Menstruation and Menstrual Disorders

BY

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TO-DAY it is regarded as an axiom that functional uterine bleedings, so interesting to the gynaecologist, are due to a disturbance of the endocrine balance which maintains the normal menstrual cycle. It is impossible, therefore, to appreciate the proper significance of these pathological bleedings unless we are well grounded in the physiology of menstruation. Since fresh discoveries are constantly being made in this fascinating field of study, it is necessary that we should revise from time to time our conceptions in regard to the nature and cause of functional uterine bleedings in the light of the most recent advances in the physiology of menstruation.

In the interpretation of the menstrual cycle two separate but closely related problems can be distinguished. The first concerns the physiological determinants of menstrual bleeding, and the second the relation between the rhythmical phases of the menstrual cycle and those of the sexual cycle in the lower animals.

PHYSIOLOGY OF MENSTRUATION.

Until recently it was generally assumed that the withdrawal of the ovarian hormones is an adequate cause of menstrual bleeding. Some clinicians, notably Novak,[1] still adhere to the traditional view. In reference to the passive or negative theory of menstruation, as it is called, I quote a passage from a paper which I contributed to the *Irish Journal of Medical Science* in 1930:

> "That the endometrial edifice which has been built up under the influence of the ovarian hormones should collapse without their support is something I can readily understand: that the endometrium, however, should shed blood on

account of this loss is too much for my credence. I prefer to think that a hormone, toxin—call it what you will—probably manufactured outside the ovary is the active cause of menstruation."

In strict logic, a negative cause is a meaningless expression. By "cause," in the strict philosophic sense, we mean that which produces an effect or "something new" by some positive influence. We must distinguish the cause, in the sense defined, from the conditions, positive or negative, under which it operates. The conditions are discovered by the same principles of inductive logic as the cause itself, and, from the practical point of view, are just as important. In the empirical sciences, therefore, our ideal should be to discover the conditions, as well as the cause, of the "something new" we are investigating. Now the withdrawal of hormonic support may be a negative condition of menstrual bleeding. It cannot, in strict logic, be the cause.

Frankl's View of the Mechanism of Bleeding.

Although Frankl's view is no longer accepted, he was the first to have formulated a theory of menstruation which satisfies the demands of the category of causality, including as it does not only the actual cause, but also the conditions, positive and negative, of menstrual bleeding. According to Frankl,[2] the corpus luteum elaborates a special hormone which is responsible for the secretory phase of the human menstrual cycle. This phase is characterized by the presence of mucus in the large tortuous glands, and of oedema and hyperaemia of the stroma (the positive condition). On the death of the ovum, the corpus luteum begins to degenerate, and the turgescence of the endometrium subsides. The efferent ducts, which have been closed by the oedematous endometrium, are now open, and so mucus escapes into the cavity of the uterus (the negative condition). The mucus which contains trypsin (the actual cause) digests the vascular endometrium. Hence the flow of menstrual blood. In other communications[3] I have criticized Frankl's theory at some considerable length. Here it is sufficient to say that his theory, although it meets the requirements of the category of causality, completely breaks down in the attempt to explain non-ovular menstruation in which the secretory phase is characteristically absent.

Human beings, the apes and the old-world monkeys, are the only animals that menstruate in the strict sense of the

word. It is remarkable that these are the only forms which have a peculiarly haemorrhagic implantation. A study of the parallelism between the haemorrhage of menstruation and that of implantation has led Hartman to abandon the passive or negative view in favour of a positive cause of menstrual bleeding. Hartmann[4] carried out a series of experiments to locate the source of the blood-producing factor. It is well known that the administration of oestrin to the castrated monkey provokes bleeding as soon as the injection is discontinued. According to Hartmann, the bleeding is prevented by removing the pituitary gland of the castrated monkey. Therefore he suggests that the pituitary body, in addition to the sex hormones (prolan A and prolan B), contains a bleeding factor which is the active cause of menstruation.

The production of bleeding[5] by the administration of anterior pituitary extract to the non-castrated monkey from which the pituitary gland has been removed established the theory.

Many criticisms have been levelled against Hartmann's experimental results and their interpretation. It was found by Saiki[6] that bleeding does not follow the administration of anterior pituitary extract to the castrated monkey from which the pituitary gland has been removed. According to Saiki, therefore, the crucial test fails when carried out under strict experimental conditions. In my opinion the inference is not logical. It is one of the fundamental principles of endocrinology that not only are certain tissues of the body sensitive to the stimulus of a particular hormone, but the same tissue varies in its response to a particular stimulus. For example, we know that follicle-ripening is produced by the follicle-stimulating principle of the anterior lobe of the pituitary gland. Yet of the many follicles produced only one responds to the full charge of the pituitary hormone and so reaches maturity. The others become atretic. Now the result of Saiki's experiment only proves that an atrophic endometrium which results from castration is insensitive to the stimulus of the bleeding factor of the anterior lobe of the pituitary gland; in other words, that a normal, active endometrium is one of the conditions under which the bleeding factor operates.

It is alleged[7] that if Hartmann's theory were true, the bleeding which follows the administration of anterior pituitary extract to the non-castrated monkey from which the pituitary gland has been removed should be immediate. Instead, it is delayed for some considerable time. Therefore it would seem that the bleeding is due to something subtracted from, rather than something

added to, the circulation. The inference is partly true and partly false. Delayed bleeding only proves that the withdrawal of oestrin, which is produced by the oestrogenic hormone contained in the anterior pituitary extract, conditions the activity of the bleeding factor which the pituitary extract also contains.

The protagonists of the exclusively negative theory of menstrual bleeding say that the bleeding which is produced by extracts of the anterior lobe is microscopic, not macroscopic. Therefore genuine menstrual bleeding must depend upon a different mechanism. Such an argument reminds me of the unfortunate lady in one of Captain Marriot's novels who tried to defend the birth of her illegitimate child on the ground that it was so small. In point of fact, Novak, who is one of Hartmann's associates, tells us that the bleeding, alhough generally microscopic, is sometimes macroscopic and very profuse. Hartmann's theory of an extra-ovarian bleeding factor will help to throw considerable light on the nature of the continuous bleeding which is so characteristic of certain types of functional uterine bleeding.

While I agree with Hartmann that a bleeding factor in the hypophysis is the cause of menstruation, I also contend that the withdrawal of the ovarian hormone or hormones, if not the cause, is an essential condition of menstrual bleeding. The discontinuance of oestrin after a certain amount has been administered to the castrated monkey is always followed by uterine bleeding. The regression, or excision, of the corpus luteum, as well as the excision of the growing Graafian follicle, invariably provokes bleeding. During non-ovular menstruation, as well as intermenstrual bleeding, blood-hormone studies in addition to observations[8] of the sexual cutaneous changes in certain species of the sub-human primates indicate a definite drop in the level of folliculin. These facts can be interpreted only to mean that the periodic waves of depression, in the folliculin-content of the blood, condition the activity of the bleeding factor of the anterior pituitary body. The prevention[9] by oestrin or folliculin of the bleeding which follows the administration of the anterior pituitary extract to the non-castrated monkey from which the pituitary gland has been removed establishes beyond doubt the truth of the theory that folliculin, at any rate, inhibits the activity of the bleeding factor of the anterior lobe of the pituitary gland.

Does the special hormone of the corpus luteum inhibit menstrual bleeding? The bleeding which follows excision of the corpus luteum is not conclusive, since that body contains folliculin as well as its more characteristic hormone, progestin. It is

necessary, of course, to postulate the withdrawal of the luteal hormone as the factor responsible for the endometrial degeneration, accompanied by slight bleeding, which occurs at the end of the luteal phase of the biphasic cycle of the bitch. The hypothesis that progestin inhibits menstrual bleeding in man and the monkey has been tested experimentally by Smith and Engle.

"These observers," says R. W. Johnstone,[10] "administered to mature monkeys anterior pituitary hormones in doses calculated to increase the formation of oestrin, adding large doses of oestrin in the last few days of the experiment. They then discontinued the injections and removed both ovaries. In this way they were able to eliminate a further source of oestrin, while at the same time they provided the appropriate stimulus to uterine bleeding on any theory of withdrawal of oestrin. None the less, they succeeded in preventing bleeding by the injection of large doses of corpus luteal extract which contained only a negligible quantity of theelin." The result of this experiment seems to contradict Novak's view[11] that of the ovarian hormones, oestrin or folliculin is the only one which inhibits menstrual bleeding. As we shall see later, there is a certain amount of clinical evidence that the luteinizing hormone of the anterior lobe of the pituitary gland also inhibits menstrual bleeding.

Relation Between Oestrus and the Menstrual Cycle.

Some few years ago R. W. Johnstone[12] contributed a paper to the *American Journal of Obstetrics and Gynecology*, in which he stated that the human menstrual cycle is monophasic, not biphasic as it is in the lower animals: that the sexual or follicular phase has been missed out in the process of evolution and the reproductive or luteal phase alone survives. In a paper which I contributed to the *British Medical Journal*[13] I advanced many arguments in favour of the view, now generally accepted, that in man and the monkey there are, in reality, two cycles. On account, however, of the partial eclipse of the sexual or follicular phase by the supervention of the reproductive or luteal phase, during the second half of the menstrual cycle the former can only be observed "as in a glass darkly." In monkeys during the non-breeding season, on account of the absence of the luteal phase, the follicular phase can be deciphered quite clearly.

It is generally agreed that uterine bleedings associated with ovarian malfunction are due to a disturbance of the mechanism which maintains the rhythmic phases of the human menstrual

cycle and their nice adjustment to each other. Therefore, in order to understand the aetiology of such bleedings we shall have to analyse, so far as we can, the nature of this complex mechanism.

At puberty the female genital organs, which have been under the influence of the growth-hormone of the anterior lobe of the pituitary body, become sensitive to the stimulus of the ovarian and pituitary hormones. It is now well known that the ovarian hormones depend for their characteristic function upon the pituitary sex hormones. Although the latter have not been successfully isolated for either experimental or therapeutic purposes, the mechanism responsible for maintaining the follicular and luteal phases of the menstrual cycle can only be understood on the assumption of two separate hormones. From the results of Kraul's[14] experiments it would seem that the ovarian hormones, which have been produced in the first instance by the pituitary hormones, in turn react upon the latter so as to heighten their effect. This reciprocal causality explains, on the one hand, the gradual development of the follicular phase during the first half of the menstrual cycle, and on the other, the gradual development of the luteal phase during the second half of the cycle.

How do we account for the fact that prolan B (the luteinizing hormone) becomes active only during the second half of the menstrual cycle? When prolan, which presumably contains both prolan A and prolan B, is administered to immature mice, we notice that many corpora lutea are formed without the intermediate act of ovulation (*corpora atretica* as they are called). There must be some mechanism, therefore, to account for the orderly sequence which occurs in the human menstrual cycle. In a previous communication[15] I referred at some length to the results of Parkes's[16] experiments upon rabbits, which seemed to show that the act of ovulation itself provides the stimulus (probably nervous in origin) which sets free the luteinizing hormone of the pituitary gland.

On account of the supervention of the luteal, upon the follicular phase, the latter is closed to direct observation during the second half of the menstrual cycle.

We know that a definite drop in the level of folliculin occurs at the beginning of the second half of the menstrual cycle. According to Zuckermann[17] this level is maintained throughout the second half of the menstrual cycle. Accordingly the follicular cycle, like that in the lower animals, reaches its maximum development at the mid-point of the cycle. Ovulation, there-

fore, like that in the lower animals, occurs at the height of pro-oestrual development. According to Zuckermann there is sufficient follicular hormone left to delay the pro-oestrual degeneration until the beginning of menstruation. This theory of delayed pro-oestrual degeneration does not seem to have any teleological significance, nor do I know of any mechanism to account for the delay. It can hardly be due to the continued secretion of oestrin by the corpus luteum because the appearance of the next menstruation is not hastened in those cycles in which ovulation does not occur.

In another communication[18] I advanced many arguments, mainly biological, in favour of the view that, except for a temporary arrest at the mid-point of the human menstrual cycle, there is a gradual development of the follicular phase, or cycle, from the end of one menstruation to the beginning of the next. The follicular phase, therefore, reaches its maximum development just before menstruation, not at the mid-point of the menstrual cycle. Ovulation, therefore, instead of occurring at the height of pro-oestrual development, takes place 14 days before the cycle is complete. The follicular and luteal cycles are, therefore, telescoped into each other during the second half of the menstrual cycle. The view which I then expressed, and which rested mainly upon biological considerations, has since been borne out by blood-analysis and other lines of investigation. An examination of the blood by Hartmann has proved that in the monkey the level of folliculin reaches its highest point just before menstruation. The intense colour of the sexual skin phenomena at the same period confirms the blood-findings.

What is the factor which completes the menstrual cycle? What, in other words, is the cause of the pro-oestrual and luteal degeneration which occurs at the same time during menstruation? That it is due to the withdrawal of the anterior pituitary sex hormones is an obvious corollary from the physiological and biological principles which I have enunciated. The problem, however, is only pushed a little farther back. What is the cause of the cessation of activity of the sex hormones? Until quite recently the problem was regarded as insoluble. The work of Kraul seemed to prove that oestrin or folliculin heightens the effect of the oestrogenic hormone of the pituitary gland. Hisaw[19] and others have proved that excess of folliculin inhibits the pituitary function with corresponding inhibition of the ovarian function. When, therefore, the follicular hormone rises to the level attained just before menstruation, instead of stimulating

the pituitary function it inhibits it. It "kills the goose that lays the golden eggs." The folliculin content of the blood rapidly diminishes. Pro-oestrual and luteal degeneration follow as a natural consequence. This thermostatic-like mechanism carries with it many important implications and, as we shall see later, helps to throw considerable light on the cause of glandular hyperplasia—the characteristic feature of the endometrial picture in metropathia haemorrhagica.

The Physiology of Inter-menstrual Bleeding.

As we shall see later, the close relation between intermenstrual bleeding and certain types of uterine bleeding should awaken gynaecological interest in the physiology of this interesting phenomenon. Microscopic intermenstrual bleeding occurs frequently in monkeys during the breeding season. Macroscopically, it occurs occasionally in women. Though it cannot be proved experimentally, we have no reason to doubt that, microscopically, it occurs in women as frequently as in the monkey. Hartmann was at first inclined to think that intermenstrual bleeding is confined to ovulational menstruation. He, therefore, formulated the theory that the ovary, not the uterus, is the source of the bleeding. One of the monkeys, however, bled intermenstrually for seven days. That event threw considerable doubt upon the ovarian origin of the bleeding. The occurrence, though rare, of intermenstrual bleeding in non-ovular menstruation has shattered Hartmann's original conception. What is the cause of the bleeding? Blood-hormone studies in the monkey supported by the sudden disappearance of the sexual skin changes at the mid-menstrual period indicate that a temporary drop in the level of folliculin ushers in the bleeding. There must be some factor, however, to account for the periodic lowering of the folliculin-content of the blood. Is it due to a temporary inhibition of the pituitary function by excess of oestrin? If such were the case, we should expect degenerative changes in the endometrium. Instead we do not find any endometrial change whatever. In any case, the drop in the folliculin-content is much too sudden, and the bleeding much too prompt, to be explained on the basis of a hormonic mechanism.

What is the teleological significance of the lowering of the folliculin-content at the time of ovulation? We know that folliculin stimulates contractions of the Fallopian tube and uterus. Until progestin, the special hormone of the corpus luteum, has had time to produce its quiescent effect upon the

tubal and uterine musculature, unless the folliculin-content of the blood is rapidly diminished, there is just the danger that the fertilized ovum may be swept out of the uterine cavity before nidation takes place. In a previous communication[20] I expressed the view that in order to prevent such a catastrophe there must be, at the time of ovulation, some mechanism (probably nervous in origin) by which the folliculin is rapidly excreted from the blood by the kidneys. This view is supported by the work of Lowe and Lange,[21] who have demonstrated the existence of oestrin in small quantities in the urine during the premenstrual phase, and at no other time.

Relation Between Intermenstrual Bleeding and the Oestrous Cycle in the Lower Animals.

Hartmann, in the attempt to prove the similarity between the human menstrual cycle and the oestrous cycle in the lower animals, draws attention to the bleeding which occurs in the bitch, not only at the time of ovulation or the end of the follicular cycle, but also at the end of the luteal or reproductive cycle. Here there seems to be an exact parallel to the intermenstrual and menstrual bleedings which occur in man and the monkey. According to Hartmann's[22] interpretation, the luteal phase in the higher animals is a post-oestrual development, as it is in the lower animals. Intermenstrual bleeding, therefore, represents a purely pro-oestrual degeneration. It is homologous with the pro-oestrual bleeding which occurs in the bitch. I do not agree with Hartmann's interpretation. In intermenstrual bleeding there is not any endometrial change whatever. In the pro-oestrual bleeding of the bitch there are marked desquamative changes in the endometrium indicating the suspension of activity of the oestrogenic hormone of the pituitary gland. It is this great difference in the endometrial picture which constitutes the strongest biological argument against Hartmann's view and in favour of the view which I have frequently advocated—that in the higher animals ovulational menstruation represents pro-oestrual and luteal degeneration telescoped into each other.

Metropathia Haemorrhagica.

In several previous communications[23] I have elaborated upon the symptomatology and pathology of this interesting condition. I have pointed out that not only is there an absence of the luteal phase of the normal menstrual cycle, but there is also a very characteristic disturbance of the follicular phase. In the light

of the new physiology of menstruation, such naïve conceptions as congestion of the uterus, or endometritis, as an adequate explanation of the bleeding associated with metropathia haemorrhagica have completely disappeared from gynaecological literature like mist before the rising sun.

I have always thought that there is a close similarity between metropathia haemorrhagica and the persistent pro-oestrual development which occurs in the rabbit and ferret in the absence of copulation. In such animals, the act of copulation appears to heighten the effect of prolan A (the ovulation-producing hormone) to the point required for rupture of the follicle. If this interpretation is correct, then we are entitled to infer that in metropathia haemorrhagica absence of the corpus luteum is due to diminished activity of the ovulation-producing hormone of the pituitary gland. The stimulus, therefore, provided by the act of ovulation to release the luteinizing hormone (prolan B) is missing. Consequently, instead of a luteal phase, there is prolonged pro-oestrual development such as we find in the rabbit and the ferret in the absence of copulation. The view which I have expressed as to the aetiology of metropathia haemorrhagica is directly opposed to that of Novak[24] and others. According to the latter this interesting type of functional uterine bleeding is due to super-folliculism which, in turn, is due to increased activity of the follicle and ovulation-producing hormone. The view which I have propounded receives considerable support from the pathological findings of Wilfred Shaw.[25] The follicular cyst, the distinctive feature of the metropathic ovary, unlike the mature follicle of the normal ovary, is unaccompanied by ripening follicles and the sclerotic ovary of metropathia haemorrhagica has all the appearance of being relatively inactive. These pathological findings are compatible with the view that in metropathia haemorrhagica the sensitivity of the ovary to the stimulus of the follicle and ovulation-producing hormone is below the normal threshold. In any case, these findings cannot be reconciled with Novak's view.

What is the cause of the continuous follicular development or glandular hyperplasia? That it is due to continued activity of the oestrus-producing hormone is generally admitted. But why is there continued activity of oestrin or folliculin? Why, in other words, is the follicular cycle not completed as in normal menstruation? According to the late Professor Graves,[26] in the absence of the corpus luteum the endometrium does not undergo the customary pre-menstrual secretory changes. Under the continued influence of oestrin or folliculin (contained in the per-

sisting follicle), no longer inhibited by the corpus luteum, it acquires, instead, an irregular growth called glandular hyperplasia. This theory rests upon the traditional view that the human corpus luteum controls or inhibits follicular growth. In my opinion, clear evidence in support of this view is wanting.

In another communication,[27] I quoted a case of mine in which surgical removal of the corpus luteum, although followed by premature bleeding, did not appear to accelerate the next period. In non-ovular menstruation, which occurs in monkeys during the non-breeding season (and in some women), the persistent absence of the corpus luteum does not appear to disturb the follicular cycle. On the assumption that the luteal phase is a post-oestrual development like that in the lower animals, the traditional view of the controlling influence of the corpus luteum is a convenient hypothesis to explain the sequence of events which take place between one menstrual cycle and another. The theory, which I have advocated in this and other communications, that ovulational menstruation represents follicular and luteal denegeration telescoped into each other rules out the luteal hermone as the responsible factor for completing the follicular phase of the human menstrual cycle.

For these and other reasons I have always taken the view that the factor responsible for completing the follicular phase is something more fundamental than the special hormone of the corpus luteum or even the luteinizing hormone of the anterior lobe of the pituitary gland: that it is due to a reciprocal relation between the ovaries and the anterior lobe of the pituitary gland, the nature of which future research would enable us to ascertain. Thanks to the work of Hisaw, already referred to, we now know that when the folliculin-content of the blood rises to the level attained at the beginning of menstruation, it inhibits the pituitary function which, in turn, arrests the production of a further supply of folliculin. Consequently both the follicular and luteal cycles are completed. In other words, menstruation takes place. If sub- rather than super-folliculism is accepted as the primary cause of metropathia haemorrhagica, then it is natural to expect that in this condition the folliculin content of the blood can never reach the level attained at the beginning of normal menstruation. Consequently, the follicular cycle is never completed. Instead, under the continued activity of folliculin, there is persistent follicular development or glandular hyperplasia.

What is the significance of the periodic bleeding which occurs

in so many cases of metropathia haemorrhagica? I am inclined to Novak's view that it is an exaggeration of intermenstrual bleeding, not of normal menstruation. If the periodic bleeding were a genuine menorrhagia, then we should expect a complete dismantling of the hyperplastic endometrium which would take some considerable time to regenerate. We should expect, in other words, an exaggeration of the pro-oestrual bleeding which occurs in the bitch. Instead, we find stationary glandular hyperplasia throughout the bleeding and non-bleeding stage. It is true that during the process of bleeding there are localized areas of superficial necrosis. These are probably the effects, not the cause, of bleeding. What is the cause of the periodic bleeding? If we accept the view that the bleeding is an exaggeration of intermenstrual bleeding, then we are entitled to infer that a drop in the folliculin-level owing to its excretion by the kidneys conditions the bleeding. I believe that this inference is supported by blood and urinary analysis. Novak agrees that a drop in the folliculin level conditions the bleeding, but he thinks that the drop is due to temporary inhibition of pituitary function by excess of folliculin—that the mechanism of bleeding, in other words, is exactly similar to that of normal menstruation. Now the arguments which I have advanced in favour of the view that the periodic bleeding of metropathia haemorrhagica is an exaggeration of intermenstrual bleeding are equally effective in proving that inhibition of pituitary function cannot be the cause of the depression of folliculin in the blood. According to my interpretation, in cases of metropathia haemorrhagica associated with periodic bleeding, the folliculin-level has a tendency to rise automatically at what corresponds to the mid-menstrual period of normal menstruation, when a rapid excretion of folliculin from the blood provokes bleeding. In other cases this periodic rise does not seem to take place. The bleeding, therefore, loses its rhythmic character. When it occurs, it may last for a month, two months, sometimes longer. The bleeding stage is succeeded by a correspondingly variable period of amenorrhoea.

It is difficult, on the exclusively negative or passive theory of menstrual bleeding, to explain why normal menstruation only lasts for a few days and the acyclic bleeding of metropathia haemorrhagica may continue for months. On the theory which I have advocated it is reasonable to expect that the bleeding will continue until there is a sufficiency of follicular hormone in the blood to inhibit the activity of the bleeding factor of the pituitary body. In normal menstruation the optimum concentration of

folliculin is reached in a few days. In metropathia haemorrhagica associated with acyclic bleeding, the accumulation of folliculin is naturally slow. Therefore, months may elapse before the optimal concentration is reached. Novak[28] regards a special bleeding factor to account for normal menstruation a physiological luxury. To account, however, for the continuous bleeding associated with many cases of metropathia haemorrhagica he regards an extra-ovarian bleeding factor—distinct from the sex hormones—a pathological necessity.

I have already stated that metropathia haemorrhagica is fundamentally due to a disturbance of the mechanism of ovulation. The fault is, in all probability, due to insufficiency of prolan A (the ovulation-producing principle). In certain cases it may be due to loss of sensitivity of the ovary to its normal stimulus. In either case, there is diminished follicular activity, with the development of a Graffian follicle cyst instead of a normal corpus luteum. Whether the ovary or the pituitary gland is the incriminating organ in a particular case should be ascertained by the therapeutic test of administering prolan A. Unfortunately, this hormone has not been sufficiently separated for therapeutic purposes.

Novak[29] thought that if progestin were available, it should be possible to convert the hyperplastic endometrium into a functional pregravid one and thus complete the cycle. Progestin is not available for general use, as it is obtainable from the corpus luteum in such small amounts. Besides, it is a highly labile substance. Since the pituitary-like hormone which is found in the urine of pregnant women has a strong luteinizing effect upon the ovaries of the rat and the mouse, it was hoped that it might serve as a substitute for progestin in that it would tempt the cystic ovary to produce its own progestin. By means of this hormone Novak has treated many cases of metropathia haemorrhagica with the most gratifying results. "So prompt is the effect in so many instances," says Novak, "that we were soon convinced that it could not be due to an actual biological change in the ovaries, and direct studies of the ovaries have since then been made bearing out this idea." It seems to me that this haemostatic effect is due to inhibition of the activity of the special bleeding factor by the luteinizing hormone of the pituitary gland.

Intermenstrual bleeding, as I have already pointed out, is characteristically microscopic, and when it becomes macroscopic, lasts, as a rule, only for a few days. The contrast between intermenstrual spotting and the periodic bleeding of metropathia

haemorrhagica which is characteristically prolonged is probably due to the inhibitory influence of the luteinizing hormone of the pituitary gland in the one case and its absence in the other. Quite recently I had under my care a patient who bleeds intermenstrually for several days. She had been bleeding for two days prior to her admission to hospital. One cubic centimetre of the luteinizing hormone (Parke Davis's preparation) was administered on her arrival. Another cubic centimetre was administered at night. Next day the blood was almost black. On the evening of that day the bleeding ceased.

In regard to metropathia haemorrhagica I have had an impressive result with the luteinizing hormone in a young girl who had just begun to menstruate. Previous to her admission to hospital she had been bleeding continuously for six weeks. One cubic centimetre of prolan B, administered twice a day, arrested the bleeding on the third day after admission. She did not menstruate then for about two months. She was bleeding for 12 days before her second admission to hospital. The administration of the luteinizing hormone had led to the same dramatic result. Her next period was quite normal, and she has remained normal ever since.

It is in the bleedings of puberty which have a natural tendency to spontaneous cure that organo-therapy is so pre-eminently successful. In the future many of these young women will be spared the inconvenience of repeated curettage, or the risk of sterility by the administration of radium or X-ray therapy. In my opinion, most of the cases of metropathia haemorrhagica occur in women nearing the menopause. In menopausal bleeding which has not any tendency to spontaneous cure, I agree with R. W. Johnstone[30] that the introduction of intra-uterine radium after preliminary curettage is the speediest and most permanent method of cure. It is very surprising that there are still gynaecologists who perform the operation of hysterectomy, as a matter of routine, in such cases.

Before taking leave of the subject of metropathia haemorrhagica, I should like to make a few remarks about that rare but interesting form in which an ovarian tumour, instead of the normal functioning ovary, forms an intermediate link in the chain of causation. Many such cases have been reported in the literature. Glandular hyperplasia, the characteristic feature of metropathia haemorrhagica, is invariably, or almost invariably, present, and the bleeding is, generally, acyclic in character. These cases occur, as a rule, after the menopause. About six

cases have been reported as occurring before puberty. A few cases have occurred during reproductive life.

In a record of 547 ovarian tumours investigated by Green Armytage,[31] 63 occurred in patients past the menopause. Uterine bleeding occurred in four cases in which the tumours were innocent and in 26 cases in which they were malignant. Green-Armytage advances the theory that an ovarian tumour in a woman after the menopause (and presumably in a young girl before puberty) may take on the function of ovarian-tissue, just as after removal of the thyroid gland for cancer metastatic tumours have been known to function like the absent thyroid gland. Two cases of continuous vaginal bleeding associated with a so-called granulosa-cell tumour in a young woman have been reported by Wilfred Shaw.[32] In another communication,[33] I referred to the case of a young woman who consulted me on account of continuous vaginal bleeding, which had been preceded by a long period of amenorrhoea—the characteristic syndrome of metropathia haemorrhagica. The removal of a small cystadenoma on the left side restored the patient to normal menstrual life. Such cases occurring during active reproductive life cannot be explained on Green-Armytage's view. In any case, his theory cannot explain why only 30 of the 63 ovarian tumours which he found after the menopause were associated with the symptoms and pathology of metropathia haemorrhagica. Novak and Long[34] take the view that granulosa-cell tumours which are characteristically associated with uterine bleeding are derived from "rests" of granulosa-cells which have been left over after the primordial follicles have been formed. The granulosa cell, according to these observers, is a typically feminine cell producing the so-called female sex hormone, folliculin. The hormonal effects produced by tumours of this variety are along the lines of femininity with over-accentuation of certain female sexual characters and functions. The only evidence that the so-called granulosa-cell tumours are derived from granulosa-cell "rests" is the close resemblance which the cells of the tumour bear to granulosa cells. On the theory of Novak and Long, we are driven to the assumption that certain cystadenomata, sarcomata, de-differentiated ovarian tumours, and even teratomata, reported[35] in the literature as related to metropathia haemorrhagica, the cells of which do not have any resemblance whatever to granulosa cells, are also derivates of the granulosa-cell "rests"—a rather big assumption. It seems to me that further histological and experimental research is needed before we can give a confident

reply to the many questions which these rare forms of metropathia haemorrhagica suggest.

Epimenorrhoea.

There is another type of functional uterine bleeding associated with ovarian malfunction in which there is a shortening of the menstrual rhythm. In many of these patients there is prolonged and profuse bleeding (epi-menorrhagia). Wilfred Shaw has proved by careful histological investigation that in these cases there is premature rupture of the Graaffian follicle as well as premature bleeding. The polycystic ovary, which is invariably present in such cases, as well as premature ovulation, is an indication that this type of functional uterine bleeding is due to superfolliculism, which, in turn, is due to increased activity of the follicle and ovulation-producing hormone of the anterior pituitary body. What is the explanation of the premature bleeding? According to Beckwith Whitehouse,[36] it is due to the presence of ova of low vitality. This view rests upon the assumption, now no longer accepted, that the ovum regulates the periodicity of the menstrual cycle. -In cases of epimenorrhoea or epimennorrhagia, the follicular phase reaches its maximum development sooner than normal. If we accept the view that excess of folliculin inhibits pituitary function, then the sooner the follicular phase reaches the high-water mark of its development the sooner is the cycle completed. Therefore, premature bleeding follows as a logical consequence of premature ovulation.

A number of French workers have succeeded in inhibiting pituitary function in such animals as the rat by the administration of insulin. Influenced by their results, I have administered insulin to a number of cases of epimenorrhoea. The results, which I hope to publish soon, are most encouraging.

Menorrhagia Simplex

The majority of cases of functional uterine bleeding associated with ovarian malfunction can be diagnosed, as a rule, by taking a careful history. Cases of metropathia haemorrhagica associated with periodic bleeding may, however, be mistaken for these obscure functional bleedings in which there is not any histological abnormality, either of the ovary or the uterine mucosa. The periodic bleeding of metropathia haemorrhagica is characteristically prolonged. The periodic bleeding in cases of uterine insufficiency, as they are called, is profuse. Patients often express the

amount of blood lost as if "running away from a tap." The periodic bleeding in metropathia haemorrhagica may, however, at times be profuse. A certain diagnosis, therefore, can only be made by microscopic examination of the endometrial scrapings.

In this connexion I should like to call attention to a condition of the endometrium called stromal hyperplasia, which is occasionally associated with metropathia haemorrhagica. There is a considerable increase in the stroma without any glandular change whatever. Novak is the only observer who has investigated this interesting condition. He has found it present in 4 per cent. of all cases of metropathia haemorrhagica. When such a condition is present, curettage may reveal an endometrium of normal thickness. The scrapings, in consequence, are usually thrown away as of no significance. In 1931 I exhibited,[37] at the Royal Academy of Medicine, a specimen of uterus and ovary from a case of irregular uterine bleeding. The ovary showed the typical follicle cyst of metropathia haemorrhagica. The uterus contained a polypus which showed typical glandular hyperplasia. The rest of the uterine mucosa showed stromal hyperplasia without any glandular changes.

The Cause of Menorrhagia Simplex.

In another communication,[38] I have discussed the aetiology of menorrhagia simplex or uterine insufficiency. Suffice it to say, that serological investigation shows that the majority of such cases are due either to deranged calcium metabolism or to definite haemorrhagic conditions such as purpura haemorrhagica. In this connexion, I should like to stress the fact that several cases of recurrent menorrhagia with severe anaemia have been reported in which there was not any overt evidence of purpura or spontaneous bruising present. Latent purpura, however, was demonstrated by the capillary resistance test. I should also like to point out that splenectomy is the only cure for menorrhagia associated with either typical or atypical purpura haemorrhagica.

Conclusion

A knowledge of the physiology of menstruation and its clinical application has widened the gynaecologist's vision far beyond the pelvic brim. As Novak has said, the gynaecologist of to-day is no longer regarded as merely an operating surgeon. With his wider vision, he no longer wastes time on such sterile discussions as the best means of suspending a displaced uterus. He is much more interested in the nature and cause of these bleedings which the suspension of the uterus has so frequently failed to cure.

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