

THE SYMPATHICOTROPIC CELLS OF THE OVARY AND TESTIS*

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During the course of the routine microscopic examination of ovaries removed at operation, certain groups of large cells morphologically resembling chromaffin cells, associated with the non-medulated nerves, were observed in the hilum of an ovary. Stimulated by the finding of a supposedly unusual structure in this site, careful examination was made of all the ovaries sent to the laboratory during the following two years, and approximately twenty-five examples of these cells occurring in one or both ovaries were found. About two hundred specimens of ovaries, singly and in pairs, were studied. Most of the material came from young women with pelvic inflammatory diseases. Several of the ovaries were essentially normal. Some were obtained at necropsy. The material came from individuals ranging in age from a few weeks to sixty years. To insure a constant method of examination of the ovary, sections were cut at right angles to the long axis, and as much of the mesovarium included as was free from trauma. The tissues were fixed in Zenker's fluid and stained with eosin and methylene blue.

Later, the region of the hilum of the testis was examined in a number of instances, and in six specimens similar cells were found. All the testicular material came from adults, and with one exception was obtained at necropsy.

LITERATURE

Few papers dealing with these cells are found in the literature. They have been variously named "chromaffin cells," "cellules pheochromes," "glande sympathicotrope," "interstitial gland cells," etc. No extensive studies of these cells have been published in English, although Lewin⁶ reported his observations in two individuals. By far the most comprehensive paper concerning these cells in adults was written by Berger² in 1923. Other articles may have been written and not found on account of the varied terminology. For

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reasons which will be brought out in the discussion of this paper, the writer will hereafter refer to the groups of cells under consideration as the *sympathicotropic cells*.

Bucura ⁴ in 1907, appears to have been the first to describe these cells and to illustrate them. He regarded them as chromaffin cells, primarily on a morphologic basis. He found the cells in the ovarian hilum of a woman 55 years old, whose ovaries had been removed as a therapeutic measure for osteomalacia. The cells were associated with the large nerves and vessels. He described unipolar ganglion cells among the large cells which he called "chromaffin cells."

Berger's elaborate paper was published in 1923 and deals mainly with the cells as found in adults, to which the name "glande sympathicotrope" was applied. He reported numerous instances, including several from pregnant women. He found these cells in the ovaries of one woman 80 years of age. It seems that his terminology is based upon the close relationship of these large cells with the sympathetic nerves. Berger found his "glande sympathicotrope" not always within or near the nerve sheaths, but at times somewhat removed therefrom, and occasionally lying in the ovarian stroma, yet near the hilum. By special technic, he found the chromaffin, argentaffin and sideraffin reactions invariably negative, but fat or lipoid globules were generally present. He described and illustrated coarse granules, pigments and crystals in the cytoplasm. Berger did not regard the cells as chromaffin foci as Bucura and de Winiwarter,^{10,11} had, and even questioned the occurrence of the ganglion cells which Bucura described.

Schäfer ⁸ in his text merely mentions these cells as occurring in the mesovarium, and names them "interstitial cells" recalling the interstitial cells of the testis. Lewin,⁶ who has recently reported the same cells in the ovaries of two elderly women, calls them "interstitial gland cells" apparently after Schäfer. Lewin found lipoid pigments in the cytoplasm and intimated a rather fantastic rôle for the cells.

Turning to the works of others, especially those of Aschoff,¹ de Winiwarter and Kohn,⁵ one finds strong evidence for the chromaffin nature of these nests of cells occurring in the ovarian and testicular hila. In 1903, both Aschoff and Kohn published long papers describing chromaffin cells in the testes and ovaries of fetuses and in the new-born. de Winiwarter's work in 1910 confirmed that of

Aschoff and Kohn. de Winiwarter introduced the term "cellules pheochromes." There seems little doubt from the embryologic researches of these authors, that the chromaffin tissue, after separating from the sympathico-chromaffin anlage, may come into close proximity to the Wolffian body and may even be incorporated with it. Later, as development proceeds, the relationship to the paroöphoron and paradidymis may become very close. When the gonads descend from their site of origin into the pelvis or scrotum, the enmeshed chromaffin cells, along with the other structures, may be carried downward and come to rest in new positions. Zuckerkandl,¹² as well as Aschoff and Kohn, has shown that chromaffin cells may be so deposited in fetuses and in the new-born as to occur along the courses of the ureters, in the broad ligaments, in the retroperitoneal tissue, in the prostate glands and elsewhere. Rieländer⁷ in several instances found chromaffin cells in relation to the paroöphoron of fetuses and the new-born. Soulié,⁹ in his extensive researches on the development of the suprarenal glands, pointed out the possibility of the occurrence of isolated or accessory chromaffin bodies. The chromaffin reaction of the cells in fetuses and in the new-born has been positive, in contrast to the negative results obtained by Berger in adult tissues. de Winiwarter has emphasized the close association of these cells with the sympathetic or non-medullated nerves of the ovaries of embryos and fetuses, a condition similar to that found in adults.

OBSERVATIONS ON THE CELLS OCCURRING IN THE OVARIES

The observations of the writer have been primarily concerned with the cells under discussion as found in the ovaries of adults. Seldom were the sympathicotropic cells found in both ovaries. In no instance could one detect the groups or clusters of cells with the naked eye. These foci are almost always in the hila of the ovaries, lying high up in the mesovarium but generally outside of the ovarian tissue proper. Occasionally, large and small groups of the cells are found in the ovarian cortex or medulla, but in such instances they are very near the hilum. The groups of cells frequently seem to be more numerous near the poles of the ovaries, but are found throughout the entire hilum.

The relation to the large or small non-medullated nerves of the ovarian hilum is a very constant and rather characteristic feature.

Frequently, one finds only a few cells in a given ovary and these perhaps are within a nerve sheath. In another instance, sufficient cells are seen within the nerve to cause a separation of its fibers and a fusiform enlargement of the nerve. In the same ovary, or even in the same section, the cells may be found surrounding the nerve very much as a mantle of wandering cells. Still other sections reveal groups of cells just touching or near a nerve, while occasionally large groups of these cells are quite removed from the nerves. In some specimens the cells are scattered along the course of the nerve, and at times sprinkled loosely among the nerve fibers. It is difficult to demonstrate any close relationship between the nerves and the group of cells occasionally seen in the ovarian tissue proper. One observes no genetic relationship with the nerves or their sheaths, other than their close association with the nerves.

The sympathicotropic cell groups show a more than casual association with the lymphatics and blood vessels. In many instances the cell masses lie along the lymphatics and are separated from them only by endothelium. The lymphatic vessels about the larger cell clusters are frequently abundant and the larger clusters of cells are well supplied with small blood vessels.

There does not appear to be a close association between the cell masses and the rudimentary tubules of the ovarian hila, as described by others, particularly in embryologic and fetal material. The cells are never found in the broad ligaments, mesosalpinx or parametrium, yet chromaffin cells have been frequently observed in the broad ligaments of fetuses by others.

The groups and clusters of cells, whether inside or outside the nerves, are generally closely packed. Those outside the nerves lie freely in the loose connective tissue of the mesovarium. A limiting membrane about the masses of cells is absent. At times the more peripheral cells of a cluster are somewhat separated from the main mass, but this is not a common feature. Very often the large groups of cells are just under the serosa covering the mesovarium.

The sympathicotropic cells are large polyhedral, round or oval cells with a relatively pale but definitely acidophilic cytoplasm. They range in size from 15 to 25 microns, averaging about 20 microns. The cells resemble epithelial cells. The nuclei are large, spherical and vesicular, containing one or more nucleoli with but little chromatin. Some cells contain two nucleoli. The depth of

staining of the cytoplasm appears to depend largely upon the fat content of the cells. In the cells containing much fat the vacuolated cytoplasm takes very little eosin, while other cells, but generally in a different ovary, have a deeper stain and fewer fat vacuoles. The cell membranes are clearly defined and delicate in properly preserved and fresh material. Among these groups of cells one very often finds scattered eosinophilic and mast cells, the significance of which is obscure.

In certain cells of a cluster, and very often in most of the cells of a given group, one may distinguish a few small and irregular pigment granules, brownish in color and frequently very dark. In some preparations one finds crystals in the cells. The crystals vary a great deal in size, some being short and others long, but they are generally broad with blunt ends and take the eosin stain. Very often the crystals present a clear streak or cleft running along the longitudinal axis, while a few others present sharp and ragged ends. In a few of the cells that contain one, two or more large crystals, the nuclei have become shriveled and pushed to one side. The exact nature of the crystals and granules is not known. The writer did not find these intracellular structures to be as numerous as the literature might lead one to believe, for many clusters of cells did not contain a single crystal.

The cells, at first glance, present a superficial resemblance to lutein cells, and certain persons viewing them have made this comment. They present a certain morphologic resemblance to chromaffin cells, and the close association with the non-medullated nerves, as well as the data obtained from embryologic, foetal and new-born material, strengthens this assumption. On the other hand, not a single ganglion cell is observed among the clusters of cells of the various sections.

The morphologic appearance of the cells is the same in all specimens examined, whether the ovaries were those of an infant, a young adult or an aged woman. One of the largest collections of cells found was in an ovary of a woman 60 years of age.

Because of the similarity of the sympatheticotropic cells to chromaffin cells, and because of the embryologic grounds which favor the possible occurrence of chromaffin cells in the ovary, an effort was made to study the chromaphil and argentophil reactions. In this connection it is well to emphasize the technical difficulties involved.

One could not see the clusters of cells in the fresh tissue and consequently it was an exceedingly difficult task to locate proper material for special technic. The occurrence of these cells is by no means constant. By laborious searches, thin pieces from six different ovaries were secured and tested for their chromaphil reaction. This tissue was fixed from six to twelve hours in a five per cent solution of sodium bichromate and five per cent formalin. This solution was then drained off and the tissue preserved twelve to eighteen hours in a five or ten per cent solution of formalin. Frozen sections were made of this fixed tissue, and counterstained with a weak solution of carbol thionin. Control tissue was obtained from the suprarenal glands of rabbits and guinea pigs. In every instance the medulla of the suprarenal glands is stained yellowish or brown, while the groups of large cells of the ovarian hila are unaffected by the chromic salts.

The ovarian sections from the same tissues used in the above experiments were treated with fat stains, particularly Scarlet red, and Sudan III. In every instance the majority of the cells contain fat, varying in amount from a single small globule to complete infiltration. It is impossible to be certain regarding the staining reactions of the pigments, but it is probable that they are lipochomes.

Considerable material was used in the chromaphil tests, and little was available for the argentophil tests. Here again the results were negative. The siderophil reaction was not tried.

PATHOLOGIC AND OTHER CHANGES DURING PREGNANCY

Six pairs of ovaries from pregnant women were examined, and in four cases the cells were found. Four of the individuals died as a result of a toxemia of pregnancy, and all were in the first few months of gestation. In the four cases, fat vacuoles are seen very infrequently. The cytoplasm of the cells takes a very deep eosin stain. In three of the cases this is the only change observed, but in one instance the cells appear to have undergone a marked hyperplasia and hypertrophy. In this case, the clusters of cells are unusually large and numerous and a single group of cells fills the low power field. They are only observed in the ovary opposite the one containing the true corpus luteum and the close relationship they bear with the non-medullated nerves as well as the numerous and large lymphatics

about certain of the masses of cells are striking features. An occasional collection of these cells is found within the ovarian stroma. The abundance of the cells, as compared with the previous specimens studied, suggests that the increase is due to hyperplasia. Many of the cells are very large, in fact a third to a half larger than those found under ordinary circumstances, probably due to hypertrophy. The irregular granules mentioned above are seen in only a few of the cells, but crystals are absent. Most of the nuclei are vesicular. Crystals were not observed in any of the specimens from pregnant women; however, they were not constant during the non-gravid state.

It is also of interest to note certain other pathologic changes in the sympathicotropic cells of this individual. The woman died from pernicious vomiting in the third month of pregnancy and the corpus luteum was found to have undergone coagulation necrosis. This phase of the case has been reported by Brannan and Cohen.* The cells in question were not mentioned by them, but reserved for this paper. The illustrations show numerous pyknotic and a few shriveled nuclei (Figs. 8 to 12). Other cells present granular disintegration of their cytoplasm, and adjacent areas show a complete loss of cells, no doubt the result of necrosis. Apparently some of the sympathicotropic cells have undergone degenerative changes and necrosis as did the cells of the corpus luteum. Leucocytes and wandering cells, however, are not observed, but they are not numerous in the necrotic corpus luteum of the opposite ovary.

In this connection, it is perhaps well to mention that the well known interstitial cells of the ovary, occurring about the atretic follicles during pregnancy, were found in both ovaries of this individual, as well as in the ovaries of two of the other cases of pregnancy showing sympathicotropic cells. The staining reactions of the two groups of cells are somewhat similar, but otherwise the cells are quite different in size, position and other characteristics. No confusion in differentiation should arise between the two sets of cells, especially when they can be observed in the same section.

* Brannan, D., and Cohen, M. Necrosis of corpus luteum of pregnancy. *Surg. Gynec. Obst.*, 1926, xlii, 228.

OBSERVATIONS ON THE CELLS OCCURRING IN THE TESTES

Undoubtedly, the same cells occur in the hila of the testicles of adults. The testicular material, however, was not abundant and was limited to six positive specimens. The cells occur in or about the non-medullated nerves of the testicular hilum, particularly near the epididymis. In none of the six testicles are the cells especially numerous, usually not more than twenty-five to thirty cells being seen in any section. In morphology, they are identical with the cells described in the ovaries, though granules and crystals are not seen. None of this tissue was subjected to special technic, because of the accidental nature of the findings.

Since the testicular hilum includes so much loose tissue, it was very difficult to examine it all, and it was probable that many groups of these cells were not found.

DISCUSSION

There is a question as to the exact nature of the cells described. The close association of the groups of cells with the non-medullated nerves of the ovarian and testicular hila was pointed out particularly by Berger. Berger called the cells "glande sympathicotrope" and regarded them as being homologous with the interstitial cells of the testis. He believed the cells arose from the nerve sheaths. Bucura considered them as chromaffin cells. Lewin called them "interstitial gland cells." de Winiwarter believed his "cellules pheochromes" of fetuses and embryos were the same as Berger's "glande sympathicotrope."

It is clear that the cell groups are not accessory chromaffin bodies, since the chromaphil, argentaphil and sideraphil reactions are negative. The three reactions were tested by Berger and the first two by the writer.

From a study of fetal and embryologic material, there are good reasons for expecting chromaffin cells in the ovaries and testes of adults, particularly in relation to the nerves. On the other hand, it is well known that chromaffin tissue undergoes regressive changes shortly after birth, and the common occurrence of this tissue in intra-uterine life is no assurance of its persistence in later years. The relationship with the non-medullated nerves is a strong point in favor of their chromaffin nature; but not in a single instance, aside from

the observation of Bucura, have ganglion cells been found. From a morphologic point of view they have certain features of chromaffin cells, but as pointed out above, they lack the biologic properties of chromaffin cells in adult tissues. Either Aschoff, Kohn, de Winiwarter and Rieländer were discussing entirely different cells, or the cells in question were chromaffin cells which in adults have lost their chrome-affinity, sidero-affinity and argento-affinity. Such a suggestion is obviously unsound, yet de Winiwarter conceives this idea in order to harmonize his views with those of Berger. Berger, later, refuses to accept de Winiwarter's ideas: hence the matter stands, at present, unsolved. The cells appear to be epithelial in nature.

Whatever the identity of this group of cells may be, it is unfortunate that the term "interstitial cells" or "interstitial gland cells" should be applied to them. Interstitial cells of the testes and ovaries are well known, and refer to different cells in each organ. Certainly a similar term should not be applied to another group of cells in the gonads. Since Berger has proposed the new and distinctive term of "cellules" or "glande sympathicotrope" as a result of the close association or affinity of the cells with the non-medullated or sympathetic nerves, it is only fair that we retain his distinctive terminology. There is nothing confusing about his terminology which may be translated as sympathicotropic gland or cells. The word cells is more exact than gland, because in many instances only a very few cells were found, and furthermore, there was practically no suggestion of a glandular structure, even in the largest clusters of the cells.

The occurrence of the sympathicotropic cells is not a constant finding in either the ovary or testicle. They may be found in the ovaries of the new-born, throughout childhood, during adult life and in old age, and probably also in the testes of the young as well as in the testes of the old. This group of cells is obviously the same in both the ovaries and testes. The inconstant occurrence of these cells in the gonads is very suggestive of some variable structure, like chromaffin or cortical adrenal rests found elsewhere. When present, however, they should be regarded as essentially normal structures. They have nothing to do with cortical adrenal rests. Berger believes that the cells arise from the nerve sheaths, but this is unproved and questionable.

So far as the function of the sympathicotropic cells is concerned, we are totally ignorant. From the close association with the lymph

vessels, one might expect an outpouring of some secretion into these vessels. Pregnancy has some influence on the cells as was shown by a change in their staining reaction, loss of fat and occasional hyperplasia and hypertrophy. The writer cannot subscribe to Lewin's ideas regarding function, and the cells have nothing to do with senile psychosis.

A few points are recorded concerning the histopathology of the cells when occurring in a case of pernicious vomiting showing necrosis of the corpus luteum. It is well to regard the hyperplasia and hypertrophy during gestation as a pathologic change, since it is not a constant feature. Berger also found an overgrowth of the sympathetic cells in some of the ovaries of pregnant women. It is possible that tumors may arise from these cells, particularly in the ovaries.

It is to be hoped that others will search for these elements in the gonads, so that before long we may have a better understanding of this obscure group of cells.

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DESCRIPTION OF PLATES

PLATE 99

- FIG. 1. A camera lucida drawing of the sympathicotropic cells of an ovarian hilum, showing morphology; observe the granules and crystals.
- FIG. 2. A camera lucida drawing of sympathicotropic cells as found in the ovarian hilum of a new-born child. Note the close relationship of the cells with the non-medullated nerve below, and also the cell lying in the center of the nerve. An arteriole and a vein are conspicuous.
- FIG. 3. A camera lucida drawing of the sympathicotropic cells occurring in the hilum of a testicle. The edge of the non-medullated nerve is shown above, in and about which the cells are found. Note the two small vessels supplying the cells.

PLATE 100

- FIGS. 4 and 5. Two groups of sympathicotropic cells from the same ovarian hilum. In Fig. 5 a small non-medullated nerve courses through the cluster of cells. Note also in Fig. 4, the proximity of the lymphatic vessels at the periphery, and the blood vessels.

PLATE 101

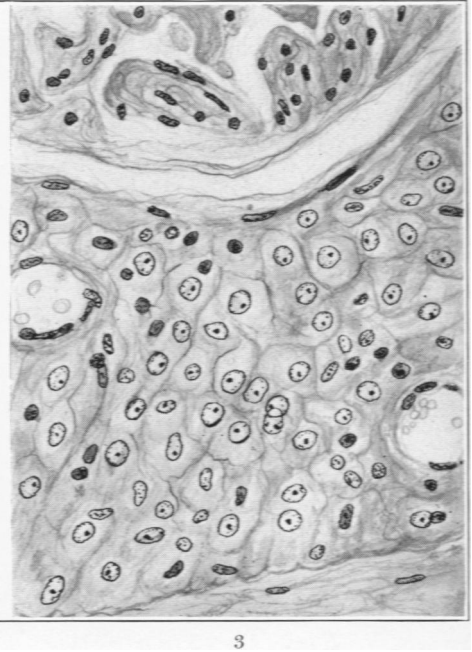
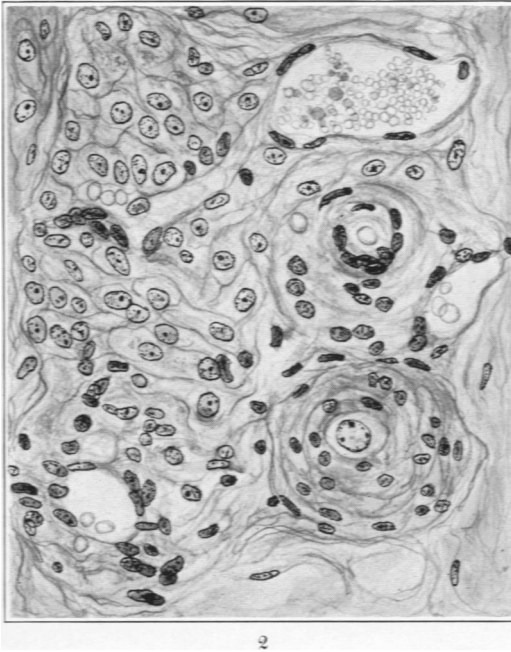
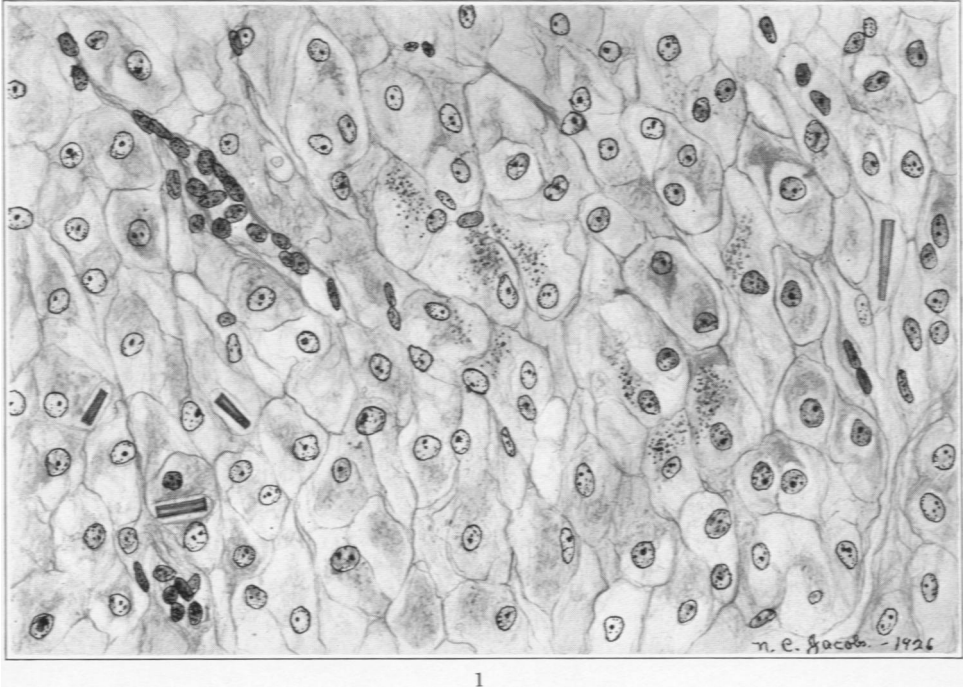
- FIG. 6. A small group of sympathicotropic cells in an ovarian hilum near a non-medullated nerve. The lymphatic and blood vessels are conspicuous.
- FIG. 7. Another patch of sympathicotropic cells from an ovarian hilum lying in denser tissue but along the side of a nerve.

PLATE 102

- FIGS. 8 and 9. Large hyperplastic masses of sympathicotropic cells in the ovarian hilum from the case of pernicious vomiting of pregnancy. Note the deeper staining of the cells which occurs during pregnancy, as compared with the normal cells of the non-gravid state shown in previous illustrations. The numerous pyknotic nuclei are to be regarded as pathologic. In Fig. 8 there is a small nerve in cross-section at upper border of the group of cells. In both figures the cells are just under the peritoneal covering of the mesovarium. In Fig. 9 are also several vessels in the midst of the cell clusters and a large lymphatic running perpendicularly.

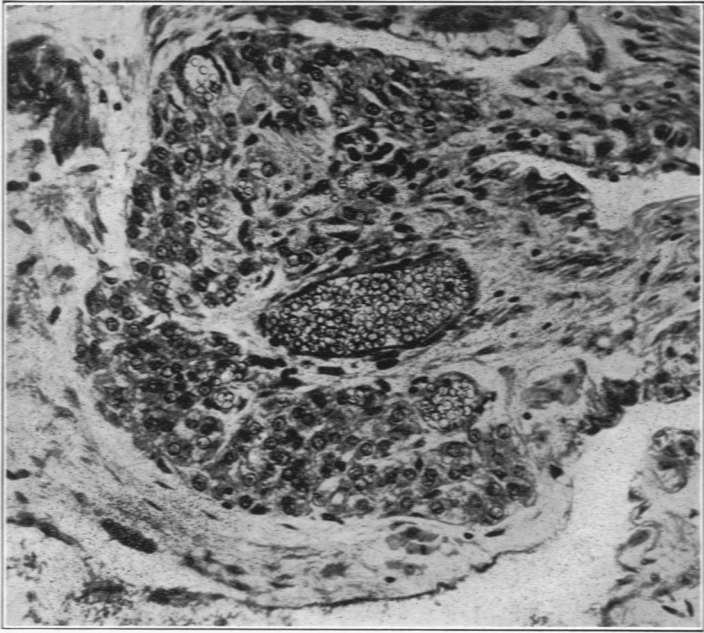
PLATE 103

- FIG. 10. A high power magnification of the same cells from another area but from the same case of pernicious vomiting of pregnancy. There are several pyknotic nuclei and disintegrating cells, particularly in the center.
- FIG. 11. A field similar to Fig. 10. Here one can see a few granules in the cells, and one large hypertrophied cell which contains granules. There is also one polymorphonuclear leucocyte near the large cell.
- FIG. 12. Same as Figs. 10 and 11 but showing more degenerative changes. Another leucocyte is shown. The edge of a small nerve is shown above and to the right.

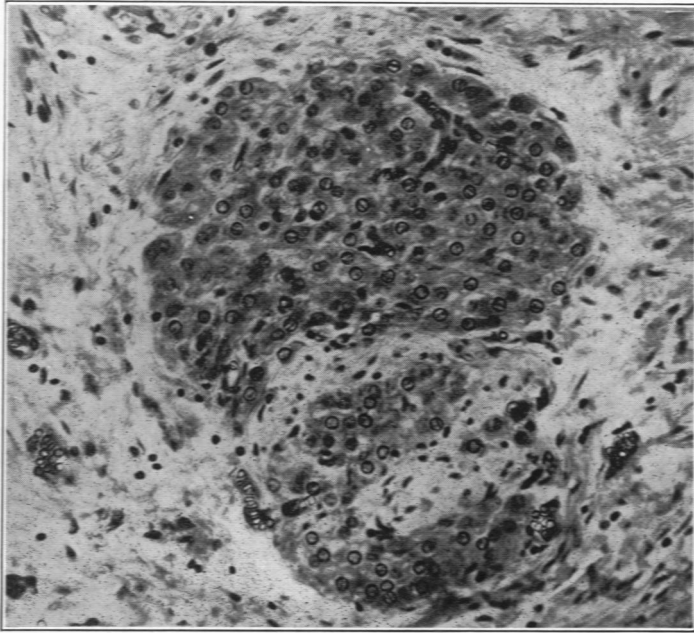


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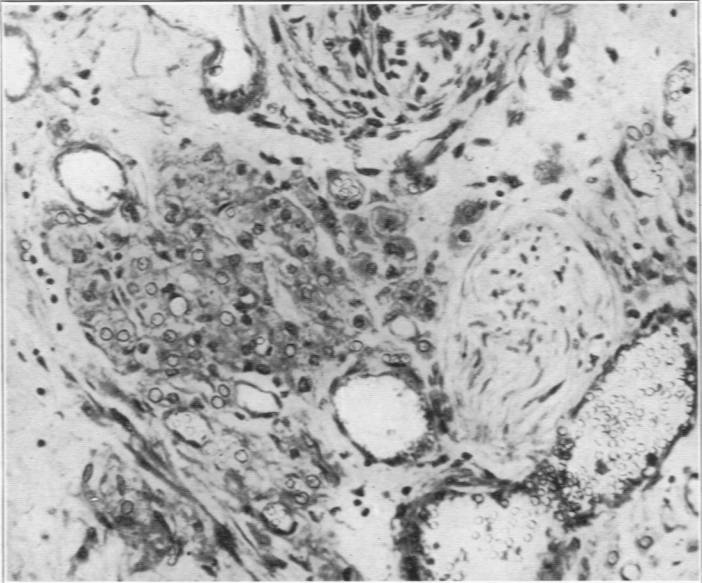
Sympathicotropic Cells of Ovary and Testis



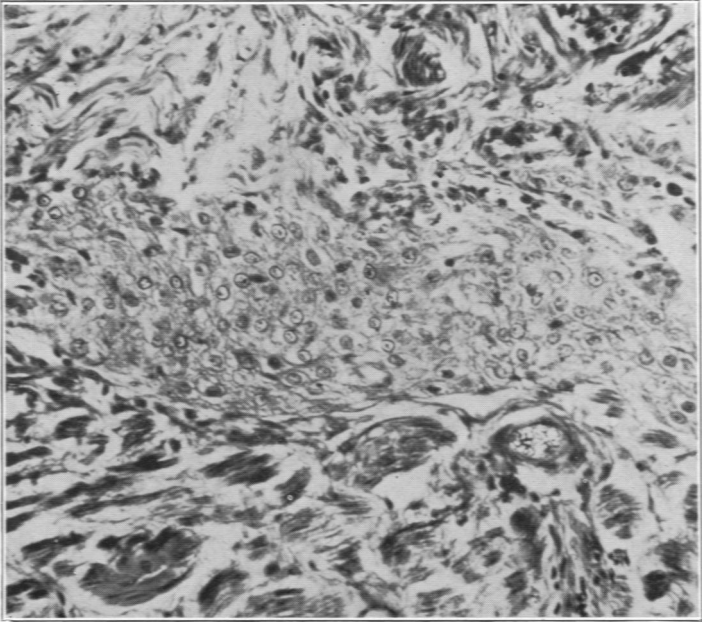
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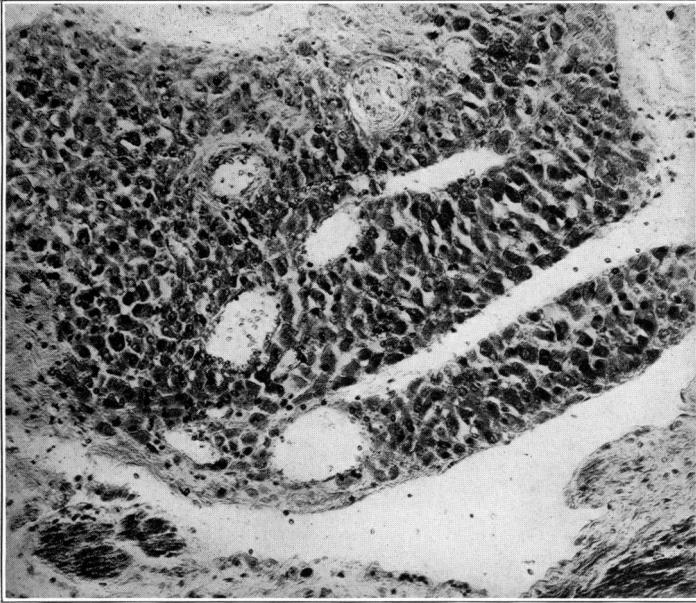
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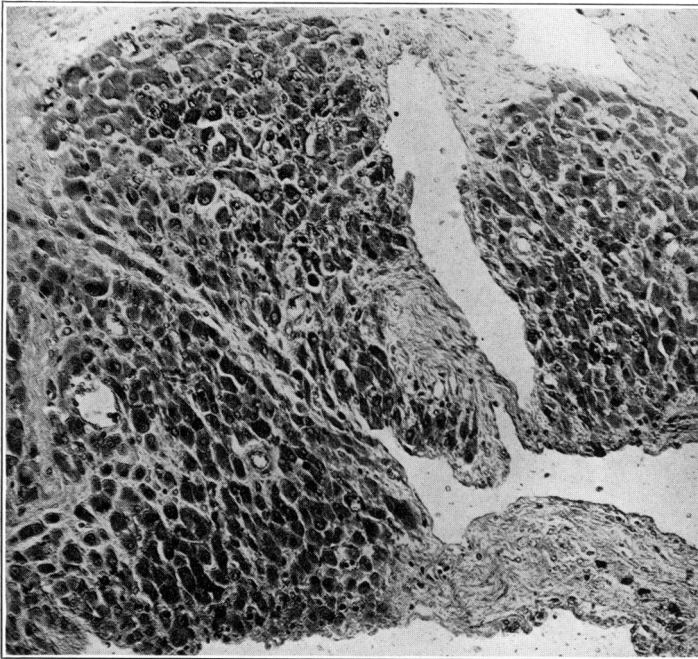
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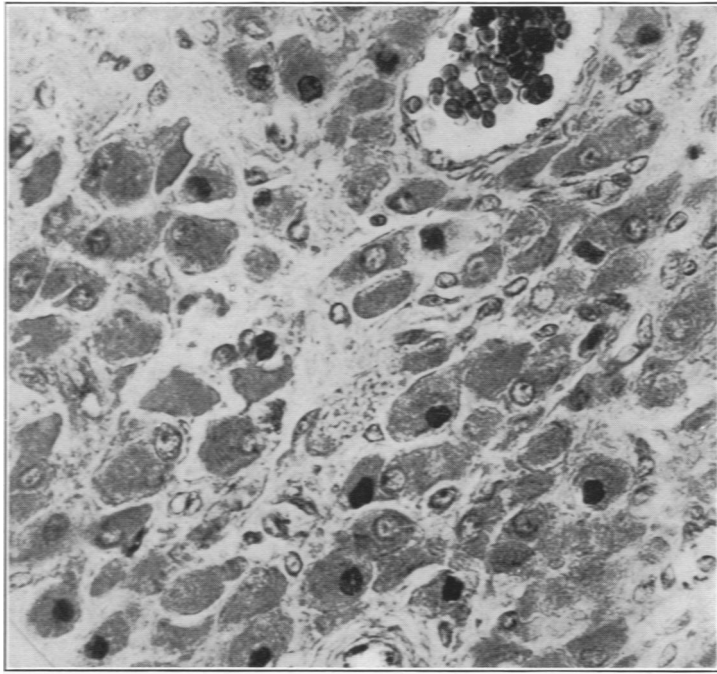
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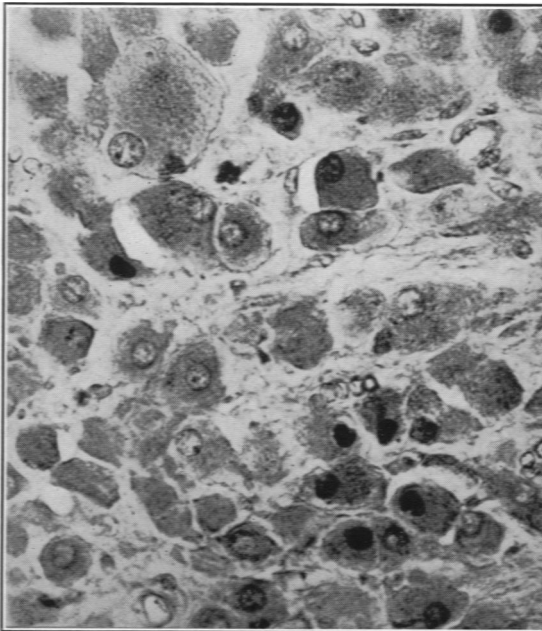
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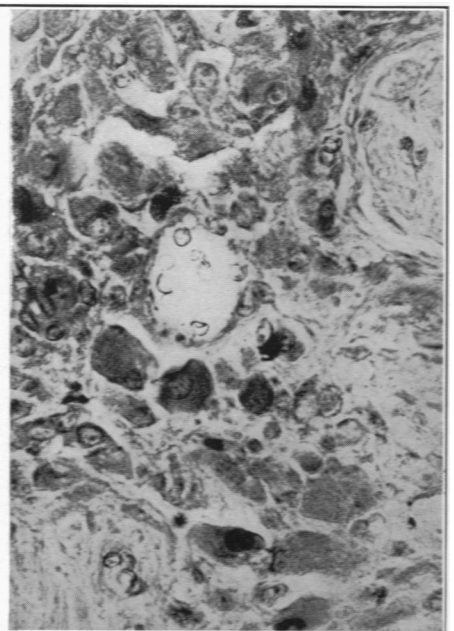
Sympathicotropic Cells of Ovary and Testis



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Sympathicotropic Cells of Ovary and Testis