The Life-History of the Ovary.

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IN considering any structural changes affecting the ovary, we must always bear in mind those due to physiological variations, produced as a consequence of the ovary's peculiar life-history. As a result of ovulation, for instance, the organ is exposed to periodical tearing of its stroma, with the subsequent formation of corpora lutea, albicantia and fibrosa. Persistence or non-absorption of these corpora albicantia and fibrosa, replacing portions of the ovarian stroma, leads to the accumulation of scar-tissue characterized by a fine, non-vascular reticulum of connective-tissue. This scar-tissue, along with hyaline changes in the neighbouring blood-vessels, is frequently taken as indicative of pathological processes.

Recently I examined in detail 132 ovaries, representative of various ages, namely, from birth to 79 years, recording their weights dimensions, and, for purposes of comparison, thickness of the blood-vessel walls. The method of measuring the thickness of vessel walls in these cases was as follows:—

A scale was prepared in Indian ink from a standard stage micrometer; and a camera lucida consisting of a neutral-tinted glass was fixed at an angle of 45° to the eye-piece of the microscope. The body and tube of the latter were placed in the horizontal plane, at a distance of ten inches above the scale, which lay flat on the table. A lens was employed to direct convergent rays from an artificial source of light upon the scale, whose image could be seen on the real object to be measured. The total thickness of the two walls of a blood-vessel along any diameter was taken and compared with the whole diameter selected, thus: if AB and CD are the two walls chosen along the diameter AD, then

$$\frac{AD}{AB + CD} = \frac{\text{Diameter}}{\text{Total wall thickness.}}$$

A vessel-index could thus be established which, however, applied to arteries and arterioles only, since veins showed no appreciable thickening of their walls.

During the later period of intra-uterine life and at birth, the ovary is elongated and flattened in outline, but gradually becomes relatively shorter and thicker as age advances, until adult life is reached. In old age its volume is reduced to nearly one-half, due to atrophy and involution, and the organ frequently becomes elongated

again. The two poles of the same ovary often differ in contour, the tubal being rounded while the uterine pole tapers off on to the ovarian ligament.

The dimensions of the healthy adult ovary in 141 cases averaged as follows: Length=3·6 cms.; Breadth=2·1 cms.; Thickness=1·3 cms. In length, variations were observed from 1·8 cms. to 6 cms.; in breadth, 1 cm. to 3·8 cms.; and in thickness, ·5 cms. to 2·6 cms. It was noticed while taking these measurements that the breadth of the two surfaces (measured from the "white line" to the convex free border), varied between 1 and 3 mm. in most instances. In 117 cases the inner surface measured less than the outer in 86 (73·5 per cent.), while it was greater than the outer in 21 cases (18·8 per cent.), and in 10 cases (8·5 per cent.) both were equal in breadth.

In transverse section the ovaries of a newly-born infant and that of an adult differ in shape at the point where the mesovarium enters the ovary. In the infant the two surfaces of the ovary itself become folded in so as to form a distinct cleft, which is traversed by the mesovarium as it unites with the ovary; in other words, the hilum of these very young ovaries appears to be invaginated.

The weight of the mature ovary varies from 2·5 gms. to 4 gms.; when it exceeds 4 gms. general enlargement or the existence of cysts may be suspected.

A network of shallow grooves marks the pale surface of the ovary, which, although smooth as a whole, exhibits a very slight waviness in addition. Deep sulci and furrows may occasionally be seen; also translucent or maroon-coloured rounded eminences, which are retrogressive cystic follicles or corpora lutea situated at the surface.

The primordial follicle zone may occasionally be seen, by the naked eye, as a pale marginal zone about 1 mm. in depth, and is sometimes referred to as the parenchyma or cortex of the ovary. This zone is frequently, but erroneously, referred to as the tunica albuginea, which occupies less than a quarter of its extent; moreover, the albuginea cannot be detected by the unaided eye.

The germinal epithelium may be absent over comparatively large areas of the surface of the ovary, for it is easily rubbed or washed off. In the furrows and other protected situations the cells are frequently heaped up to five or six rows in depth. In shape these cells may be columnar, cubical, tall and slender, or merely flattened squamous outlines. In young subjects large, round cells may sometimes be seen in the layer of surface epithelium, and, according to one view, give rise ultimately to primordial follicles. In one or two cases examined the germinal epithelial cells were distinctly vacuolated. While it is difficult to preserve the germinal epithelium *in situ* after sectioning ovaries, there is little doubt that under normal conditions this epithelium remains unaltered at the climacterium; in one instance I noticed that it was present in the form of regularly

arranged cubical cells at the age of seventy years. A curious effect upon germinal epithelium was noticed, probably from pressure by thin sero-fibrinous deposits, namely, alteration in size and angle of inclination from the vertical to the horizontal planes of the columnar variety of cell. Columnar germinal epithelium, instead of standing erect or at right angles to the basement membrane, inclined gradually over to the right or left of the vertical position, each cell slanting a little more than its neighbour, until those cells farthest removed from the vertical become parallel to the basement membrane, *i.e.*, lay sideways upon it. It is not unlikely that these germinal epithelial cells, which appear like squames, take origin in this manner. I saw no instance of ciliated germinal epithelium at the time of ovulation, and, although this condition is generally denied, it does not seem unlikely for it to occur, since germinal epithelium may become changed in order to take on a new function. Change of function is to be observed in those cases where small surface-cysts, frequently containing fluid, are lined entirely by germinal epithelium. They are formed by invagination of the surface bearing this same epithelium, and are apparently confined to the outer portion of the parenchymatous zone. These cysts, after becoming round in shape (for they are often irregular) may easily be confounded with cysts of degeneration of the smaller follicles. In both, the lining epithelium is similar, namely, more or less cubical. It is almost impossible to detect the difference between one of the invagination-cysts and a follicle having undergone small-cyst degeneration. Inclusion-cysts of a similar character occur between sero-fibrinous adhesions and the surface of the ovary. The epithelium lining this variety is derived either entirely from the germinal epithelium, or from both germinal and endothelium, the latter usually lining that portion of the wall of the cyst formed by the said adhesions. Both invagination and inclusion-cysts should take their place in the category of the ovarian cystic formations.

At birth I generally found that the stroma immediately under the germinal epithelium was denser in some parts than in others, but showing little or no parallel arrangement of the fibres. At puberty, these connective-tissue fibres may be seen in two or more layers running parallel to each other, but becoming lost to view in consecutive fields of the microscope owing to their change of course and direction. There is much variation in the number of these parallel layers of connective-tissue, for in the same organ one to four or five may be seen running in the same direction, or, rarely, on the other hand, none at all. The commonest distribution is for one layer to run parallel to the surface, either just below the germinal epithelium, in which case the fibres are packed closely together and poor in cells, or are .04 mm. to .06 mm. distant from it. Frequently both these layers are present; and running between them at

right angles is an intermediate layer. In cases where three or more parallel layers are noticed, the parallel distribution of fibres can only be traced for a very short distance, the innermost becoming lost to view in the general stroma of the parenchymatous zone or cortex. Still another set of connective-tissue fibres is noticeable (generally in older ovaries), in which the fibres are shorter, and run out towards the surface; by the fusion of these with fibres running in other directions nodes are formed which add materially to the strength of the albuginea as a whole. As a result of the estimation of its approximate thickness (its precise inner limits being indeterminable), the albuginea showed a variation between .03 mm. and .3 mm. in this series.

One rarely found that the cortical zone itself exceeded 1.5 mm. in depth; and, as the tunica albuginea is nothing more than a modification of the connective-tissue in the outermost portion of the parenchymatous zone, due to age influences, I consider that it probably never exceeds .5 mm. in depth.

A rapid increase in thickness of the albuginea occurs in the first 20 years of life; afterwards it remains about the same for the next 20 years; then it gradually shows an increase again up to between 50 and 60 years of age. It then decreases from atrophic changes, and seldom shows definite parallel distribution of its fibres. The average thickness in 107 cases for all ages between 16 and 70 years of age I calculated to be .11 mm. Four of the 107 cases examined possessed a tunica albuginea exceeding .17 mm., and 47 exceeded 1 mm. Two of these 47 cases had been diagnosed as chronic ovaritis, but examination proved them to be cystic ovaries without evidence of inflammation.

In a large number of sections of healthy ovaries I found primordial follicles to be scarce, while retrogressive changes in older Graafian follicles were exceedingly common. It was interesting to note that one primordial follicle contained two ova. Primordial or resting follicles possess, as a rule, one layer of flattened cells as a wall-lining, whereas the commencement of follicular activity is marked by the layer of cells, now cuboidal in shape, becoming two rows deep. Before menstrual life is entered upon there are occasional instances to be noticed of primordial follicles disappearing. I have seen Cicatrices, indicating the site of a previously existing follicle, which had been absorbed by young connective-tissue cells and leucocytes. Although there is a marked diminution in the number of primordial follicles after the menopause, some may still persist even in old age, though rarely so. One case showed, at the age of 70, an occasional apparently healthy primitive follicle among others which were degenerated and undergoing absorption. In the neighbourhood of recent corpora lutea fatty changes often occur in the ovum; yet quite healthy follicles may be seen in the vicinity of corpora albicantia.

Between the theca interna of the Graafian follicle and the cells of the membrana granulosa, a definite membrane is distinguishable, which acts as a basement membrane for the latter; the cells of the first row of the granulosa are situated upon it and are chiefly cuboidal or low columnar in character, and contrast with the rest of the cells, which are ovoid in form.

White fibrous tissue forms the main bulk of the parenchymatous zone, and contains some elastic fibres; capillaries and larger blood-vessels are scanty. Owing to the presence, here and there, of mature Graafian follicles, corpora lutea, and albicantia, together with follicles undergoing cystic changes, this zone is encroached upon or obliterated in these situations; and conversely, in areas in which such are absent, the stroma is correspondingly increased in thickness.

In the deeper portion of the zona vasculosa, and in the neighbourhood of corpora albicantia, the arteries possess walls which, relative to the size of the vessel, appear much thicker than those in the rest of the stroma. From puberty up to the menopause the arterioles show a definite increase in wall-thickness in the parenchymatous, vascular and hilar zones. Sometimes changes, resulting in considerable narrowing of the lumen, are met with at about the time of onset of first menstruation; while the same, together with complete obliteration is noticeable after the age of 35. These vessel-changes, sometimes referred to as "obliterative arteritis," are invariably accompanied by advanced retrogressive changes in the neighbouring corpora lutea. In such instances the hyaline degeneration of blood-vessel walls, with diminution of their nucleated cellular elements, are as much a physiological process as are the stages of retrogression of the corpus luteum. Excepting those instances where a new vessel is formed inside the lumen of an old, functionless blood-vessel, those degenerated vessels merge into, and become incorporated with the corpora albicantia formation. As a result of this fusion, the dimensions of the corpora albicantia and fibrosa are undoubtedly increased. Closely resembling these physiological changes are those described in *angio-dystrophia ovarii*.

The connective-tissue, which is said to be increased in chronic ovaritis, varies very much in amount normally. The small scars, produced by the rupture of mature Graafian follicles; the final products of retrogression or organization of the corpora lutea, which constitute corpora albicantia and fibrosa; together with those obliterated hyaline vessels, many of which become incorporated with the corpora albicantia and fibrosa, afford us an example of the amount of connective tissue irritation, which is produced by the process of ovulation. Add to this, menstrual congestion and hyperæmia, resulting from other vascular disturbances, such as gestation and malpositions of the ovary from bands of adhesive pelvic peritonitis, and we then get the appearances variously described as the *sclerotic*,

sclero-cystic (that is, sclerosis with small-cyst degeneration, or, *sclerosis* with lutein cysts), and the *cirrhotic* ovary. The connective-tissue of the ovary, with the aid of leucocytes, is capable of removing, in time, a great portion, or even all traces of the existence of a Graafian follicle. This accounts for our not being able to trace in the two ovaries of a subject the exact number of corpora lutea, albicantia and fibrosa corresponding to the frequency of ovulation from its onset. Upon the rate of absorption, therefore, depends the number of retrogressive corpora albicantia and fibrosa one can find: if it is slow, the ovary of a middle-aged subject will reveal a sclerotic or cirrhotic condition; if active, on the other hand, we may fail to find traces of more than one or two retrogressive corpora lutea as a result of all these physiological changes. All that may remain of a previously existing corpus luteum are ribbon-shaped, tortuous bands of fine connective-tissue. Other bands occur more or less straight in direction, and frequently terminate in a leash of fibres which may closely resemble connective-tissue of true inflammatory origin. The amount of connective-tissue in the ovary cannot very well be estimated for purposes of comparison, as has been done in the case of the uterus, the reasons being that ovulation produces a continual alteration, and that the rate of absorption of the retrogressive products is so variable.

Round-celled infiltration may occur normally around the larger vessels, and also in the stroma in the vicinity of the corpus luteum.

The foregoing phenomena, and, especially, marked changes in vessels, secondary to retrogressive processes in the corpus luteum, and the formation of what may be termed cicatrices (in the form of corpora albicantia and fibrosa), have not yet been sufficiently recognized by the majority of observers as being due to purely physiological causes. Now, the so-called chronic ovaritis usually described, does not present appearances sufficiently convincing to distinguish it as an inflammatory condition; or, if so, all traces of it are removed comparatively early by the same agency which causes the disappearance of a large number of corpora albicantia and fibrosa in health, namely, the invasion by the connective-tissue cells of the ovarian stroma. Chronic idiopathic or primary chronic ovaritis, to my mind, *does not exist*, tubercle and syphilis excepted—both very rare conditions. All inflammations of the ovary are *secondary* to uterine or tubal lesions or acute infections, toxic diseases, etc. Definite increase in the connective-tissue—over and above that which occurs within normal limits—is probably due to true hypertrophy or hyperplasia, rather than to chronic inflammation.