

RECENT ADVANCES IN SEX AND REPRODUCTIVE PHYSIOLOGY

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47 ILLUSTRATIONS



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FOREWORD

THE very numerous and urgent requests for information and for assistance that now are addressed by medical practitioners to those of us who are reputed to be acquainted with recent advances in sex and reproductive physiology have made it abundantly clear that some such book as this had become a necessity. The rapidity of the advances in knowledge in this particular field has been eagerly watched by the clinician, since it seemed to promise that reinforcement which alone could give a proper understanding, and therefore a control, of the phenomena of conception, pregnancy and parturition; phenomena which, because of their seeming inevitability, have for so long challenged man's dominion.

Man has turned from the adventurous conquest of his environment to the conquest of himself. To-day is the day of biological invention, eagerly used for the control of the undesirable and the unwanted. Sex and reproduction are no longer hedged around by myth and taboo; they are no longer accepted as mysteries that defy understanding. They are matters inviting examination and explanation; they are regarded as expressions of physico-chemical forces, the nature of which is to be displayed. It is accepted that when knowledge is sufficient, control will be absolute, and, though knowledge is not yet sufficient, readers of this book must be persuaded to the view that this will not always be so.

Having been forced to the view that, if only for self-protection, such a book as this must be written, the question arose as to who should write it. It is one that

I myself should have liked to have written ; in fact, I had promised myself that I would do so, but during these last few years whilst the author has been a colleague of mine, I have been slowly, though perhaps rather willingly, driven to the conclusion that not I, but he, must undertake the task. Having read this book, I now know that the one that I would have written would not have been so good. Its author knows his subject and, what is equally important, enjoys discussing it. He can rest assured that the book he has written is not only a successful attempt to synthesise all that is known of this particular subject, but that it must prove to be exceedingly helpful to the very large number of clinicians who seek to incorporate into their practice recent advances in science.

F. A. E. C.

PREFACE

THERE are few subjects which of recent years have grown so rapidly as the study of the sex hormones, for not only have the actions of some of these hormones been determined with a great measure of accuracy, but pure active extracts have been prepared and in one case the actual chemical composition of the hormone established. Mainly as a result of this rapid advance the numerous data are scattered in many publications in various languages, and it has been difficult for any one not in close touch with or actively engaged in research on such problems to keep abreast of the vast literature which has so quickly accumulated. Nor has the approach to the subject been made any easier by the controversies which have quite naturally arisen regarding certain vital aspects of it. Reputable schools of research have held and still hold opposite points of view on many questions in sex physiology; and in addition there can be no doubt that many publications on the subject are of but transient interest and do not add materially to our understanding of the problem as a whole.

The presentation of knowledge in this field has therefore necessarily involved a very careful evaluation of various hypotheses, and though an attempt has been made to present as impartially as possible the relevant evidence regarding these, it has been found desirable to accept for the purpose of description certain theories which at the present time appear to be supported by the weight of evidence. At the same time it has been necessary to treat very briefly or even to dismiss altogether other data which appear to have no permanent

bearing on the development of the subject. From the very nature of the evidence, which is constantly growing and fluctuating, mistakes may have been made in the process of evaluation and sifting, but with further work a clearer perspective of the field will doubtless be obtained.

It must be emphasised that this volume deals essentially with the sexual and reproductive phenomena in the female in relation to the activity of the sex hormones, and that other matter has been introduced only for the purpose of clarifying these main aspects of the subject. Thus the work on the cyclical changes in the sex organs and the properties of the structures composing these organs have been described at some length; but it has been assumed that the reader possesses some acquaintance with the anatomy and physiology of these organs.

The discovery and isolation of the sex hormones have given rise to the hope that they might be used in the human subject for diagnostic and therapeutic purposes. Such an object can only be successfully realised if the clinician possesses an adequate knowledge of the mode of action of these hormones in relation to the physiological processes and also understands the changes which occur in abnormal conditions. It has therefore been my aim to stress those experimental data which throw light on changes in primates and especially in the human subject, and to describe in some detail those findings which have been obtained from the investigation of conditions in man. It is hoped that the information thus gathered may prove of use to those whose aim it is to apply more widely the fruits of research in this subject.

I should like to offer my thanks to all those authors who have so kindly allowed me to reproduce certain figures and photographs (cited in the appropriate legend), and also to the Council of the Royal Society and the Editors of the *Archiv für Gynäkologie*, the

American *Journal of Anatomy*, the American *Journal of Physiology*, the *Journal of Physiology*, the *Journal of the American Medical Association*, the "Memoirs" of the University of California, the publications of the Carnegie Institution of Washington, the *Quarterly Journal of Experimental Physiology* and the *Zentralblatt für Gynäkologie*, who have given me a similar permission. Messrs. Julius Springer, Longmans, Green & Co., Oliver and Boyd and Williams and Wilkins have kindly allowed me to use illustrations from the *Archiv für Gynäkologie*, the "Internal Secretions of the Ovary," "Reproduction in the Rabbit," and "Sex and Internal Secretions," respectively.

To Miss M. Wilson, who read both manuscript and proofs and made many invaluable alterations and corrections, I am very deeply indebted. And finally, it is with great pleasure and gratitude that I acknowledge the continual encouragement and many helpful suggestions which I have received from Professor Crew, to whom I owe the opportunities which have made this work possible.

J. M. ROBSON.

EDINBURGH.

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RECENT ADVANCES IN SEX AND REPRODUCTIVE PHYSIOLOGY

CHAPTER I

THE NATURE OF THE SEX CYCLE

THE morphological changes which are connected with sexual activity only take place for a limited period of the life span in the female. This is true both for the human species and for a large number of animals. In the early stages of life, the growth of the sex organs takes place probably at the same rate as that of the rest of the body, and no specific cyclical changes are to be observed. Then, and usually with dramatic suddenness, a change takes place, and the whole sexual apparatus becomes active. This period of activity, which lasts for a more or less clearly defined time, is succeeded by a period in which no specific changes are evident and in which the sex organs are involved in a gradual atrophy. The factors which in the life cycle limit the duration of the specific morphological changes are at present imperfectly understood : but it is at least definitely known that three groups of organs, the pituitary, the ovary, and the secondary sex organs, working harmoniously together and completely interdependent, are involved. A realisation of the importance of this co-ordination and interdependence of definite organs is essential for the proper understanding of the control of the sex cycle.

In the female the secondary sex organs, and more especially the uterus, in which alterations vitally connected with reproduction occur, are of great clinical

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importance. The morphological changes in the uterus and other secondary sex organs (vagina, Fallopian tubes, etc.) have recently been shown to be under the control of specific substances produced by the ovary. These ovarian hormones, secreted at various stages of the ovarian activity, act upon the uterine endometrium and muscle and other organs, and bring about the alterations which are typical of the different stages of the uterine cycle. Furthermore, it has been shown that both the morphological and the secretory changes which take place in the ovary are in turn subject to a specific harmonic control, for the anterior lobe of the pituitary secretes substances which, acting upon the ovary, produce two types of effects :—

(1) Various changes in structure (*e.g.*, follicular maturation, ovulation, formation of luteal tissue) and

(2) The initiation of the secretion of the specific hormones elaborated by the ovary.

The important conception outlined above, which has been clearly demonstrated by recent experimental work, may be briefly stated thus. The anterior lobe of the pituitary controls the activity of the ovaries, which in turn control the activity of the uterus and other secondary sex organs.

Of course, additional mechanisms have to be considered ; it seems likely that pituitary activity is not independent of ovarian secretion or of the changes occurring in the uterus ; and other factors too are probably involved, some specific, such as hormones produced in definite organs, and others non-specific in nature. During pregnancy, for example, the placenta probably becomes an important secretory organ, which plays a vital part in maintaining gestation and initiating parturition. It is essential, however, before examining in greater detail the changes that take place, to realise the basic conception of the functional inter-relationships

which underlie the sexual activities, and which may be represented thus: anterior pituitary lobe → ovaries → uterus and other secondary sex organs. It may also be mentioned at this stage that the factors which determine the activity of the pituitary anterior lobe (to which the stimuli responsible for initiating the activity of the sex organs have so far been traced) have not yet been identified. Nevertheless, it can be asserted that the anterior pituitary lobe secretes the specific hormones during the whole period of sexual activity in the female subject, though there are, of course, great variations in the rate of secretion, corresponding to various phases of the menstrual and of the pregnancy cycle. It must, however, be added, that the anterior lobe contains its specific hormones, not only during the period of sexual activity, but also before and after this phase, *i.e.*, in the immature and in the senile animal. Moreover, the ovaries of both the immature and the senile organism are capable of reacting to the anterior pituitary hormones. To what extent this holds for the human subject has not yet been definitely established, though the available evidence does not suggest that the conditions are essentially different from those in the experimental animal.

No satisfactory explanation of these curious observations is yet available, but this whole question will be considered more fully at a later stage. It appears likely that quantitative factors are to some extent involved, and that the pituitary must pour into the circulation a certain quantity of hormone before any effect on the ovary is produced. In addition, the possibility that inhibitory substances may be concerned in determining the period of ovarian activity cannot be ruled out; and evidence will be adduced later which suggests that inhibitory effects can play an important part in determining the reactivity of the ovary.

There are thus a number of changes involving known organs and producing definite morphological and secretory effects during the period of active sexual life. In addition, certain psychical changes, associated with mating, occur. The recent work which has shown the importance of hormones in determining the functional variations in the sexual organs has also demonstrated, to some extent, the relation of hormones to sexual reflexes. The time of occurrence of specific psychical phenomena varies in different animals and in the human subject. In certain animals, mating only occurs at fixed periods and in conjunction with definite morphological changes and hormonal activity. In other animals and in man, the variations are not so strongly marked; and, indeed, in the human subject, mating can occur at almost any time. The mating reflexes are, in fact, subject to a number of external factors, *i.e.*, health, hunger, temperature, season, climate, etc. (and the same applies to the anatomical changes). In addition, there is probably a rhythm during the menstrual cycle.

It will thus be necessary when considering the mode of action of the hormones in various animals and in the human subject, to determine their relation both to the definite changes occurring in certain organs and to the reflexes associated with sexual and reproductive activity. The changes which must be studied may then conveniently be classed under three headings:—

- (1) Morphological changes not associated with pregnancy.
- (2) Morphological changes associated with pregnancy.
- (3) Alterations related to sexual and reproductive reflexes.

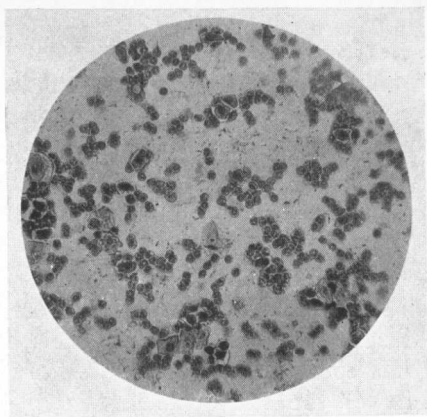
It will be subsequently seen that, although much progress has been made in the understanding of the causation of the morphological changes associated with the sexual and reproductive cycles, the factors respon-

sible for activating the mating and the maternal reflexes (see Wiesner and Sheard, 1933) are, to a great extent, still obscure.

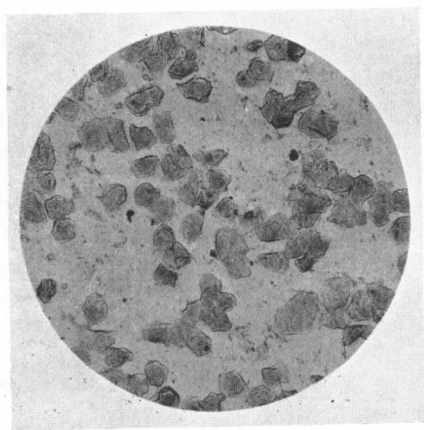
Instead of devoting more space to a generalised description of the sex cycle, it will probably be more useful to consider actual examples in some detail.

The Sex Cycle in the Mouse

The sex cycle of the mouse (similar to that of the rat) has been chosen because it has been studied in great detail and because, though it differs in many important respects from that of the primates, its elucidation has contributed very materially towards an understanding of the sex cycle in the higher animals and in man. It has been known for some considerable time that in these rodents the females will mate only at certain definite periods when they are in heat (or oestrus). These oestrous periods occur at definite intervals of time (usually 5 or 6 days) and last for 1-2 days as a rule. During the intervals between oestrus (dioestrus) the animals do not mate. Oestrus is accompanied by certain definite changes in the uterus, vagina and ovaries. The uterus becomes enlarged and distended with a fluid secreted by the endometrium, thus producing the appearance typical of oestrus. The changes in the vagina are also characteristic, and have proved such a useful instrument in the investigation of the sex hormones and the conditions under their control that they merit a rather fuller description. The state of the vaginal epithelium is, according to the technique developed by Stockard and Papanicolaou (1917), determined by taking smears from the animal. This is done by introducing a loop of wire into the vagina and removing part of the desquamated cellular content. The latter is then spread on a slide, stained and examined microscopically. During the dioestrous period the vagina



1.



2.

FIG. 1.—Vaginal smears taken in the mouse; (1) during diestrus; (2) during oestrus.

of the mouse is lined by epithelial nucleated cells; these become keratinised during oestrus, so that when this

phase is at its height only cornified cells are to be found in the smear; towards the end of œstrus the vaginal epithelium is invaded by leucocytes which practically make up the entire smear in the ensuing post-œstrous period. By a study of the cellular content of the vagina it is thus possible to determine the exact stage of the œstrous cycle of the animal investigated. Not only do specific changes occur in the uterus and vagina, but definite alterations also take place in the ovaries. In the period immediately preceding œstrus there is a marked and rapid growth of the Graafian follicles, which gradually approach to the surface of the ovaries. During this follicular maturation the ovum is also undergoing various changes preparatory to its "extrusion" and during œstrus a number of the follicles rupture and the ova are thus set free and pass into the Fallopian tubes. The morphological changes in the uterus, vagina and ovaries are accompanied by activation of the mating reflexes, and, under suitable conditions, the animal will receive the male. If mating occurs a disturbance in the rhythm of the œstrous cycle ensues. If fertilisation of the ova takes place and the animal becomes pregnant, then the œstrus is delayed for 19-20 days (*i.e.*, the duration of pregnancy). During this period, too, definite changes are again observed in the uterus, vagina and ovaries. In the site of the ovulated follicles corpora lutea are formed, and these remain active during the whole period of gestation.

In some circumstances mating may take place and yet not result in the fertilisation of the ova. Nevertheless the alterations typical of pregnancy still occur in the ovaries, vagina and uterus, though in the latter there are neither developing embryos nor placental formation. The changes so brought about have been termed pseudo-pregnancy. During pseudo-pregnancy corpora lutea develop in the ovaries, and exert their specific endocrine

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functions (to be described later), whilst the uterus and vagina show the same alterations (apart from placental formation) as are exhibited during a true pregnancy. The duration of these changes is, however, considerably shorter than that of pregnancy, and extends usually over a period of about 11 days.

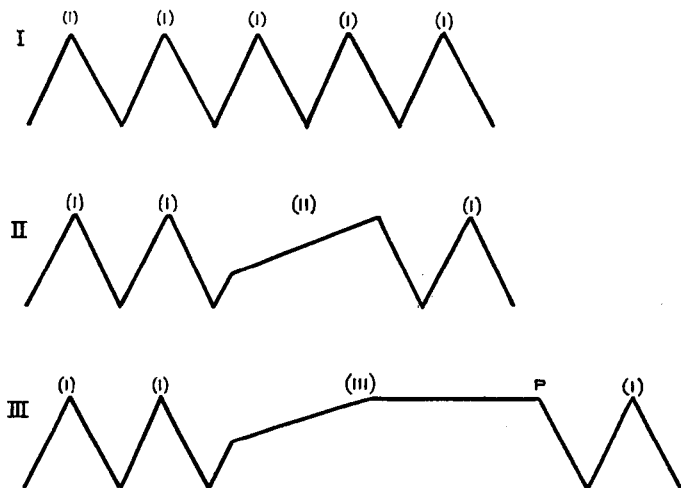


FIG. 2.—Diagram illustrating the various phases of the sex cycle in the lower rodents (rat and mouse).

- I. The normal regular œstrous cycle.
- II. The œstrous cycle interrupted by pseudo-pregnancy.
- III. The œstrous cycle interrupted by pregnancy.

(i.) = Œstrus.
(ii.) = Pseudo-pregnancy.
(iii.) = Pregnancy.
P = Parturition.

The sequence of events in the sex cycle of the mouse has been represented diagrammatically in Fig. 2. In the top tracing (I) the normal undisturbed œstrous cycle is depicted in which heat, together with its typical changes in the uterus, vagina and ovaries, occur at regular intervals of 5–6 days. At each œstrus, ovulation

takes place, but the corpora lutea formed are inactive and have no effect on the time or the onset of the next œstrous period. The second curve (II) shows the series of events which result from a fertile mating at œstrus. Here, under the control of the ovaries and their corpora lutea, definite changes take place in the uterus. These changes last for about 19–20 days, and the next œstrus is thus delayed until after parturition. Suckling of the litter may interfere with the occurrence of subsequent œstrous periods, but ultimately regular cycles are again established. In the third tracing is represented the sequence of events observed when the mating is not fertile; pseudo-pregnancy results, and the specific changes in the sexual organs last for about 11 days, after which regular œstrous cycles are re-established.

The important fact to be emphasised is that the regular succession of œstrous cycles in the sexually mature animal can be physiologically interrupted in two ways :—

- (1) By pregnancy.
- (2) By a series of changes similar to those occurring during pregnancy in spite of the absence of developing embryos and placenta. These latter changes (pseudo-pregnancy) are of shorter duration than true pregnancy. The significance of these facts in relation to the phenomena occurring in the higher animals and in man will be subsequently discussed.

The Sex Cycle in the Rabbit

In the interpretation of the significance of the menstrual cycle in higher primates, and its relation to the sex cycle in lower animals, a study of the variations in the rabbit has been of considerable value, and the results obtained must be considered in some detail. Unlike the lower rodents, the period of œstrus in the rabbit is more or less continuous, and lasts for a number

of months during each year. The actual duration depends on various environmental and nutritional conditions, and, in favourable circumstances, the period of œstrus (or absence of œstrus) occupies only a month or two (October and November as a rule—Hammond and Marshall, 1925). This applies to the animal under domesticated conditions, whereas in the wild state œstrus generally extends over not more than six months every year, and the animal may be in œstrus during the entire winter (Marshall, 1910). The rabbit will mate at any time during the whole of the œstrous period, but, in addition, it will also mate during pseudo-pregnancy and during pregnancy; in this respect it differs markedly from the lower rodents in which such a phenomenon is very rare.

During the period of œstrus very definite changes are observed in the uterus; these will be described in the next chapter. The alterations of the vaginal epithelium, however, are not sufficiently definite to be significant for diagnostic purposes, and the smear method cannot therefore be employed in the rabbit. The ovaries also assume a typical state, and always contain a number of fairly large follicles ready to undergo a final maturation stage and ovulation. In the mouse and rat, it will be remembered, ovulation occurs regularly at each œstrous period. In the rabbit, however, the conditions are quite different and ovulation never (or very rarely) occurs spontaneously. On the contrary, it follows the performance of a very definite act, namely, mating. This functional relationship is of such interest that it demands further discussion. Normal mating is, as a rule, followed by follicular maturation, ovulation and the formation of corpora lutea, and these results follow, regardless of whether fertilisation has occurred or not. The same effect can be brought about by artificial stimulation of the vagina or the cervix, and is thus not