NORMAL STRUCTURE OF ENDOMETRIUM AND DECIDUA AND THE MENSTRUAL CYCLE.*

BY

JOHN H. TEACHER, M.A., M.D.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF GLASGOW.

THE mucous membrane of the uterus differs from that of all other organs of the body in that it goes through regular cycles of change during a certain long period of its existence—namely, the reproductive period. The menstrual cycle, ovulation, and pregnancy introduce complex normal variations in structure, and when to these are added pathological changes, interpretation becomes very difficult indeed. For normal and pathological alike, a knowledge of the time relations to the cycle, the age of the patient, and the history of pregnancy and abortion is most important. Conversely, the stage of the cycle to which curettings belong must often be guessed from our knowledge of the normal in cases where no history is available, or where the history is obscure from continuous or irregular bleeding.

In the development of the endometrium into decidua there is increase in thickness, which is caused by congestion and oedema, swelling of certain of the stroma cells, and changes in the glands, which increase in size and become tortuous.

The earliest change occurs in the glands. About three days after fertilization the ovum reaches the uterus, and up to about the tenth day it lies free, being nourished by the secretion of the glands.¹ It must then implant itself or perish. Only after implantation has taken place do the decidua cells attain their characteristic form, while the glands, their work accomplished, undergo involution.

The glands develop with the prodigality of nature all through the endometrium, and the epithelium, for lack of room to expand, forms papilliform ingrowths of such luxuriance that in longitudinal section each side of the gland may present an appearance which has been described as "saw-like." These glandular changes were formerly described as pathological, under the name "endometritis glandularis hyperplastica," although Gebhardt recognized their likeness to "pregnancy glands."

Since the work of Hitschmann and Adler,¹ published in 1908, it has been accepted that these changes represent normal development, which is called "pre-menstrual." "Endometritis glandularis" as an entity has disappeared, but the "pre-menstrual" gland still puzzles the pathologist, and can figure as papilloma or even adenocarcinoma.

The menstrual cycle may be conveniently divided into four phases: (1) Menstruation, or the breaking down or destructive phase. Physiologically the appearance of the bleeding is regarded as marking the end of a cycle, but it is customary and convenient to date from it, as if it were the beginning. (2) The post-menstrual phase or period of repair. (3) The interval or period of rest during which there is little change in the structure of the membrane. (4) The pre-menstrual phase, during which the changes develop. We may assume that the proliferation corresponds to the early stage in the development of the endometrium into decidua. It is customary to call all degrees of this up to very definite decidua "pre-menstrual," but I desire to be able to say that certain developments are due to ovulation or to ovulation and fertilization of the ovum, or that they are pathological. To do this involves an attack on the generally accepted theory of menstruation and its relations to the ovary, but I have no compunction about attacking this theory, for I consider that its foundations are unsound in certain respects.

The orthodox theory asserts that the menstrual cycle is dependent on the ovaries acting as an endocrine organ through the Graafian follicles and corpus luteum; that the internal secretion sensitizes the endometrium and causes proliferation; and that the proliferative changes are to be regarded as preparation for the reception of the fertilized ovum. If the ovum is not fertilized, the menstrual break-

ing down occurs in due course, and the ripening of a new follicle initiates the period of repair, and ovulation and the development of the corpus luteum again bring about the pre-menstrual reaction. If fertilization occurs, the corpus luteum governs the development of decidua and placenta. It is clear on grounds of experimental comparative physiology that the corpus luteum is necessary for the establishment and for the continuance of at least the early stages of pregnancy.

In the extreme form of the theory it is asserted that: (1) there is no menstruation without ovulation—ovulation must therefore go on all the year round in the absence of pregnancy or disease; (2) that ovulation occurs about the middle of each cycle dating from the commencement of the bleeding; (3) that the ovaries work month-about.

Whether the ovum is fertilized or not, the follicle proceeds to develop into a corpus luteum. In the case of the normally menstruating female, therefore, it is said to be possible to take a pair of ovaries and count the corpora lutea, and by estimating their state of development or retrogression to arrange them in regular series covering four to six months. This can be done, although we have never been able to do it properly. But we are of the opinion that such seriation is capable of another explanation (see below).

The chronology of the corpus luteum for the orthodox theory of the cycle has been constructed by study of the ovaries in the living subject at operation and histologically in material obtained by operation and post mortem. Gynaecologists differ strongly about the results of counting and dating corpora lutea in the living human subject, and we have found the histological method unconvincing. We hold that there is only one method by which the ages of human corpora lutea and decidua can be determined—namely, from the history of properly dated young human ova.

The corpus luteum found in the absence of pregnancy is commonly called the "corpus luteum of menstruation" or "corpus menstruationis." We hold that these terms express erroneous ideas, and therefore should not be used. A corpus luteum signifies one thing—the ripening of an ovum; its relation to menstruation is problematical.

The theory we accept was formulated by Heape² more than thirty years ago in opposition to old theories of menstruation, from which the present orthodox theory is descended. His main point was that ovulation and menstruation were independent functions in certain fundamental respects. The observations were made on wild monkeys, and the work has recently been confirmed and made more precise by G. W. Corner,³ Hartmann,⁴ and others studying the colony of rhesus monkeys at the Carnegie Institute of Washington, Baltimore. They find that in monkeys the occurrence of menstruation is *not dependent on ovulation*, but goes on more or less regularly all the year round, although ovulation, the absence of which is tested by the absence of corpora lutea, is in complete abeyance. Moreover, in the absence of ovulation, the cyclical changes in the endometrium do not occur, and the bleeding may take place from an endometrium in the resting stage. If ovulation occurs in a given cycle the resultant corpus luteum acts to bring about the so-called "pre-menstrual" changes in the endometrium. Corner rejects the term "pre-menstrual" and substitutes "pro-gestational."

Corner refers to cases in which his monkeys, although menstruating regularly, showed only one corpus luteum between the two ovaries. We have frequently seen this in the human subject, but usually the menstrual history was not obtainable or was uncertain. We have, however, a very few cases in which a single young corpus luteum was present in patients who had been menstruating regularly, and Corner refers to similar cases. The Teacher-Bryce Ovum No. 2, the age of which is reckoned as 19 days, is the earliest specimen in which the whole uterus and ovaries are available for study, and there is only one recent and one very old corpus luteum. It is clear that the subject was fertilized at the first ovulation after a period in which that function was in abeyance, but it is not *absolutely* certain that menstruation had been resumed after her previous pregnancy. Properly dated this case

* Read in the Section of Bacteriology, Pathology, Physiology, and Biochemistry at the Annual Meeting of the British Medical Association, Winnipeg, 1930.

would have furnished most valuable information about the chronology of the corpus luteum as well as the endometrium in relation to the menstrual cycle; it is from this side that our strongest objections to the orthodox theory come.

In 1908 Bryce and the writer⁵ used the precise and trustworthy history of the Teacher-Bryce Ovum No. 1 to correlate the data of twelve young ova in the history of which the date of the termination of pregnancy in relation to the menstrual cycle was known. These data gave a series in which dimensions and ages gradually increased and supplied a mode of reckoning the age of very young ova which was so clear and consistent that it was accepted and adopted in Keibel and Mall's *Embryology* (1910).⁶ A second table was then constructed to ascertain at which periods of the month fertilization and implantation would have occurred in the case of these ova on the basis of the first table. The results were inconsistent with the old theories of menstruation and ovulation, but they agreed with the theory of Heape.

The statement of the controversy made in 1908 is obsolete, but the method of research was taken up by Grosser⁷ in 1923, and the tables were reconstructed with much new material, the conclusions being revised in accordance with our present knowledge of menstruation, ovulation, and pregnancy. The result is a chronology of the menstrual cycle founded on actual records of dates of coitus and termination of pregnancy which is inconsistent with the accepted theory.

The second table shows that ovulation—with which cohabitation and fertilization must be regarded as practically synchronous—can take place at any period from the second to the twenty-fourth day of the cycle. No period can be definitely indicated as the usual date of ovulation. Fertilization, even as late as the twenty-fourth day, prevents the menstrual breakdown, while early fertilization produces the decidual reaction. We conclude that the fate of the ovum governs the changes in the endometrium and the corpus luteum as well.

The second theory, therefore, asserts that: (1) The menstrual cycle in the human subject normally proceeds all the year round, but ovulation and corpus luteum formation occur only from time to time. (2) There is no regular date of ovulation. The lunar rhythm of the cycle is therefore not due to ovulation, and we are ignorant of its origin. (3) In the absence of fertilization it is probable that several ovulations occur in succession, as in poly-oestrous mammals like the mare or guinea-pig. Possibly they occur at monthly intervals, and from each ovary alternately, which would explain why the arrangement of corpora lutea in series can be made in a large proportion of suitable cases (Ruhl⁸).

According to this theory the changes in the ovary and the uterus both depend on the fate of the ovum. The most momentous occurrence in the life-history of the genital apparatus is the union of the male and female elements, and it is reasonable to suppose that this event would communicate some stimulus to the maternal organism. Normally it would be picked up by the mucous membrane of the Fallopian tube, and the immediate response of ovary and uterus would be growth of lutein tissue and endometrial glands.

Menstruation is a cyclical process which provides for the maintenance of the endometrium in a suitable condition for producing the decidua of pregnancy; but the ovum is not dependent on "pre-menstrual" reaction for a suitable nidus. The uterus is capable of developing a decidua of conservation whenever it is called upon to receive and nourish a fertilized ovum.

The occurrence of slight proliferative changes in the endometrium near the end of a period would be interpreted as normal pre-menstrual reaction occurring apart from ovulation. Hirschmann and Adler emphasized the invariability of the reaction. Aschoff⁹ refers to cases, possibly abnormal, where it has not developed. Probably there is always some reaction. A more pronounced reaction at any period would suggest that ovulation and corpus luteum formation had occurred, while early decidua would indicate fertilization also. We have seen well-developed reaction long before its time on the orthodox view of the cycle, and we could find the ruptured follicle or early corpus

luteum, but we could not find the ovum. Possibly the date of implantation had not been reached.

Two other interesting possibilities are: (1) failure to implant the ovum, or (2) the rejection of the ovum soon after implantation. In such cases "menstruation" would occur from a membrane that could hardly be called anything but early decidua. From a medico-legal point of view, however, it would not be justifiable to diagnose the occurrence of pregnancy from the finding of such a membrane. Classical decidua or trophoblast must be found.

To give an example of the practical bearing of this theory, some of our specimens have come from cases in which curetting was done on account of sterility, and the surgeon demanded to know whether he had been so unlucky as to have interrupted an early pregnancy. We did not care to assert this, but we hope we were justified in saying that such membranes showed that ovulation was occurring, or in some cases ovulation and fertilization as well. Prognosis, therefore, was hopeful. In these cases the theory of Heape appears to us more helpful than the orthodox theory.

It is obvious that the two theories have much in common, but there is sharp contradiction in the time relations. For the discovery of the truth we want accurately dated young human ova. These may be supplied by the new method of Allen and his collaborators,¹⁰ who have washed free ova out of the tubes at operations, or by the older methods. All depends on co-operation between the gynaecologist, the pathologist, and the embryologist, so that the material may be found and properly handled.

REFERENCES.

- ¹ Hirschmann and Adler: *Uterusschleimhaut mit Berücksichtigung der Menstruation*, *Monats. f. Geb. u. Gynäk.*, 1908, vol. 27, p. 1.
- ² Heape, Walter: The Menstruation and Ovulation of *Macacus rhesus*, *Phil. Trans. Roy. Soc.*, 1897, 1898B, p. 135; and *Obstet. Trans.*, 1898, vol. 40, p. 166.
- ³ Corner, G. W.: *Journ. Amer. Med. Assoc.*, 1927, 89, p. 1838; and Reports of Carnegie Institute, Washington.
- ⁴ Hartmann: Menstruation without Ovulation in *Macacus rhesus*, *Abstr. Anat. Record*, 1927, 35, 13.
- ⁵ Bryce, Teacher, and Munro Kerr: *Early Development and Embedding of the Human Ovum*, 1908.
- ⁶ Keibel and Mall: *Human Embryology*, 1910 (Lippincott).
- ⁷ Grosser, O.: *Junge Menschliche Embryonen, Ergebnisse der Anatomie und Entwicklungsgeschichte*, 1924, 25, p. 391; and *Biologie und Pathologie des Weibes*, vi.
- ⁸ Ruhl: On Alteration of Function of the two Ovaries, *Arch. f. Gynäk.*, 1925, 124, p. 1.
- ⁹ Aschoff: *Lectures on Pathology*, 1924, p. 179.
- ¹⁰ Allen, E., Pratt, Newall, and Bland: Recovery of Human Ova from the Uterine Tubes, *Journ. Amer. Med. Assoc.*, November 6th, 1928, vol. 91, No. 14, p. 1018.
- ¹¹ Teacher: Implantation of the Human Ovum, *Journ. Obstet. and Gynaecol.*, 31, p. 166; and *Zeit. f. Anat. u. Entwickl.*, 1925, 76, p. 360.

SODIUM AMYTAL AND OTHER DERIVATIVES OF BARBITURIC ACID.*

BY

L. G. ZERFAS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, INDIANA UNIVERSITY MEDICAL SCHOOL.

(From the Lilly Laboratories for Clinical Research, City Hospital, Indianapolis.)

APPROXIMATELY two years have elapsed since the first studies were made on the clinical use of sodium iso-amyl-ethyl-barbituric acid (sodium amytal). In a preliminary report¹ certain clinical observations were recorded, and attention was called to the need of further pharmacological and clinical work before definite conclusions could be drawn as to the safety, contraindications, and limitations of this compound. Since that time various experimental and clinical observations have been made by different investigators, so that the status of this drug is now more clearly defined. The purpose of this paper is to review briefly the data relating to sodium amytal and similar compounds.

CHARACTERISTICS COMMON TO DERIVATIVES OF BARBITURIC ACID.

All derivatives of barbituric acid have certain characteristics in common which have long been recognized.

1. They are primarily hypnotics; only occasionally will amounts ordinarily producing hypnosis produce analgesia

* Read in opening a discussion in the Section of Anaesthesia at the Annual Meeting of the British Medical Association, Winnipeg, 1930.