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OESTRUS-PRODUCING HORMONES *

BY

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I propose in this introduction to give a general outline of our present knowledge concerning the oestrus-producing hormones, so that with this background it will be possible for subsequent speakers to develop their own particular views in the various fields in which they work. No detailed account can be given owing to the lack of time and space. Those who require fuller descriptions are advised to consult the general references given at the end of this communication.

It will be noted that the title is in the plural, and refers to the oestrus-producing hormones. Presumably we are required to consider all the naturally occurring oestrus-producing substances. It will not be out of place to refer to oestrus-producing substances from other sources, since the knowledge of these helps us to understand the chemical relations of the naturally occurring substances.

The phenomenon of oestrus has been described on so many occasions that I do not think it is necessary to consider it fully here. To summarize we may say that oestrus is the outward and physical sign of the sexual cycle of animals, passing as it does from a stage of quiescence or rest to conditions of intense activity, during which time the animal is capable of impregnation. The biological changes connected with oestrus differ very considerably in the different animals. For the purpose of studying the hormones responsible for these changes the rat and mouse have been found most convenient. It is possible to keep large numbers of these animals relatively cheaply, and, at the same time, the progress of the oestrous cycle may be judged very readily by a study of the vaginal smear. It is for this reason, and for this alone, that the rat and mouse have been used. In many ways it is perhaps a little unfortunate, since in the minds of many people—particularly clinicians—any talk of oestrus-producing hormones automatically calls up a picture of rats and mice. Again, it is perhaps unfortunate that we have come to think in terms of these small rodents when we consider the necessity of associating the corpus luteum hormone with the cycle. Removal of the ovaries causes cessation of the oestrous cycle, and consequently these castrated animals are suitable for a study of the chemistry and biological activities of oestrus-producing substances.

Nature of the Hormones

In the first place active material was prepared from ovaries by extraction with volatile solvents. Later the active material was demonstrated in the placenta, and this was used as a valuable source of the substance. By the application of the most refined chemical methods it

is possible to show that the material contains only carbon, hydrogen, and oxygen, but as to the group of bodies to which it belongs there was until recently no indication. The brilliant researches of Aschheim and Zondek revealed the presence of an oestrus-producing substance in the urine of pregnant women. Here the material was relatively uncontaminated, and it was possible for organic chemists to study the constitution of the compound with much greater certainty.

Again it will be quite impossible to summarize the various stages leading to the generally accepted constitution of to-day. In general terms it may be stated that we are fairly certain that the oestrus-producing hormones in the urine of pregnant women belong to the group of sterols, and have in common a partially hydrogenated phenanthrene ring. Their relationship is shown in the following diagram.

Ketohydroxy-oestrin. Trihydroxy-oestrin. Dihydro-oestrin.

The Chemistry of the Hormones

It can be seen that in the urine of pregnancy ketohydroxy-oestrin and trihydroxy-oestrin are found, the former being considerably more active than the latter. It has been shown that trihydroxy-oestrin can be converted into ketohydroxy-oestrin by vacuum distillation with potassium bisulphate. Further interesting chemical compounds may be obtained by hydrogenating ketohydroxy-oestrin. The first of these, obtained by Schwenk and Hildebrandt,¹ is dihydro-folliculin. This compound is many times more potent than ketohydroxy-oestrin. If it be further hydrogenated by continuing this treatment the compound takes on the properties of the male sex hormone and passes out of the range of our discussion.

Up to the present, therefore, we have three oestrus-producing hormones—namely, trihydroxy-, ketohydroxy-, and dihydro-oestrin, of which the latter is by far the most powerful. At the present time we have no knowledge of the type of oestrin which is present in either the circulating blood, the ovary, or the placenta.

There are certain other oestrus-producing substances to be found in nature. Plants contain a compound capable of producing oestrus. This has been shown to have the same kind of structure as oestrin, and has been called tokokinin.

* Read in opening a discussion in the Section of Pathology, Bacteriology, and Biochemistry at the Annual Meeting of the British Medical Association, Bournemouth, 1934.

A very interesting observation was made by Aschheim and Hohlweg,² who showed that extracts of coal and mineral fuel oil were capable of producing oestrus. They attributed this interesting phenomenon to the tokokin of buried prehistoric forests which had resisted the process of carbonization.

Attempts to synthesize ketohydroxy-oestrin have not as yet met with success, and the failure may be due to the extremely complicated nature of the processes involved. But certain interesting results have developed out of the applications of synthetic organic chemistry to the study of oestrus-producing compounds. We³ have been able to show that a series of compounds obtained in the organic chemistry laboratory are capable of producing all the known phenomena of oestrus. In the main these compounds can be divided into two classes, derivatives of phenanthrene and dibenzanthracene. As an example of the former 1-keto-1:2:3:4-tetrahydro-phenanthrene, and of the latter 9:10-dihydro-9:10-dialkyl-1:2:5:6-dibenzanthracene may be cited. It is very interesting to note that the order of activity varies with the alkyl group, the maximum being at the three carbon atom stage. When the dipropyl compound is made it is more active than trihydroxy-oestrin. It has also been shown that two of the carcinogenic hydrocarbons are oestrogenic,⁴ whilst vitamin D in very large doses is capable of producing oestrus. From these observations it can be seen that the naturally occurring oestrus-producing hormones are linked on the one hand with carcinogenic substances and on the other hand with the vitamins and certain plant sterols. It must be noted that these compounds which produce oestrus in the rodent will also produce various of the secondary sexual characteristics in larger animals.

The specificity of the oestrus-producing hormones is not restricted to any one group of animals. Thus, by injecting oestrin into cocks or capons, it is possible to produce an alteration in the plumage from the male to the female type. It is also interesting to note that a synthetic compound can also do this. [Professor Dodds then showed a slide demonstrating the effect of 1-keto-1:2:3:4-tetrahydro-phenanthrene on the plumage of the capon, in that, following injection, an immediate change took place from the male to the female type of feather.]

Kaufmann's Work on Human Subjects

A long and elaborate series of researches have shown that all female animals respond to injections of these oestrus-producing hormones, provided sufficient quantities are given. Dr. Parkes will, I hope, describe to us his experiments with the baboon, since this work indicates the importance of dosage. Dr. Parkes's experiments prove successfully that the response to oestrin varies with the body weight. In other words, the amount required to produce oestrus is in direct proportion to the body weight. This has also been shown by Schoeller.

From the baboon we pass to the most recent and interesting development of this work—namely, that of Kaufmann.⁵ This worker has shown that, provided sufficient of the hormone be given together with the corpus luteum hormone, it is then possible to produce menstrual changes in the uterus even in ovariectomized women. These results have been checked very carefully by curettage and careful microscopical examination, ovariectomized women being, of course, the subjects of the investigation. Kaufmann has shown that if on the first day of the treatment 250,000 mouse units be given, and this be followed by similar doses on the fourth, eighth, eleventh, and fifteenth days, and that if on the nineteenth, twentieth, twenty-first, twenty-second, and twenty-third days seven rabbit units of the corpus luteum

be given, the full menstrual period will commence on the twenty-fifth day. The great point of Kaufmann's work is that it is always possible to induce menstruation by this method, and I think this is the first occasion that it has been possible to state definitely that this natural phenomenon can be produced at will in castrated women.

I myself have fully confirmed Kaufmann's work, and I believe that others who will speak after me will describe their own experiments, which are also of a confirmatory nature. It must be noted that these results can only be obtained in ovariectomized women when enormous doses are used. It would be very interesting to know whether it would always be necessary to use these doses even in castrated women, since experience with animals shows that once a series of regular cycles have been induced in castrated animals the amount required is nothing like so great as that necessary to initiate the first changes after castration. There can be no doubt that if the ovaries are present very much smaller quantities are required to produce these effects, and in some cases it has been possible to produce them without the use of corpus luteum hormone.

Kaufmann also brings out another interesting point, which makes plain the pathology of certain gynaecological conditions. In some cases he demonstrated with large doses, using over 5 million international units, spread over several weeks, the development of a pathological and clinical picture of cystic hyperplasia of the endometrium. As he points out, however, there is very little fear of developing this condition with the doses used in the treatment of ordinary conditions. These results have the utmost value, and for the first time they prove successfully that these hormones have a definite place in therapeutics.

Practical Applications

Having once established the fact that menstruation may be initiated at will, it is necessary to consider the practical applications of these new weapons. Judging from the fact that it is possible to produce menstruation in women long past the time of menopause, it would appear that the menses can be induced in persons suffering from both primary and secondary amenorrhoea. It has always been felt that some other hormone would be required for the treatment of primary amenorrhoea, but in view of Kaufmann's results this would not appear to be true, provided that sufficient oestrus-producing hormone and corpus luteum be administered.

In menopausal cases very good results have been reported with doses of 50,000 mouse units twice per week, with alleviation of the psychic symptoms. In a private communication to me recently Kaufmann has described very successful treatment of chronic conditions of inflammation of the vulva associated with the menopause and senility. It would appear that there is a very valuable field of application for the hormones in these conditions. Again, the use of the corpus luteum hormone has resulted in the controlling of certain types of menorrhagia, and also patients suffering from successive abortions have been successfully brought to term.

In conclusion, only the barest outline of the clinical possibilities of these substances has been given, but I hope that those who will follow me will give their own experiences. It is perhaps not going too far to say that the biochemist and biologist have placed an entirely new set of weapons in the hands of the practitioner and physician, and many gynaecological conditions which we have hitherto considered would only respond to surgical intervention will now be able to be treated with injections of the hormones.

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THE PROBLEM OF THE SEPTIC HAND *

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The problem of the septic hand is of interest to all. The public should be warned not to suck or squeeze minor injuries and to seek medical advice more frequently. Nurses should be forbidden to hand instruments, especially knives and needles, to the operator. The surgeon should always sew towards himself and pull out the thread horizontally, not vertically, if the hand and eye of the assistant are not to be endangered.

Most septic hands arise from puncture wounds. The thorn, needle, and safety-pin, however contaminated as they enter the tissues, are cleansed as they penetrate, by the glove in the case of the surgeon and American artisans who often work in gloves, and by the horny hand of toil; yet beneath the thickened epithelium over the heads of the metacarpal bones, known in the North of England as

FIG. 1.—The horizontal use of a razor blade to remove the epithelium in pricked fingers, thereby extracting thorns and relieving tension.

a "seg," infection may occur, which, if not relieved of tension, macerates and infects the underlying tissues, leading to palmar abscess. Realizing, therefore, that in the superficial layers of the epithelium the penetrating object has left most of its infecting organisms, it is our duty to remove with a razor blade the surface epithelium over the punctured area (Fig. 1), thereby relieving tension during the inflammatory reaction which must follow all trauma, whether infection is present or not. Through this weak spot serum will ooze, carrying to the surface products of the inflammation.

All pricked fingers should be kept dry, or dressed with spirit, and never until infection is established should they be subjected to fomentations, hot or cold. A splint should be applied to prevent the patient squeezing the wound and to ease the pain of muscle spasm.

* Read in the Section of Surgery at the Annual Meeting of the British Medical Association, Bournemouth, 1934.

If the septic hand is to be prevented more consideration should be given to trivial conditions involving the fingers, especially the nails. The nail is often the source of mechanical irritation which is delaying recovery. Conservative treatment of the nail is essential; if it must be sacrificed then it should be dissected off, and not wrenched from its bed, but, wherever possible, it should be preserved to splint the nail bed and to keep for the soft regenerating nail an area of adequate width to avoid irregular nail formation. When the nail bed requires removal for recurring deformity of the nail the distal half of the phalanx should be excised to relieve tension on sutures.

The crushed finger or subungual haematoma, if associated with fluid beneath the cuticle, should be drained by insertion of a sharp hook, tenotomy knife, or needle beneath the cuticle—the first step in the treatment of paronychia—to avoid maceration and diminish the tendency to infection.

The Congealed Hand or Finger

Imagine the healthy hand or finger plunged into boiling water; the result would be that all avascular structures would undergo aseptic necrosis, the palmar fascia, the dorsal expansion of the fingers, and the deep fascia on the back of the hand suffering most. In 1929, under the title of "Sore Fingers and Such Trivialities,"¹ I published in the *Lancet* an attack on this brutal method of treating injured tissues, and pointed out how it was possible to recognize the severity of previous hot-water treatment by the fact that the nail bed of other fingers, which must be simultaneously plunged into the bowl of hot water, became tender and even developed paronychia; also the annular nature of the swelling so characteristic of the carbolic finger and so different from the irregular edge of a spreading infection. The effect of treatment is dramatic, and many must have observed the immediate improvement that has followed the change to a dry dressing or cold compress: pain ceases and sleep follows.

If the possibility of a congealed finger or hand is recognized and improvement has followed a change in the treatment, it becomes urgently necessary to get these fingers moving to prevent stiffness. With the institution of active movement there may be complete recovery; not infrequently, however, small areas of fascia contract, giving rise to a Dupuytren's contracture, or these areas soften, and at the end of two or three weeks liquefaction of the fascia occurs and abscesses form about the base and dorsum of the finger or below the styloid processes of the radius and ulna, sites which have been subjected to greatest pressure as the finger or hand was held in scalding water.

The Septic Hand

Boils usually form on the dorsal surface of the index and middle fingers at their base, and may involve the opposite hand about the same time, so that soap and the nailbrush become a factor in the causation. When boils are present the finger should be splinted and painted with iodine. If the follicle shows signs of sloughing, denude the area with a razor blade and apply a thick paste of glycerin and magnesium oxide or sulphate. This will save many fingers from an incision. If a localized cellulitis forms round the boil, then an incision stretched widely open by a pair of Spencer Wells or the crucial incision is necessary; but these should never be made under ethyl chloride, otherwise an extensive slough of the avascular fibrous tissue beneath will delay healing and render the graver forms of septic finger possible.

Minor degrees of paronychia have already been considered. If pus develops at the base of the nail, the nail bed should be exposed by lateral incisions and the reflection of the tissues, dissecting off the nail and removing its proximal portion.