle, and therefore the first ovulation would precede the first menstruation. The time of ovulation in the human cycle is now generally agreed to be some 13-17 days after the beginning of the previous menstruation, and therefore to fall about midway between two menstrual periods. On this evidence, therefore, the pseudopregnancy theory of menstruation would appear more probable. On such an interpretation ovulation takes place, the corpus luteum develops in the ovary, and pre-gestational changes take place in the uterus. Then, when pregnancy fails to supervene, retrogressive changes occur in the corpus luteum, the endometrium breaks down and menstruation occurs. In other words, menstruation is the removal of an unwanted proliferation of the uterus, and occurs, therefore, because conception has not taken place. On this view, alone, however, menstruation would be dependent upon the preliminary development of the corpus luteum in the ovary, and it is now well known that menstruation will occur in the absence of ovulation. Since it is known that the oestrous changes of the accessory organs of lower mammals may occur without a morphological cycle in the ovary, this fact, of course, favours the view that the breakdown involved is pro-oestrous in nature.

Fortunately, however, it has been possible to turn to the lower primates for investigation of this problem. All Old World monkeys appear to menstruate and to have a cycle essentially comparable to that occurring in the human. On the other hand, many of them also have an obvious external sign of the time of ovulation, and to this extent more closely resemble the lower mammals. Such monkeys, therefore, are extremely valuable in any attempt to homologize the sexual cycle of man with that of the lower mammals. In the baboon, for instance, the follicular phase, during which the development of the Graafian follicle takes place, is characterized by the appearance of an enormous swelling of the vulva and pudendal region. At the end of the follicular phase, when ovulation takes place, this external swelling undergoes a sudden subsidence and is reabsorbed within about two days. About 10 days later, a period of menstruation of the usual type appears.

The start of the cycle in the baboon, either at puberty or following a period of lactation, is characterized by the appearance of the external swelling, and there can be no doubt whatever, therefore, that in this animal the follicular phase occurs and passes away some time before the onset of the corresponding menstruation. It is thus possible to say that the latter is not a straightforward pre-ovulation phenomenon. On the other hand, when the monkey fails to ovulate, the same external sign of the follicular phase appears, followed by menstruation as usual, and the total length of the cycle, as well as the time relations of the phases, is the same as in the normal ovulating animal. There is, however, one important difference between the uterine cycle in the ovulating and in the non-ovulating monkey, namely, that the typical pre-menstrual development of the uterus only occurs when

the corpus luteum is present in the ovary. Where ovulation has not taken place, menstruation, though occurring at the normal time, takes place from an undeveloped resting endometrium. It is thus necessary to suppose that whereas the pre-menstrual development of the uterus is dependent, as would be expected, upon the presence of the corpus luteum, the actual factor causing necrosis and breakdown of the epithelium is not set in action by the atrophy of the corpus luteum, although operating at the same time, and is independent of any morphological ovarian cycle.

Evidence has lately become available as to the site of origin of the substance concerned. Some years ago it was shown by Allen that menstruation could occur in ovariectomized monkeys after a series of injections of oestrin. Since the hormone is associated with the follicular phase of the cycle in the normal animal, these experiments appeared to simulate the condition of affairs found in the non-ovulating monkey. Very recently, however, Hartman has shown that this effect of injection of the ovariectomized monkey is completely lacking if the animal is hypophysectomized. It is thus necessary to suppose that Allen's results were due to activation of

the pituitary body by the injection of oestrin, and that the substance causing necrosis of the endometrium is probably hypophyseal in origin.

The importance of studying the nature of this factor causing necrosis has been emphasized for some years by Shaw, and it seems probable that further progress with the study of the mechanism of the human menstrual cycle will be dependent upon some working hypothesis of the factor involved in the necrosis of the endometrium. From the point of view of the subject under discussion, namely, the factors concerned in menorrhagia unaccompanied by uterine disease, it is quite evident that this necrosis factor is of prime importance. In cases of menorrhagia, the morphological cycle in the ovary may be abnormal or even entirely suppressed, and a condition may be found analogous with that in the non-ovulating monkey, except that the period of destruction of the endometrium is prolonged indefinitely. This would appear to point to the possibility that the factor causing necrosis loses its normal cyclic activity and functions persistently. If such an explanation can be substantiated, an important basis will have been found for the experimental attack upon the problems of menorrhagia.

VARICOSE ULCER*

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(With Special Plate)

The femoral artery delivers a very large quantity of blood to the leg every twenty-four hours, probably more than a thousand pints. The arterial blood is delivered with all the force of the heart and gravity behind it, but when

Of this group, it is fairly certain that the last two factors are the most important. Should the veins become incompetent to return the blood to the heart from blockage, atony of their muscular coats, or failure of the valves, serious stagnation phenomena will result, and that naturally in the region most remote from the heart, because here the effect of gravity is at its maximum. The support of shoes and boots and the pressure on the soles prevent oedema and stagnation in the feet. Figures 1, 2, and 3 show the regions in which ulcers develop according to the type of footwear worn. The upper confine of this ulcer-

FIG. 1.—The ulcer-bearing area when boots are habitually worn.

FIG. 2.—The larger area affected when lace-up shoes are used.

FIG. 3.—Ulcers and eczema also occur in the small area on the dorsum of the foot when shoes with a single strap are worn.

this force is dissipated in the capillary bed there comes into play a wonderfully complicated mechanism whereby this large volume of blood is returned to the heart against gravity. Let there be a drop in efficiency of one part in two hundred in this return mechanism, and serious changes will occur in the leg.

Many factors assist in the return of the venous blood, such as the elasticity of the skin, the contraction of the leg muscles, abdominal and thoracic aspiration, *vis a tergo* of capillary pressure, muscular tone and contractions of the vein walls, and the elaborate valving of the veins.

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ative region is constant, and the lower corresponds to the limits of foot support. By a simple consideration of this area which carries probably 99 per cent. of the indolent ulcers affecting mankind, we see both the cause and the proper line of treatment. The final cause in all cases is gravity, which is too much for the legs of erect-standing mankind, and the best treatment is *constant support*.

The name varicose ulcer is an oxymoron, and is not comprehensive enough, because many of these ulcers have other causes, such as venous thrombosis, ankylosis of joints, paralysis of the leg muscles, lymphatic blockage, etc. More comprehensive descriptions are: *ulcus cruris*, *indolent ulcer of the leg*, *chronic leg ulcer*, *stasis ulcer*,