Department of Reviews and Abstracts

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Collective Review

The Ovary and Its Physiologic Functions

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THE concept of the physiologic processes of the female genitalia, as generally accepted, has undergone extraordinary changes in recent years. Yet in spite of the great, indeed wonderful progress that has been made during the last two decades, the mysterious function of menstruation and ovulation continues to occupy a prominent place in the thought and problem of gynecologists. Both of these important problems are essentially of a physiologic character, which reflect fundamental laws that have a close bearing upon practical gynecology, as well as on the general problems of biology.

The biologic investigations are largely in the morphologic stage: in the main by reason of the fact, that the morphology offers greater difficulties to an adequate explanation and interpretation than the physiologic processes.

The contributions to our knowledge are mainly pieces or parts of pieces, limited to one phase of the subject, restricted to one portion of the internal genitalia and covering only a meager subdivision. Aside from these fundamental problems, there are the endocrine glands, which in a measure are of more immediate practical interest in regard to questions of development, monstrosities, and sex differences.

HISTORICAL

The earliest mention of the ovary is accredited to Herophilus (Alexandria, 300 B.C.) and received its name from Steno in the seventeenth century A.D. (Fasbender).[1]

GROSS STRUCTURE

The ovaries are organs which belong to the class of externally secreting glands and ductless glands. The reproductive glands represent a different class from any of the other externally secreting glands, for their secretion-products, although discharged by a duct (fallopian tube) on a free surface, do not merely consist of substances formed in and extruded from cells, but of complete cells (ova) which become detached as such from the ovary that forms them, and are carried away from it along with a fluid (liquor folliculi) likewise produced by the gland. Minot[2] places the ovary along with the organs which produce the erythrocytes and leucocytes under the general head of cytogenic glands.

The ovaries are two small, somewhat flattened, solid-looking ovoid bodies lying one on each side of the pelvis, and projecting into the

peritoneal cavity at the posterior part of the broad ligament, which is itself formed of a fold of peritoneum. The ovaries of different women vary much in size apparently without any relation to fertility. In the nullipara the ovary presents a more or less smooth surface; in older women, it becomes larger, more round and irregular in outline due to the maturation of the follicles. After menopause the ovary shrinks, and in old women, it may be as small as a navy bean and made up chiefly of fibrous and scar tissue.

The surface of the ovary is covered with a single layer of cuboidal epithelium. In very rare instances this may be ciliated (von Velits and Williams).[3] Although it is the direct representation of the embryonic hypoblasts, its function is only protective. It is stated by Bland-Sutton[4] that the ovary is sometimes surrounded with a peritoneal hood, which is the homologue of the *tunica vaginalis testis;* but this statement lacks confirmation by other observers. Graves[5] attributes extraordinary potentialities for growth to this layer and considers this the chief factor in the etiology of parenchymatous ovarian cysts.

It is not the intent and purpose to give a minute and complete resumé of the embryology of the ovary, especially as to parental characteristics and variations, the origin of sex and growth; yet an accurate idea of the structure of the ovary can only be clearly understood by a study of its development.

Although important preliminary contributions were made by Valentine[6] and Pflüger,[7] it was not until Waldeyer[8] in 1870 published his epoch-making monograph upon the ovary and ovum, that a more accurate description of the development of the chick ovary was obtained. He found that the celomic epithelial cells covering the wolffian body became larger and differentiated from the surrounding tissues. This epithelium was designated as germinal epithelium, and its cells soon became differentiated into two groups. The large clear cells or primordial ova surrounded by the second group of small epithelial cells, which extend downward as Pflüger tubules, or egg nests. These are broken up into smaller and smaller masses, until eventually isolated primordial ova are found which are surrounded by a single layer of epithelium. Nagel,[9] Klein and von Franque[10] have observed occasionally more than one nucleus in the primordial ovum.

Recent observations, however, have thrown some doubt on the real site of origin of these cells, for in the elasmobrachii they have been found to be formed by emigration of cells from the yolk sac. This is also true of an early human embryo of 4.9 mm. in length. Ingals[11] has described large sex cells under the peritoneum at the root of the mesentery in the region of the first five trunk segments.

If further investigations should show these observations to be correct, then primitive sex cells must be considered differentiated during the very early division of the fertilized ovum, as is the case in the lower classes of the animal kingdom.

It is entirely unknown to us how the transformation of undifferentiated cells into sexual cells is accomplished. One can observe with the microscope alterations in the structure of the cells, but the cause of this alteration remains a hidden mystery. (Minot.)[12]

It would indicate that the ova are not formed in the embryo as a whole but from early differentiated cells of the fertilized ovum. The germ-plasm would be the continuous stream of living substances connecting all generations (Wilson).[13]

Weissmann[14] concludes that protoplasm possesses the property of potential immortality. This latter part of his theory has been the subject of much interesting investigation[15] with some contradictory results. It has been shown by Woodruff[16] that a specimen of paramecium isolated and kept in a varying culture medium during a period of five years "possessed the potentiality to produce similar cells to the number represented by 2 raised to the 3029th power or a volume of protoplasm approximately 10^{1000} times the volume of the earth.

In a later paper Waldeyer[17] (1901) states that the formation of primordial ova was not as simple as he previously described but was a very complex process. This was later confirmed by the work of Nagel,[18] Skrobansky,[19] and McIllroy.[20] The researches of Winiwarter[21] have shown that the changes occurring in the cortical zone derived from the germinal epithelium are of a very complex character.

THE MICROSCOPIC STRUCTURE

The general structure of the ovary can best be studied in cross section, when the organ is seen to be made up of two portions—the cortex and medulla. The primordial ova and graafian follicles are situated in this outer layer or cortex. It is composed of spindle-shaped connective tissue cells, throughout which are scattered the primordial ova and graafian follicles in various stages of development. In the most external portion of the cortex there is a single layer of cuboidal cells, resting upon a thin layer of fibrous tissue, which gives the ovary its whitish appearance, and which is called the tunica albuginea.

The medulla is composed of loose connective tissue and contains large numbers of blood vessels, both arteries and veins; and, according to His,[22] Köllicker[23] and Rouget,[24] a considerable number of non-striated muscle fibers, whose presence caused the last named observer to class the medulla among erectile tissues. The exact arrangement of the blood vessels has been studied exhaustively by J. G. Clark.[25]

According to Waldeyer[8] each ovary at birth contains at least 100,000 oocytes, the majority of which disappear before the age of puberty; so that at this time only 30,000 or 40,000 remain. It is explicitly added that this is merely an estimate and probably too low rather than too high. All authorities do not agree on the number of oocytes. Henle[26] estimated the number of follicles in an eighteen-year-old woman and stated that there were not less than 72,000 ova in both ovaries.

Heyse[28] employed a more exact method and concludes that the number of follicles in both ovaries is 35,200. Sappey[28] determined the number of ova in each ovary as 300,000.

The most recent contribution is that of v. Hansemann[29] with the tabulated results of Hayato Arai.[30] He gives the number of ova in one (?) ovary of man at different ages as:

1 to 2 years	48,808
2 to 5 years	46,174
5 to 6 years	30,339
8 years	25,665
10 years	20,862
14 years	16,390
17 to 18 years	5,000 to 7,000

Though there is some doubt whether the numbers given by v. Hansemann are for one or both ovaries, yet they demonstrate clearly that there are many more ova present during the earliest years of life

than at puberty, and that even after puberty the numbers show a significant decrease. Marshall[33] states that not more than 400 ova reach maturity.

It is evident that a very large number of follicles, after attaining a certain amount of growth and development, undergo degeneration (atresia)—the ovum becomes shrivelled and eventually disappears; the follicular epithelium degenerates—a process shared by the theca interna; and the cavity remains for some time as an irregular cyst which eventually disappears. Stevens[31] has given an exhaustive account of the atretic follicle. Schochet[32] has shown that the liquor folliculi contains a proteolytic enzyme, and suggests that atresia is caused by the digestion, or alteration of the ovum by this enzyme.

THE INTERSTITIAL CELLS

Limon[34] has described accumulations of characteristic epitheloid cells, which are frequently observed in the neighborhood of the hilum in the fetus and in lower animals. These observations were confirmed by Aimé[35] and Bouin.[36] The origin of these interstitial cells is not clear, but as they are supposed to take part in the formation of internal secretion, they are designated as interstitial glands. L. Fraenkel[37] and A. Shaeffer[38] pointed out that the interstitial cells are absent in the adult ovary and are not constant in all species of lower animals.

Since the earliest work by Brown-Séquard[39] on the internal secretion of the testis, it has been generally conceded that the ovaries elaborate an internal secretion. Steinach[40] states that the internal secretion of the interstitial cells in the ovary has a specific influence in guiding the development of sexual characteristics. Some evidence for this view is found in the functional relationship that appears to exist between the ovary and other ductless glands. According to Hatai[41] removal of the ovary causes an enlargement of the thymus and affects the hypophysis and adrenals (decrease in weight). Shaffer[42] has shown that extracts of the ovaries contain two substances, one of which (interstitial cells) inhibits contractility of plain muscle, especially the muscle of the uterus, while the other augments this contractility.

The exact nature of the reciprocal relationships between the ductless glands cannot be explained at the present time. However, when one wishes to cloud or confuse the issue, or when one wishes to give an evasive answer, it is customary to refer to the ductless glands. Much further research is necessary before we shall be able safely to correlate the histologic structure with the hormonopoietic function of the interstitial cells.

NERVES OF OVARY

The nerves are derived from the ovarian plexus and are distributed in the ovary as three trunks. The fibers are chiefly nonmedullated, communicate very freely with one another, and are furnished with microscopic ganglia and with groups of specialized cells (phoecochrome cells of Winiwarter).[43] Winterhalter[44] has described a sympathetic ganglion of the ovary, but von Herff[45] denies the existence of a ganglion with the exception of a few sympathetic cells in and about the blood vessels. This coincides with the opinion of other investigators, Mandl,[46] and Vallet,[47] that the nonmedullated fibers for the most part are distributed along the blood vessels.

OVULATION

Ovulation comprises the growth, development and rupture of the graafian follicle. From birth until the cessation of sexual life, graafian follicles are constantly being developed. During the growth and maturation of the ovum, cells of the graafian follicle, after increasing greatly in number, begin to liquefy. It is thought, that the different chemical composition of the liquor, thus forming in the follicle, induces an endosmosis by which the liquor folliculi increases faster than would seem possible solely as the result of liquefaction of follicular cells. The follicle distends so that, following the direction of least resistance, one side of it approaches the free surface of the ovary, producing a bulging on this surface, a dispersing of the ovarian stroma, and the thinning of its tunica albuginea and the epithelium. The final result is a compression of the blood capillaries lying between the follicle and the ovarian surface. It was supposed by Waldeyer,[8, 17] His[22] and von Baer that nourishment was cut off from a preformed nonvascular area in the follicle, and that rupture was the result of atrophy of the stroma. The ovum is thus extruded with its granular epithelium cover by the liquor folliculi. This granular material when set free, takes up water, and therefore, as is specially noticeable in the ovum of the rabbit, swells up into a clear gelatinous envelope, which has been termed the albumin.

Clark[48] has shown that the conception of a preformed, nonvascular area is incorrect. He further states that there is a deeper lying cause for follicle rupture than mere growth and its pushing forward toward the ovarian surface.

Schochet[49] proved that the liquor folliculi contains a specific proteolytic enzyme, and suggests that ovulation is a result of the digestive action of this enzyme.

Simultaneously with the enlargement of the follicle, the nucleus of the ovum undergoes a succession of remarkable synaptic changes (Winiwarter,[50] Lane-Claypon).[51]

MENSTRUATION AND OVULATION

There are many observations recorded in regard to the time ovulation takes place in mammals. For instance Sobotta,[52] for the mouse, and Rubaschkin,[53] for the guinea pig, ascertained that ovulation occurs during heat and is independent of coitus. Loeb[54] has confirmed this last observation for the guinea pig.

For man, two opposing hypotheses have coexisted for a number of years. Gendrin,[55] Pflüger[7] and Bischopp hold that menstruation is dependent upon ovulation, and coincident with it. The opposite view, of which Riegel is the chief exponent, maintains that ovulation and menstruation are two entirely independent functions.

Clinical experience has substantiated this latter view, since it has been shown that ovulation and subsequent pregnancies have taken place without menstruation, as is demonstrated by the instances of conception occurring before the establishment of menstruation or after menopause, as well as during lactation.[56]

According to Heape,[57] ovulation and menstruation are not associated, since in monkeys, menstruation may occur periodically all the year round, but the season for ovulation and conception is limited. This has been confirmed by von Herwerden[58] for monkeys and aberrant lemur.

Runge[59] states that enlarged follicles are by no means uncommon in ovaries of young children. Loeb[54] has observed relatively large follicles in the ovaries of eighteen-day-old guinea pigs. From these numerous observations it must be concluded that ovulation and menstruation are two independent functions; but that the latter is absolutely dependent upon the presence of the ovaries.

CORPUS LUTEUM

Those graafian follicles that attain maturity and burst, develop into corpora lutea. Bischoff stated that the corpus luteum owes its origin mainly to the granulosa stratum of the wall of the empty follicle, which as it increases in extent occupies more and more of the follicle cavity. On the other hand von Baer considered that the corpus luteum was wholly due to a hyperplasia of the polyhedral interstitial stroma cells (of connective tissue origin) and thus represents cells of the theca interna together with a development of blood vessels. This view has been confirmed by the more recent works of Beigel,[60] Clark,[48] Hegar[61] and many others. However, these observations are at variance with those of Sobotta,[52] Stratz, Cohn,[62] Van der Stricht,[63] and Marshall,[64] who maintain that the corpus luteum owes its origin to a simple hyperplasia of the epithelial cells of the membrana granulosa; while Loeb[54] believes that the lutein cells are partly of connective tissue origin and partly of epithelial origin as observed in the guinea pig.

The structural appearance of the corpus luteum with its large cleft like spaces (lymphatics of His)[22] is not unlike that met in the cortical part of the suprarenal glands. Exner and Buckel do not confirm the existence of lymph vessels in the corpora lutea. The peculiar yellow pigment or granules in the cells give the corpus luteum its characteristic color. In its center we find a blood clot undergoing organization. Why a physiologic process like ovulation and menstruation should be associated with hemorrhage, is not definitely understood. Ries[65] emphasizes that every essential function of the female reproductive organs is associated with hemorrhage. Occasionally the central clot is absent, and such is the rule in many lower animals, as, e.g., in the rabbit and mouse. Later, the corpora lutea are rapidly absorbed, so that in a short time the degenerated lutein cells are replaced by newly formed connective tissue cells. These resemble closely the surrounding ovarian stroma cells. Clark[48] has estimated that if the follicles were obliterated by scar tissue, the result would be a fibroma 5000 times as large as the original ovary.

Various functions have been ascribed to the corpus luteum. De Graaf described it as a conglomerated glandular body, and it was considered by all earlier authorities a positive evidence of existing pregnancy. It is said that Sir Astley Cooper[3] and Denmann asserted under oath that a certain woman was pregnant because a corpus luteum had been found in one of her ovaries. Others believed that the presence of a corpus luteum indicated that the individual had indulged in sexual relations, or had at least been subjected to marked sexual excitement. It was not until after the appearance of the work of Bischoff, Raciborski, Negrier and Bouchet[3] that these fallacious views were abandoned.

The functional value of the corpus luteum was not appreciated before the epoch making investigations of Fraenkel.[66] In a later contribution, Fraenkel[67] states that the corpus luteum is a gland that is

renewed every four weeks in woman during her reproductive life, and at varying intervals in animals. It controls the nutrition of the uterus in a cyclic fashion, prevents it from either relapsing into its infantile or passing into its senile state; and prepares the endometrium for the reception of the ovum. If the ovum be fertilized the corpus luteum continues to exist and to maintain the augmented nutrition of the uterus during pregnancy. If the ovum is not fertilized, the corpus luteum merely produces the hyperemia of menstruation and then degenerates. There is strictly speaking only one corpus luteum, which regenerates itself periodically in slightly different situations and controls the uterine life from puberty to menopause. Menstruation is caused by the secretory activity of the corpus luteum, not by the pressure of the growing follicles on the ovarian nerves. The secretory activity causes the four-weekly hyperemia which makes possible the implantation of the fertilized ovum or leads to menstruation. Anomalous uterine bleeding and some forms of sterility may be due to pathologic conditions of the corpus luteum. Amenorrhea and uterine atrophy may follow the same cause. Lactation atrophy is a good example. During lactation, as a rule, there is no ovulation, therefore, no fresh corpora lutea are formed. This theory was substantiated by observations on the rabbit and also on woman (95 operative cases). If the corpus luteum was destroyed by a cautery the next succeeding menstrual flow failed to occur. This theory is not hypothetical but rests on a secure foundation of experimental facts. Though most convincing, Frank[68] and Marshall have not accepted this view as entirely accurate. In the marsupials the corpus luteum is well developed, yet in these animals implantation of the ovum can hardly be said to occur; only apposition, and not implantation of the ovum is seen in the ingulates in which the corpus luteum is highly developed; and finally it has been demonstrated that in women the corpus luteum might be removed in the early weeks of pregnancy without any disturbance to the ovum.

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5310 MICHIGAN AVENUE.

Selected Abstracts

Gonorrhea in the Female

Norris and Mickelberg: Diagnosis of Gonorrhea in the Female by Staining Methods. Journal American Medical Association, 1921, lxxvi, 164.

In the acute stage of gonorrhea, both in the adult and child, the diagnosis is usually easily made from the history and clinical symptoms; if doubtful, it can be established by a smear. In chronic cases, the diagnosis is often difficult. Smears, to be of value, must be very carefully examined to guard against errors. Gonococci not only are few in number and often atypical, but may be confused with other bacteria of similar morphology. Gram's stain, if carefully made, will usually clear up the doubt. Owing to frequent sources of error, the authors believe that, unless done by an expert, stained films are of no value and, even when made by the most experienced, too much weight should not be placed on the findings. Diplococcus catarrhalis is almost identical with the gonococcus, both morphologically and tinctorially.

Material should be taken from the cervix, urethra, Skene's or Bartholin's glands, preferably by means of a medicine dropper the end of which has been drawn out to the thickness of a coarse capillary tube. In very young children the vagina is washed with dilute bichloride solution by means of a soft rubber eye syringe. The child's hips are raised and the solution forced out and sucked in a number of times; the washings are then centrifuged at slow speed and the sediment examined.

In concluding the authors state that, in their opinion the usefulness of staining methods has been overestimated; that clinical evidence is of greater value, even when the films are prepared by an expert; that, under most favorable circumstances, positive smears can be obtained only in a small proportion of cases; and, that, from a practical standpoint, all cases should be regarded as gonorrheal unless proved otherwise.

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