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OBSERVATIONS ON THE PHYSIOLOGY OF THE FEMALE GENITAL ORGANS.

BY
W. BLAIR BELL, and PANTLAND HICK,
M.D., B.S.LOND., M.B., B.S.LOND.,
ASSISTANT GYNAECOLOGICAL MEDICAL REGISTRAR,
SURGEON, ROYAL INFIRMARY, ROYAL INFIRMARY,
LIVERPOOL. LIVERPOOL.

III.—THE CORRELATION OF THE UTERUS AND OVARIES.

In this paper we shall give the results (for the most part histological) of several series of experiments which bear upon the correlation of the ovaries and uterus, apart from the metabolic relations existing between these organs in regard to menstruation, which have already been discussed.

The experiments performed consisted of :

- A.—1. Removal of ovaries and subsequent histological examination of the uterus.
2. Removal of ovaries during pregnancy.
- B.—Removal of uterus and subsequent examination of the ovaries.
- C.—Ligation of uterine cornua :
 1. Without removal of ovaries.
 2. Synchronous with removal of ovaries.
 3. Subsequent to removal of ovaries.

The animals operated upon were for the most part rabbits. Three bitches were also used.

Most of the above experiments have been carried out by Bond, Marshall and other observers, but, inasmuch as there have been to some extent conflicting statements made in respect to the results obtained, we have been tempted to carry out these experiments ourselves in order that we might make up our own minds on several of the contentious matters, and on those points concerning which, on

questions of the greatest importance, such as the effect of the removal of the uterus upon the ovaries, will only be settled by prolonged experiments upon monkeys, or by clinical observation on the human subject; but of this we shall have more to say later. The fact, however, remains that the adult rabbit's ovary is of a very different histological structure from the dog's ovary or the human ovary. It has, however, been a matter of surprise to us that we have not come across adequate appreciation by those who have used rabbits in their experiments of the great difference between the histological structure of these ovaries and that of the human ovary. This difference only becomes marked in the adult rabbit, and may be summarized by the statement that in every normal rabbit—whether virgin or multiparous—the ovary is mainly composed of large cells, sometimes hardly to be differentiated from those which fill the corpora lutea, while there is practically no ordinary stroma. The ova themselves do not appear to be numerous, and are situated near the periphery. (See Fig. 1.) The adult rabbit's ovary, in fact, appears to be of an extremely glandular nature (see also Fig. 2), and in this respect entirely different from the dog's and the human ovary. (See Figs. 3 and 4 respectively.)

These large glandular "stroma" correspond, of course, with the "interstitial" cells which have been investigated by Miss Lane-Claypon.¹ In her opinion, based on careful histological work, these cells are derived from the germinal epithelium, as also are the ova and follicular cells. We have not conducted any detailed research into their origin, but it seems to us that this method of origin is a little strange, seeing that in the ovary of the young rabbit these interstitial cells are entirely absent or very few in number, while primordial ova seem to be more plentiful than in the adult (see Fig. 5).

Whatever their origin, there is no doubt that the presence of the interstitial cells makes the ovary a more glandular organ in the rabbit than in the human subject—the very friability of the adult rabbit's ovary being of itself evidence of a considerable difference of structure from that obtaining in most other mammals. Fraenkel² has recently made a long and important contribution on the subject of *la glande interstitielle de l'ovaire*, as it was originally called by Limon. After examining 45 species of mammals he concluded that these cells vary in extent in all, but are most marked

Fig. 1.—Adult rabbit's ovary. × 200.

Fig. 2.—Adult rabbit's ovary showing interstitial (glandular) cells. × 600.

theoretical and clinical grounds, we have held views contrary to the results generally obtained. We may say briefly that for the most part our results correspond with those obtained by other observers, but we have been forced to the conclusion that the rabbit is not the best animal on which to carry out experiments, the results of which are estimated by histological examinations of the ovaries, if we wish to compare these results with conditions obtaining in the human subject. Indeed, we believe that certain

in rodents. (We have found them constant in rabbits.) In his (Fraenkel's) experience he has found no trace of this glandular formation in the human subject. In view of these investigations by Fraenkel, and by ourselves in a very small way, we would suggest that the variation may be in proportion to the activity of the thyroid gland, which is notably inactive in rabbits.

Attention has already been called to the close relationship which exists between the ovaries and the thyroid

gland in regard to the menstrual function and to the calcium metabolism (see Papers I and II).

RESULTS OF EXPERIMENTS.

SERIES A.

I.—Effect of Oöphorectomy upon the Uterus.

In this experiment we wished to discover, if possible,

Fig. 3.—Bitch's ovary. $\times 200$.

whether the atrophy which is known to occur in the uterus after removal of the ovaries affects more the endometrium or the muscular layer. For the experiment we used one bitch and rabbits. The following are illustrative of the results obtained:

(a) Sable mongrel bitch, aged 6 weeks. Oöphorectomy performed. Animal killed and uterus removed nine and a half months later. It will be seen from Fig. 6 that there is a general arrest of growth which affects the whole uterus, and further that there is some degree of atrophy—most apparent in the muscle layer—which is readily seen on comparison with the uterus from a twin sister, removed on the same day that double oöphorectomy was performed on this bitch (see Fig. 7). Had the uterus, shown in Fig. 6, which was 10 months old, remained *in statu quo* after oöphorectomy, it should have resembled that shown in Fig. 7. There is, therefore, arrest of growth and then atrophy, and the latter most marked in the muscle layer.

(b) Doe, aged 6 weeks. Oöphorectomy. Animal killed two months later and uterus examined. A section is seen in Fig. 8. The same condition of affairs is seen in this as was evident in the last case. There is some atrophy of the endometrium, but want of development and atrophy are most apparent in the muscular layer. At one point there is an area of exceptional thinning. This is most unusual and is difficult to account for. In connexion with these two cases it may be contended that, owing to the fact that the uteri had never become active (see Paper IV), the muscle layer had in consequence not developed. This point will be further alluded to presently.

(c) Doe, full grown. Oöphorectomy. Animal killed and uterus examined three months later. A section of this uterus (see Fig. 9) shows that the changes which have occurred are most marked in the muscle layer, and that the endometrium is still apparently normal. This is better seen in the section than in the photomicrograph of it.

(d) Doe, full grown. Oöphorectomy. Animal killed and uterus examined three and a half months later. The condition alluded to is seen in this case most clearly (see Fig. 10). The endometrium is quite thick, while the muscular layer is represented by a very narrow band. This animal was pregnant when the ovaries were removed.

It may be of interest to mention here the case of a patient, aged 35, from whom the uterus was removed by

Fig. 5.—Ovary from rabbit a few weeks old. $\times 200$.

one of us by operation (owing to extensive adhesions to the appendix, etc.). The ovaries had both been removed (by another surgeon) for dysmenorrhoea four years previously, which of course influenced us in removing the uterus. The organ removed was examined microscopically (Fig. 11). The glands exist in large numbers and stain well. The delicate stroma of the endometrium and the muscle fibres are both replaced by fibrous tissue.

It would appear, then, that when the ovaries are removed in a young animal the uterus remains in an infantile condition, and undergoes slight general atrophy, which condition may be changed into one of general fibrosis of the organ after many years.

This condition of fibrosis is shown in Fig. 12, which is a section of an infantile uterus removed from a human adult. At the same time a rudimentary uterus may coexist with functioning ovaries, although this uterus may be a mass of fibrous tissue, as is seen in Fig. 13—a section of a rudimentary uterus removed by one of us from a hernial sac. (Owing to the extreme hardness, it was impossible to obtain a good section.) In this case the ovaries were proved to be active, or at any rate to contain corpora lutea on histological examination (Fig. 14).

Conclusions.

1. Removal of the ovaries in young animals causes the uterus to remain infantile—atrophic changes eventually occurring.
2. Removal of the ovaries in adult animals produces first of all an atrophic change in the muscular layers; and this

Fig. 4.—Human ovary (adult) $\times 200$, with segment showing structure of the stroma $\times 600$.

Fig. 6.—Young bitch's uterus nine and a half months after oophorectomy. $\times 200$.

Fig. 7.—Bitch's uterus at age of 6 weeks. $\times 200$.

Fig. 8.—Young rabbit's uterus after oophorectomy. $\times 200$.

Fig. 9.—Rabbit's uterus after oophorectomy. $\times 200$.

Fig. 10.—Rabbit's uterus after oophorectomy. $\times 200$.

Fig. 11.—Uterus of woman four years after oophorectomy. $\times 200$.

in time may cause atrophy of the endometrium, probably by interfering with the circulation, the whole organ becoming invaded by fibrous tissue after sufficient lapse of time.

3. Functional ovaries may coexist with infantile uteri.

Fig. 12.—Infantile uterus from adult woman. $\times 200$.

II.—Removal of Ovaries during Pregnancy.

In these experiments we endeavoured to remove the ovaries of rabbits at different stages of pregnancy as estimated from their connexion with the buck. The following are illustrative cases:

(a) Black doe. Opened in the anticipation that she was a few days pregnant. As pregnancy could not be detected, the ovaries and uterus were examined and handled and the abdomen closed. There was no further connexion with the buck. Twenty-three days later one young one was born alive. This case was therefore regarded in the light of a control experiment.

(b) Grey doe. Oöphorectomy was performed on the seventh day. The uterus was enlarged and small nodules visible. No abortion was seen to occur. On the thirty-third day after operation the abdomen was opened, and the uterine cornua were found to be very small. Abortion had undoubtedly occurred.

(c) Black doe. Oöphorectomy was performed on the fourteenth day of pregnancy. Abortion took place on the following day. The animal was killed twenty days later and the uterus found to be quite small.

(d) White and grey doe. Oöphorectomy was performed on the twentieth day of pregnancy. Abortion occurred on the following day.

Other similar experiments were performed, with the invariable result that abortion occurred in every case in which oöphorectomy was performed. Great care was taken in all cases not to expose the uterus, nor to handle it, and the operation was always completed in two or three minutes.

There has been much discussion in connexion with this question since ignipuncture was first performed upon the corpora lutea of pregnancy, and Fraenkel⁸ claimed that

the secretion of the corpus luteum was necessary for the implantation of the ovum. There are, however, still those who assert that the operative manipulations cause the abortion which usually occurs. We are inclined to think that it is not the operative manipulation altogether, in

Fig. 13.—Rudimentary uterus from the hernial sac of an adult woman. $\times 200$.

view of our control experiment; at the same time, we do not think that a comparison can be made between rabbits and the human subject in this respect, for there are undoubted cases on record in which the

ovaries have been removed from women early in pregnancy (six weeks), and where there could be no doubt that the whole of both ovaries was removed, and yet the pregnancy continued to full time. A good example of this is the case reported by J. E. Gemmell,⁴ with the subsequent history of which he has kindly acquainted us.

It would be fair, therefore, to say that while the internal secretion of the ovary is favourable to the continuation of pregnancy (and this will be easily understood by a reference to what we have already stated in connexion with the relation between the ovary and the calcium metabolism), on the other hand, this secretion is not absolutely essential in that respect—at any rate, in the human subject. That our experiments and those of others on rabbits have given positive results may be explained by a consideration of what has already been said in this paper as to the structure of the rabbit's ovary.

Fig. 14.—Ovary from hernial sac of an adult woman (same case as Fig. 13). $\times 200$.

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(To be continued.)

THE University of Geneva will celebrate the tercentenary of its foundation in July of the present year.