

# THE AMERICAN JOURNAL OF PATHOLOGY

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VOLUME VI

MAY, 1930

NUMBER 3

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## CONTRIBUTION TO THE STUDY OF THE SYMPATHETIC NERVES OF THE APPENDIX. THE MUSCULONERVOUS COMPLEX OF THE SUBMUCOSA\*

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Describing the lesions following acute appendicitis, pathologists speak of cicatricial scleroses of the submucosa which invade the circular muscle and dissociate its bundles more or less. Their illustrations show the muscle bundles separated from one another and turned from their normal course so that some of them seem to lose themselves in the fibrous connective tissue of the submucosa; the boundary between the submucosa and the circular muscle is no longer so clearly marked as in the normal intestine.

Beyond question, up to a certain point, postinflammatory sclerosis explains this partial dislocation of the muscularis and the musculoconnective tissue interpenetration; but, if this were the only cause, we should be obliged to admit that all appendices without exception have been diseased, even those of nurslings and of the new-born, for all of them present in different degrees the same ill-defined boundary between the circular muscle and the submucosa. From this observation what conclusion can be drawn other than that this lack of precision of the boundary does not result exclusively from sclerosis, but that it corresponds at least in part to a normal structure? This was the point of departure of the present study.

I first observed this condition in beginning my investigation of nerve proliferation in the appendicular mucosa and the origin of argentaffin cell tumors (carcinoids). While pursuing this work I

\* Received for publication February 12, 1930.

acquired the idea, little by little, of a submucous muscular mechanism, then of a submucous musculonervous complex, present in all appendices. My brief description in 1924 and again in 1928 has attracted no attention. If I now return to the subject it is because this complex seems to me worthy of notice by its constancy and by its peculiarities, both in the normal and the pathological state.

As we shall see, marked variations in the musculonervous complex are habitually accompanied by obvious changes, always of the same order, in the other appendicular constituents, always involving the submucosa, often the mucosa and sometimes the muscular coat. From this observation arose the idea that these changes are not unconnected with those of the mechanism itself and that their study is capable of throwing light on its significance. I shall not, therefore, limit the description to the complex itself but, in connection with each example studied, I shall indicate the condition of the other appendicular structures.

#### I. APPENDICES OF THE NEW-BORN

*Normal Type:* (Figs. 1 and 3.) In the first place we must describe this complex in the surely normal appendix, that of the new-born or of the nursling. At this age the appendicular mucosa is habitually poor in lymph nodules and rich in crypts of Lieberkühn. The muscularis mucosae forms an almost continuous layer beneath the tips of the crypts, interrupted only in the region of certain lymph nodules.

The submucosa is thin and already fibrous. Study of the bundles of circular muscle surrounding it shows that from time to time certain bundles change their course and pass obliquely into the fibrous connective tissue in which they seem to lose themselves. In the submucosa, centrally from these oblique muscle bundles, we find other, more slender bundles presenting at most eight to ten contractile fibers abreast, which seem to be isolated in the fibrous connective tissue. From the muscularis mucosae in the same sector, muscle bundles here and there detach themselves and bury themselves in the submucosa. Serial sections show that the muscle bundles of each group, the one issuing from the circular muscle, the other from the muscularis mucosae, converge and anastomose in the middle of the submucosa. Sometimes one or two muscle bundles cross this middle zone and join the two groups in one network.

I cannot say that this union is constant. The oblique course of the bundles makes it difficult to draw a conclusion. However, union is beyond question in certain instances where each group is conical in form. The base of one is continuous with the circular muscle, that of the other with the muscularis mucosae. Their apices are joined by one or two more or less oblique anastomotic bundles. In other specimens the ordinary location of the two groups in the same sector and the direction of their bundles toward each other indicates a certain correlation between them, even if they are not actually joined together. They form a whole which I propose to call the muscular mechanism or complex of the submucosa.

Each cross-section of an appendix shows elements belonging to several (two to four) of these mechanisms. We should note also these two points: (1) The arteries destined for the submucosa travel among the bundles emanating from the muscularis mucosae; and (2) Meissnerian nerves are always present between the bundles of a whole complex. As to their relations with the muscular mechanism, the evidence is not so good as that which we shall be able to offer later on.

## II. APPENDICES OF CHILDREN AND ADOLESCENTS

*Normal Type:* Appendices removed from children and adolescents are much richer in lymph nodules, although their number and size vary greatly, not only from one specimen to another but also in different regions of the same specimen. Sometimes they are isolated, sometimes grouped in masses and more or less continuous at their borders. They may be small and lodged entirely in the mucosa, or they may encroach on the submucosa; and in this event, the most frequent, there is no muscularis mucosae beneath them.

Crypts of Lieberkühn are found only in the spaces between the lymph nodules at points where the nodules are not too closely approximated. It is only at these points, remaining glandular, that the muscularis mucosae persists. It is in these sectors provided with a muscularis mucosae, and consequently with crypts of Lieberkühn, that we find the anastomotic muscular mechanisms with the features already described. The submucosa is two or three times thicker than at an earlier age.

*Pathological Types:* In certain subjects in whom lymphatic tissue is developed to the utmost, such as status lymphaticus and certain

instances of chronic appendicitis, the lymph nodules are continuous or even heaped up in several layers, leaving space for only a small number of crypts beneath which no trace of a muscularis mucosae can be found. In these specimens a few bundles are seen to detach themselves from the circular muscle, but no contractile (smooth muscle) cell continues through the lymphoid tissue, encroaching on the submucosa. The internal half of the mechanism is wanting, as is the muscularis mucosae itself.

In children and adolescents, after one or more appendicular crises, quite frequently there is seen a reversal of the conditions just described, consisting in rarefaction of the lymph nodules and sclerous thickening of the submucosa. Often in this thickened submucosa the muscular mechanisms are more prominent than in the normal state. These variations indicate already on the one hand an inverse proportion between the richness of the mucosa in lymph nodules and in the number of the crypts; on the other hand a certain correlation between the gland content of the mucosa and the development of the muscular mechanisms of the submucosa. These contacts and relations are much more obvious in the adult, as we shall see.

### III. ADULT APPENDICES

All pathologists know how variable is the number of lymph nodules in the adult appendix. Study of a large number of specimens shows that on the average the number of these nodules is less than in children and that at times they are almost or completely absent. This lack of lymphoid nodules is habitually associated with former appendicular symptoms, acute crises or chronic appendicitis without acute inflammatory attacks, as if the spontaneous lymphoid involution had been hastened by these inflammations.

1. *Appendices with Numerous Lymph Nodules, Normal Type:* (Fig. 4.) The aspect of the mucosa is similar to that observed in the adolescent. The muscular mechanism presents no notable change. It is always found in the sectors provided with crypts.

In one specimen, exceptional it is true, I observed a mechanism more typical than usual (Fig. 2). Instead of showing along its whole length a plexiform structure, it was reduced to a perfectly straight and radial bundle visible in its entire length in one section, extending between the muscularis mucosae and the circular muscle,

to which latter it was attached by two or three oblique bundles. A branch of Meissner's plexus wound around it like a climbing plant. An artery of the mucosa traversed the muscularis mucosae in the immediate vicinity of its insertion.

2. *Appendices with Scanty Lymph Nodules, though Present in all Complete Cross-Sections. Passage from the Normal to the Pathological Type:* Sometimes the muscular mechanisms resemble those described above: they correspond to the normal type. Sometimes their bundles are obviously larger and more numerous. The mechanisms themselves are not increased in number. Their general form remains the same but they are seen more readily because of the greater number of their constituent bundles.

Along their whole length these mechanisms are mingled intimately with Meissnerian nerve filaments, distinctly larger and more numerous than in the normal state. These filaments, studded with tiny ganglia, form a plexus between the muscle bundles.

3. *Appendices with Very Scanty or Absent Lymph Nodules. Pathological Types:* (Figs. 5, 6 and 7.) This extreme diminution of lymph nodules is seen especially in the adult, seldom in the adolescent. Such an appendix almost invariably has a clinical history; repeated crises or a syndrome of chronic appendicitis. Its external appearance varies greatly. The length and caliber may be normal. It may be short, 3 to 4 cm., and correspondingly broad, 1 to 2 cm., or the tip may be swollen in the form of a pendulum. More rarely it is enlarged in all dimensions, 10 or even 15 cm. long, 1 to 2 cm. broad. Often it is buried in fibro-adipose peritoneum.

On examining sections with the naked eye, after fixation, the most striking features are the extreme narrowing of the lumen to such a degree that it seems to have been obliterated, and the thickening, often enormous, of the appendicular wall. The thickening involves the submucosa especially, but also in addition in extreme examples, the muscularis.

Appendices which combine these three fundamental features, narrowing of the lumen, extreme diminution or absence of the lymph nodules and thickening of the submucosa, present also more or less complex changes in their histological constituents. At first sight their situation, nature and extent seem to be capricious. Study of a large number of specimens has enabled me to establish a certain order among them. The most constant change affects the

muscles and nerves of the submucosa. This may be the only lesion but it is often accompanied by a curious alteration in the nerve plexus of the mucosa, to which may be added hypertrophy of the muscle coat and even of Auerbach's plexus. In this order, then, we shall study them: first the submucosa, followed by the mucosa and the muscularis.

#### SUBMUCOSA

The thickness of the submucosa, always excessive, varies from 0.25 to 0.5 cm. It is constantly fibrous, poor in fat cells but always of loose texture, especially in the middle. In this region there is often an imperfect cleavage into two concentric layers, the one fusing with the mucosa, the other with the circular muscle.

The muscular mechanisms and Meissner's plexus are prominent, obviously hypertrophied. The hypertrophy may affect only Meissner's plexus; its nerves are broad, elongated and tortuous, the ganglia larger, more numerous and richer in cells than in the normal state while the muscular mechanism, moderately but distinctly enlarged, contains only a few bundles. In the neighborhood of the circular muscle these bundles are thick; toward the muscularis mucosae they are slender and plexiform, always mingled with Meissnerian nerve filaments.

The Meissnerian hyperplasia, though present, may be masked more or less by hyperplasia of the muscular mechanisms, the contractile fibers striking the attention by their bright color (Fig. 8). The muscle bundles continuous with those of the circular muscle occupy the outer half of the submucosa. They ramify in different directions. Some of them converge toward the middle zone of the submucosa forming cones broader and better furnished with fibers than in the normal mechanisms; others run parallel with the axis of the appendix and seem to establish longitudinal anastomoses between the hyperplastic mechanisms from one segment of the appendix to another. Whatever direction they take the bundles are cylindrical. In the neighborhood of the circular muscle their fibers run parallel with one another. As they bury themselves in the submucosa the fibers become oblique, wavy, and they arrange themselves in the interior of the bundle in fascicles anastomosing with one another so that each bundle has a plexiform structure.

The nerves, hyperplastic and studded with tiny ganglia, ramify

among the muscle bundles, often run along with them and give off branches which encircle them or penetrate their interior to follow a course parallel to the fascicles.

The inner half of the submucosa presents many muscle fibers, sometimes grouped in bundles intimately anastomosing, sometimes interlaced in a close-meshed plexus. Anastomosing with those of the muscularis mucosae these fibers may group themselves in plexiform sheets that parallel the muscularis mucosae and reduplicate it externally. These fibers or these bundles converge toward the summits of the muscle cones emanating from the circular muscle and anastomose with them here and there.

The interstices of this robust muscle plexus are occupied by a very rich and delicate nervous plexus containing many ganglion cells, and by arteries destined for the mucosa (Fig. 15). The abundance of the nerves, and especially of the muscles, varies within wide limits. In certain specimens their mass may be estimated at one-half to two-thirds of the tissue present in the submucosa; that is to say, the total thickening of the submucosa is due in great part to their presence.

Such is the aspect of the musculonervous complex in most examples of lymphoid atrophy of the mucosa. However, I shall now describe the curious structure presented in some of my specimens by those muscle bundles, which issuing from the circular muscle assume a longitudinal direction (Figs. 16 and 17). These large bundles, round in cross-section and plexiform in structure, are not in direct contact with the connective tissue of the submucosa but are separated from it by a continuous sheath of varying thickness formed by a plexus of non-medullated nerve fibers. The nerve fibers are voluminous and appear edematous. The nerves sheathe the bundles only in their longitudinal ramifications; when the bundles take another direction the nerve sheath resolves itself into ordinary filaments. The nerve fibers are pressed closely together, anastomosing in a plexus of meshes elongated in the direction of the muscle bundles which they surround. Here and there the sheaths present small sympathetic ganglia with large cells. From time to time they are seen to give off small branches which penetrate the bundles and disappear between the muscle cells. This peculiar structure, though rare, shows very well the remarkable union of muscle and nerve in the complexes which are the subject of this study.

With these musculonervous hyperplasias are constantly associated important changes in the arteries. In the outer zone of the submucosa the lumina of the vessels are enlarged; their walls are thickened by hypertrophy of the muscle fibers as well as by interstitial sclerosis. Often there is notable thickening of the intima. The adventitia presents a nerve plexus of large tortuous fibers. The branches of the arteries directed toward the mucosa, are more numerous than normal, tortuous, winding and mingled with muscle and nerve fibers. In short, all of the nervous and muscular elements of the submucosa undergo more or less hyperplasia, those of the arteries as well as those which belong to the musculonervous complexes.

#### MUCOSA

Except for its poverty in lymph nodules the mucosa of the appendix may present nothing abnormal (Fig. 8). The crypts of Lieberkühn are numerous, straight and parallel as in the colon. Their tips may extend to the immediate vicinity of the muscularis mucosae. The mucosa does not contain an excessive number of nerves and the meshes of its stroma are filled with lymphocytes, plasma cells, and usually a few polymorphonuclear eosinophiles.

However, it may present more or less pronounced hyperplasia and even neuromas of the subglandular portion of the intramucous plexus. In this event the nerves always contain argentaffin cells, the form and origin of which I have described elsewhere. The meshes of the subglandular stroma, formed in large part by the hypertrophied nerves, are reduced to narrow clefts filled with lymphocytes. These cells are less numerous as the nerve hyperplasia is more pronounced. There results a relatively clear appearance of the deep region of the mucosa, which I have emphasized in former writings as a probable sign of hyperplasia of the subglandular plexus. Nerve lesions of this kind have no relation to the musculonervous hyperplasia of the submucosa. They may coexist, but the fact that the nerve lesions may be found without submucous hyperplasia shows that they do not depend upon it, in contrast to those which we are about to describe.

Here too the mucosa presents a stroma clear and poor in lymphocytes; but this appearance, instead of being restricted to the subglandular region and due to hypertrophy of its nerve fibers, extends



through the entire thickness of the mucosa. In addition, the stroma seems to be edematous and the enlarged meshes of its reticulum contain abundant fluid poor in free cells.

Often this edematous mucosa is thickened. The crypts are sometimes straight, sometimes sinuous and broadened. In this event their epithelium, as well as that of the appendicular lumen, presents some anomalies, larger, taller and broader cells clearly hypertrophied and hollowed by deeper calices than normal. Argentaffin cells are few (Figs. 12 and 14).

In studying this edematous mucosa as colored with the trichrome stain, an extreme richness of nerves is often observed. These nerves form a large part of the meshes of the reticulum but, in contrast to that which occurs in argentaffin cell nerve hyperplasia they are remarkably slender, containing one, two or at most three neuroglia tubes abreast. In certain specimens the nerves form multiple neuromas, which we shall now consider.

1. In the deeper half of the mucosa, there are diffuse neuromas which occupy large sectors. Their fibers are slender and closely approximated, leaving no room between them for a lymphatic space. Their course is capricious. Often they run more or less parallel and form whorls. These neuromas surround the lower half or lower third of the crypts. Their borders are ill-defined and continuous with the more loosely-meshed plexus of the general mucosa.

2. Circumscribed neuromas, always numerous and of small dimensions, which occupy the middle or the middle and upper region of the mucosa.

(a) The first group (Figs. 9, 10 and 11), consists of small round masses which after staining with the anilin blue trichrome appear as small, round blue spots situated between the tips of contiguous crypts, never between them and the muscularis mucosae. Their diameter averages one and one-half times that of the crypt. Their number may be enormous: I have counted forty in each cross-section of an appendix. They consist of a spherical mass of non-medullated fibers pressed closely together and anastomosing, united to the rest of the plexus of the mucosa by many fibers escaping from its surface. Each fiber of the neuroma is enclosed in a relatively thick collagen sheath, hyaline and fused together, giving the whole mass its blue tint with the trichrome stain. The collagen sheath is permeated by a network of argyrophil fibers (Laidlaw's technique), which are con-

tinuous with the reticulum of the adjacent mucosa. These neuromas never contain ganglion or argentaffin cells.

(b) The second and, in my experience, the most frequent form is situated between the crypts, stretching out parallel to them in the upper three-fourths of the mucosa (Figs. 12, 13, and 14). Some of these tumors are swollen in pendulum form, the pedicle occupying the level of the tips of the crypts while the swollen portion often reaches the superficial epithelium between two glandular orifices. These neuromas may be numerous, twenty-five to thirty per cross-section. Their structure is identical with that of the rounded neuromas just described. Over their entire surface they are continuous with the nerve plexus in the mucosa. In certain specimens their pedicle is in direct continuity with nerves emanating from the hyperplastic plexus of Meissner.

In short, whether diffuse or spherical, elongated or pendulum-shaped, these neuromas appear to be the result of localized hyperplasia of the nerve plexus of the mucosa, a hyperplasia characterized by lengthening of the fibers and the formation of spheres. The fibers remain very slender and are enclosed in relatively thick hyaline collagen sheaths. These neuromas are continuous with the hyperplastic plexus of Meissner of the submucosa. They never contain argentaffin or ganglion cells. Contrary to the argentaffin cell neuromas, which are situated exclusively between the muscularis mucosae and the tips of the crypts, they occupy the interglandular region of the mucosa and extend as far as the basal epithelium lining the lumen of the appendix.\*

#### MUSCULARIS AND AUERBACH'S PLEXUS

Other changes, inconstant but, when they exist, always in combination affect: (1) The muscular coats, especially the circular muscle. The bundles are large and formed of hypertrophied fibers similar to those of the gravid uterus (Fig. 8). This hypertrophy involves even the smooth muscle of the meso-appendix. (2) Auerbach's

\* I should say here that all attempts at silver impregnation of these hyperplastic nerves, those of the mucosa as well as those of the musclonervous complexes, have been futile. Critics will doubtless say, as has already been charged concerning the argentaffin cell neuromas, that I have seen nothing but neurinomatous proliferation. I must reply that, while positive impregnation of neurites has great value, a negative result proves nothing either way, considering the inconstancy of the method, especially for the myenteric sympathetic of the appendix.

plexus itself. The nerves are more voluminous and the ganglion cells are two or three times larger than normal: the filaments ramifying among the muscle bundles are prominent and studded with numerous ganglia.

When an appendix presents all of these hypertrophies and hyperplasias at once, muscular, nervous, vascular and even epithelial, its dimensions may become considerable; its length may attain 12 to 15 cm. and its external diameter 3 cm. Most frequently the length remains normal and the diameter only is increased.

In sections stained by ordinary methods, the most striking features are the size and abundance of the nerves and ganglion cells. In the submucosa the abundant elongated nuclei may be mistaken for nuclei of Remak, whereas a portion of them, usually the larger portion, belongs in reality to the muscle fibers, as shown by the trichrome stain.

#### DISCUSSION

The lesions just described are of frequent occurrence. Not a week passes that my collection is not enriched with two or three specimens of musculonervous hyperplasia of the appendicular submucosa. Only the extreme examples with intramucous neuromas, hypertrophy of Auerbach's plexus and of the muscle coats and gigantism are relatively rare. Study of a large number of specimens shows that these giant appendices do not form an isolated group but that they are connected with the normal appendix by an infinite number of intermediate types. That these latter have not been described hitherto is doubtless due to the universal employment of techniques (hematoxylin and eosin, and Van Gieson), which do not reveal the muscles and nerves of the mucosa with sufficient clearness to strike the attention.

The literature contains a few observations, some of which should be revised in the light of the facts related here. Various authors have described ganglioneuromas, neurofibromatosis, Rankenneuromas, ganglioneuromas with or without gigantism of a given portion of the intestine. The site of the lesions is sometimes the small intestine (Pick, Baltisberger), sometimes the appendix (Heine, Oberndorfer, Schmincke, Schultz). The descriptions of these last four authors, especially that of Oberndorfer, suggest the thought that their specimens might represent musculonervous hyperplasia

carried to the extreme. At my request, Professor Oberndorfer had the kindness to send me some of his preparations. I recognized all of the features which he has described and illustrated so perfectly and my impression is that his giant appendix fits into the category of lesions described in this paper: thickening of the mucosa, lengthening of the crypts with hypertrophy of the cells, enormous diffuse intramucous neuroma, submucosa thickened and containing a gigantic nerve plexus and many muscle bundles, hypertrophy of Auerbach's plexus and thickening of the muscle coat.

At first sight, some details seem to differ from those that I have observed. Thus, in his Figures 37 and 38, Oberndorfer (1929) represents the "nerve" bundles surrounded by ganglion cells. I question if these bundles are really nervous and not muscular, enclosed in a nerve sheath like those in my illustrations. I also question if the "syncytiale Bänder" of his Figure 39 do not relate to muscle rather than to nerve elements or, more exactly, neurinomatous elements. Oberndorfer's stains, (hematoxylin and eosin, and iron hematoxylin) do not permit a definite answer to these questions.

Finally, Oberndorfer notes thickening of the nerves of the meso-appendix. I have observed nothing of this in my specimens, but none of them offers such extraordinary nerve hyperplasia as that of Oberndorfer. Is it not plausible that when pushed to the extreme the nerve hyperplasia may extend beyond the parietal plexus of the appendix and include the nerves of the meso-appendix itself?

In view of the participation of its various constituents in the enlargement of the appendix, Pick concludes that gigantism is "coordinated with" a fault in embryonic development, an excessive and tumoral growth of the local nervous system. For him, as for Oberndorfer, it is a congenital malformation. This view may be valid in certain instances. In my opinion it cannot be applied wholly to those which form the subject of this paper nor, perhaps, to Oberndorfer's specimen. While the influence of an excessive development of the sympathetic nerves on the growth of the other constituents of the appendix appears to me to be plausible enough, there is nothing in the instances cited in this paper to prove that the excessive growth has an embryonic origin. Its constant occurrence after frank crises, its primary situation in Meissner's plexus of the submucosa, its extension to a mucosa impoverished in lymph nodules

and enriched in crypts, then to the muscular coat and, finally, its frequency, seem rather to make of it an acquired lesion. This excessive growth is probably the result of appendicular inflammations, associated on the one hand with nerve regeneration following ulceration and on the other hand with a new growth of the mucous plexus more or less perfectly adapted to the new crypts that have replaced the involuted lymph nodules.

Other studies on the appendix have enabled me to verify the existence of nerve hyperplasias different from those described here, situated in the subglandular portion of the mucous plexus and there only. They are preceded by the migration of cells from the intestinal epithelium into the nerves. After penetrating the nerves these cells become loaded with silver-reducing granules and differentiate in various ways, some taking the form of ganglion cells, others of cells of Remak, while still others, cylindrical or spherical, elaborate fats which they eliminate directly into the nerves. Subsequently these nerves grow, lengthen and broaden to the point of forming neuromas; they are always situated beneath the tips of the crypts and are capable of pushing the muscularis mucosae into the submucosa (Fig. 18).

The epithelial covering of the mucosa often disappears and the lumen of the appendix becomes obliterated. The neuromas survive and even increase in obliterated appendices; they disappear if their argentaffin cells disappear. Their origin and their persistence are thus bound to the presence of these cells just as the existence of nerves of any kind is bound up with the presence of cells.

The impossibility of demonstrating neurites in these "neuromas" by the usual methods of silver impregnation has been urged as an objection to my views, and most writers have concluded that these growths are really neurinomas. In accepting this latter view we should be obliged to admit that the greater part of the nerves of the normal appendicular mucosa do not contain neurites either, because silver impregnations are negative for them also. Is this not placing too great reliance on the most capricious, the least reliable of techniques?

From another viewpoint the proliferation of Schwann cells in authentic neurinomas exhibits remarkable autonomy, but, in the argentaffin cell neuromas, proliferation and persistence of the nerve filaments is controlled by the presence of the cells emigrated from

the intestinal epithelium, just as the existence of nerves is bound up with the presence of the ganglion cells on which they depend. If, then, the hypothesis of the neuron is applicable to these neuromas it is certain that we must seek their trophic centers in the argentaffin cells and not elsewhere.

These observations have led me to the idea of a nervous system peculiar to the intestinal mucosa, of entodermic origin, a neurentoderm, characterized by the presence of ganglionic, neuroglial and secretory cells provided with silver-reducing granules, the neurites of which, indistinguishable by Cajal's methods, mingle with those of the sympathetic and form the plexus of the mucosa. This plexus then would contain two kinds of fibers, the one, centripetal, belonging to the neurentoderm, the other, centrifugal, starting from the sympathetic ganglia and arriving at the intestinal surface. Because of the organogenic analogies of this hypothetical system with the argentaffin cells and the placodic neuro-epithelium of the olfactory mucosa, I have thought that its function might be sensory rather than motor.

However, the conditions described in this paper have a totally different aspect. Meissner's plexus undergoes hyperplasia, either of its fibers only or of its ganglion cells also. There is a corresponding hyperplasia of the muscular mechanisms and of the arteries of the submucosa. At a further stage the hyperplasia involves certain nerve filaments of the mucosa, the centrifugal fibers just pictured which remain slender, lengthen and form superficial neuromas without argentaffin cells. At a still more advanced stage the muscle coat and Auerbach's plexus hypertrophy in their turn. These appendices have no tendency whatever to obliteration. If it occurs it is not the result of regression of the epithelium but of inflammatory ulceration. It is obvious that the site of these hyperplasias is a motor nervous system and the muscles which depend on it, above all the Meissnerian level of the intestinal sympathetic nervous system and the muscular mechanisms of the submucosa.

The neuro-argentaffin hyperplasias on the one hand and the sympathicomuscular hyperplasias on the other may exist in a pure state, which demonstrates their reciprocal independence and the independence of the two systems of nerves from which they arise. They are not incompatible. They may coexist in the same ap-

pendix, either in different regions or associated in the same sector, each preserving its own characteristics (Fig. 19).

Why not, then, admit the existence in the appendix of two groups of nerves, associated, mingled, indistinguishable in the normal state but recognizable under pathological conditions by their isolated or combined hyperplasias? The one is the argentaffin group, the other the myenteric group. Have these two groups distinct origins, as I am inclined to believe, or are they both of sympathetic origin, as stated by most neurologists? New researches will doubtless answer this question.

The significance of the musculonervous complex remains for me quite obscure. It is not easy to understand what mechanical rôle could be played by these contractile bundles buried in the submucosa. Nor is it easy to picture the organogenic processes of which they might be vestiges. They belong exclusively to the appendix. Does not their close association with motor nerves permit us to compare them with the neuromuscular nodes described by Keith in the muscularis of the colon, so little studied since, which play a part in intestinal motility? Still another problem.

#### SUMMARY

The submucosa of the normal appendix contains muscle bundles, continuous on the one hand with those of the circular muscle and on the other hand with those of the muscularis mucosae. These two muscle groups often anastomose in the middle zone of the submucosa. They are in intimate relation with certain parts of Meissner's plexus. Muscle and nerve together form a complex which we may term the musculonervous complex of the appendicular submucosa.

Under influences that we cannot yet define, but connected no doubt with inflammatory crises, the muscle bundles and the nerves become more numerous, acquire more and more intimate relations, and by their accumulation contribute to the thickening of the submucosa. At the same time the arteries enlarge, their muscle coat hypertrophies and the arterial nerves become more prominent.

The mucosa presents certain changes which in the order of frequency are: decrease in number or complete absence of lymph

nodules, scarcity of lymphocytes in the stroma, and diffuse hyperplasia of its nerve plexus, to which may be added more localized hyperplasias in the form of ill-defined neuromas or circumscribed neuromas situated in the middle or upper part of the mucosa. In extreme examples there is in addition hypertrophy or hyperplasia of the muscle coat and of Auerbach's plexus.

To sum up, there is hyperplasia and hypertrophy either of the sympathetic nerves or of the appendicular muscles, or of both, in other words, of the motor apparatus of the appendix, together with atrophy of the lymphoid tissue. This series of lesions seems to begin by the formation of these musculonervous complexes.

I am again indebted to my friend, Dr. George F. Laidlaw, for his kindness in translating this paper.

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## DESCRIPTION OF PLATES

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### PLATE 45

FIG. 1. Appendix removed from an infant of 4 months during an operation for congenital hernia. General view of a sector of the wall. Cross-section. (*m*) mucosa; (*mm*) muscularis mucosae perforated in the center by an arteriole destined for the mucosa and interrupted at the edge of the photograph by a primitive follicle; (*sm*) submucosa; (*c*) circular muscle; (*l*) longitudinal muscle; (*p*) peritoneum.

Note the muscle bundles (gray) anastomosing with those of the circular muscle, which invade the submucosa where they form a plexus continuous with slender muscle bundles emanating from the muscularis mucosae (cut nearly transversely) near the point of penetration of the artery. In the photograph the bundles appear as small gray circles near the broad lymph capillaries. This group of bundles forms a muscle complex. With the magnification employed, the nerves of Meissner's plexus ramifying in their meshes are not visible. This appendix is represented in Fig. 3 in its entirety.



I

Masson

Musculonervous Complex of Appendix

PLATE 46

FIG. 2. Normal appendix from a patient 20 years of age. Above, the deep region of the mucosa rich in lymphoid tissue and bordered by the muscularis mucosae. Below, the circular muscle. Between the two, the submucosa traversed by a muscle bundle which unites the circular muscle and the muscularis mucosae. A Meissnerian nerve (black) accompanies it and winds around it. In this section it is visible only in the external portion of its course, but in serial sections it may be followed as far as the neighborhood of the muscularis mucosae where it ceases to be impregnated by the silver.

This musculonervous complex is typical in its simplicity but infrequent. A complete section of this appendix is represented in Fig. 4.



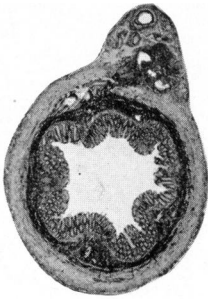
PLATE 47

All the appendices represented in this Plate have been photographed with the same magnification in order to show the differences between normal appendices and those affected by hyperplasia of the musculonervous complex of the submucosa.

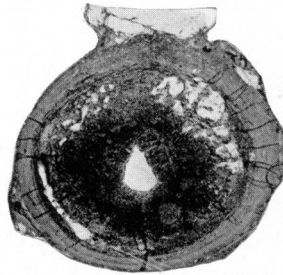
FIG. 3. Infant of 4 months (see Fig. 1). Broad lumen, mucosa rich in crypts and poor in lymphoid follicles, submucosa thin, muscle coat thin.

FIG. 4. Male, 20 years of age (see Fig. 2). Lumen relatively narrow, mucosa rich in lymphoid tissue, submucosa thicker, muscle coat scarcely thicker than in the infant.

FIGS. 5, 6 and 7. Different degrees of hyperplasia of the musculonervous complex of the submucosa. Lumen narrow, mucosa rich in crypts, poor in follicles (6) or deprived of follicles (5 and 7). Muscularis mucosae continuous and thickened. Enormous thickening of the submucosa which splits incompletely into two concentric layers. Thickening of the muscle coat.



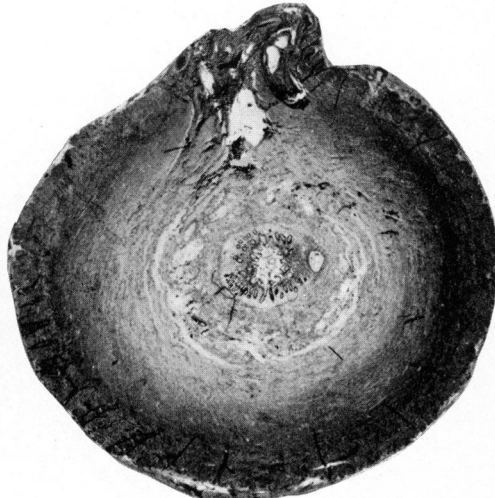
3



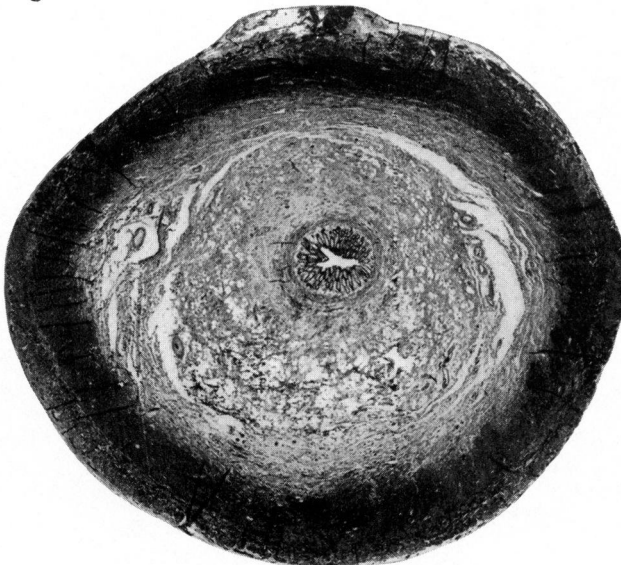
4



5



6



7

PLATE 48

FIG. 8. Appendix of Fig. 6 enlarged. (Obs. 126 M.) Trichrome.

Mucosa rich in crypts, the stroma clear, edematous, poor in lymphocytes. There are no intramucous neuromas in this specimen. Muscularis mucosae thickened. Submucosa enormous, crowded with muscle bundles in the interstices of which the connective tissue (black) is scanty. In the middle zone of this submucosa may be seen arterioles with hypertrophied walls.

Circular muscle greatly hypertrophied. No interstitial sclerosis. Its limits on the side of the submucosa are indistinct on account of the many muscle bundles that escape to form the hyperplastic muscle complex of the submucosa. Longitudinal muscle coat scarcely thickened. Peritoneum thin.



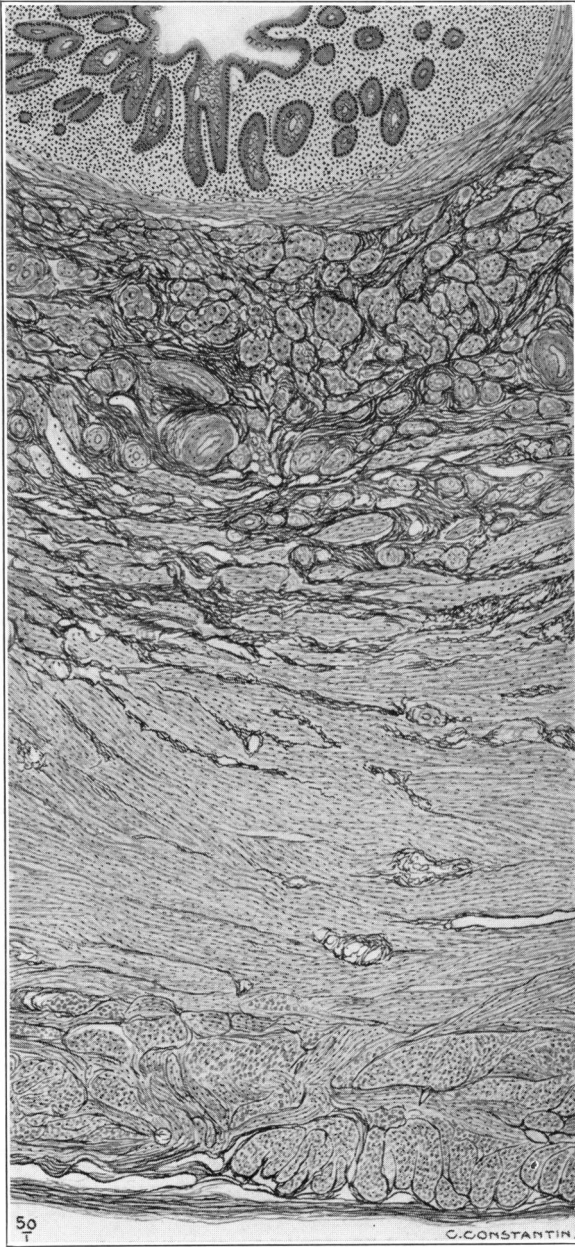


PLATE 49

FIG. 9. (Obs. 142 M.) Trichrome.

General view of a mucosa containing many spherical neuromas. Thirty may be counted in the figure. One of them is represented at a higher magnification in the corner of the figure.

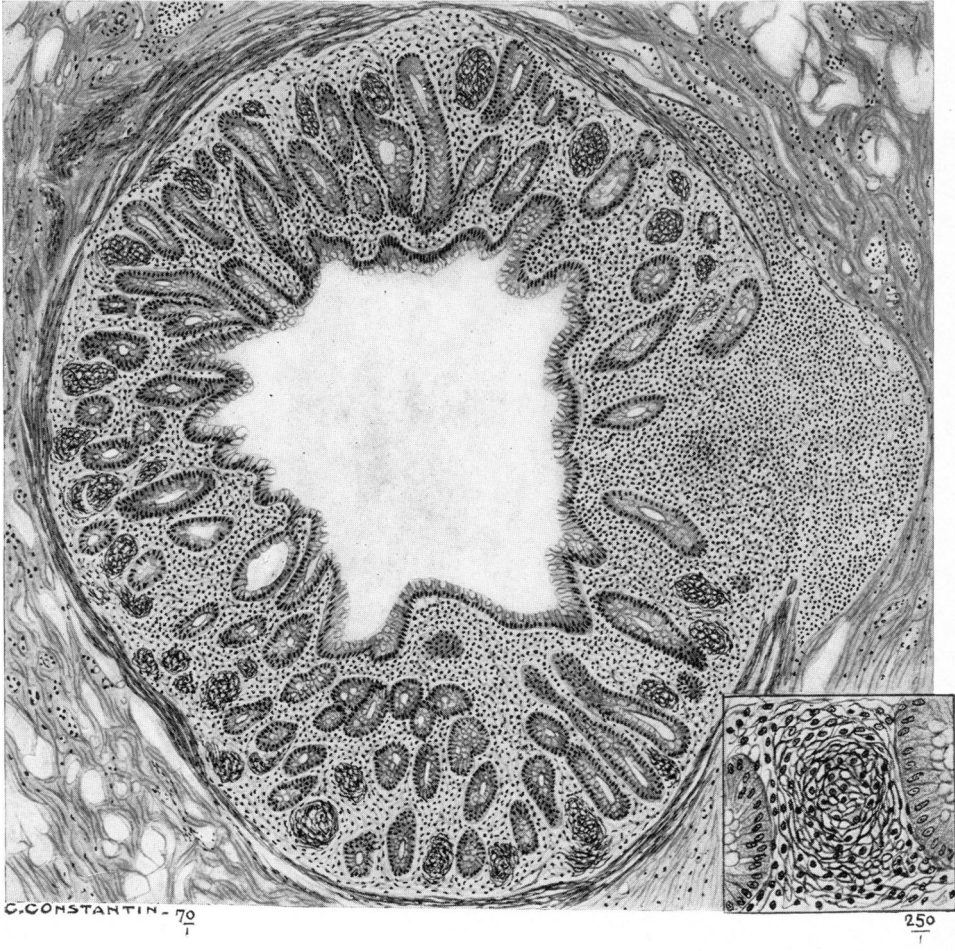


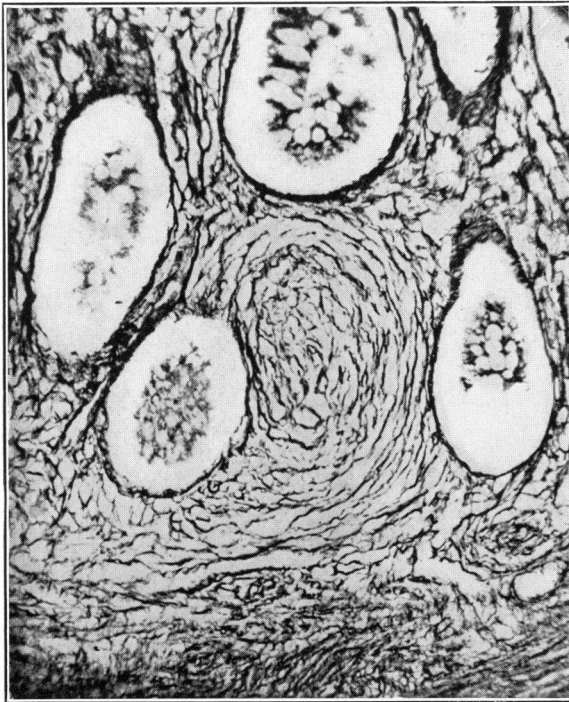
PLATE 50

FIGS. 10 and 11. (Obs. 142 M.) Laidlaw's silver technique.

The reticulin which surrounds the nerve fibers is continuous with that of the stroma of the mucosa: it leaves the fibers colorless while outlining the contours clearly.



10



11

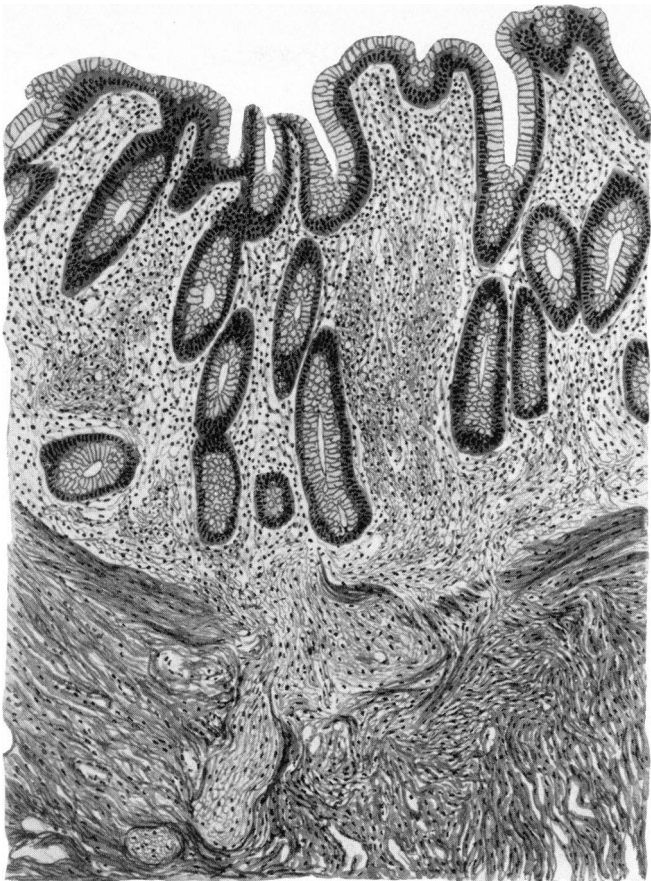
PLATE 51

FIG. 12. Same case as that of the general view, Fig. 7. (Obs. 68 M.) Trichrome.

Intramucous neuromas in pendulum form. Mucosa thickened, edematous. Crypts large and tortuous. Between them are two elongated neuromas connected by their bases with a diffuse neuroma which dissociates the muscularis mucosae and continues as a very broad Meissnerian nerve. The submucosa is traversed by innumerable nerve filaments invisible with this magnification.

FIG. 13. (Obs. 68 M.) Laidlaw's silver technique.

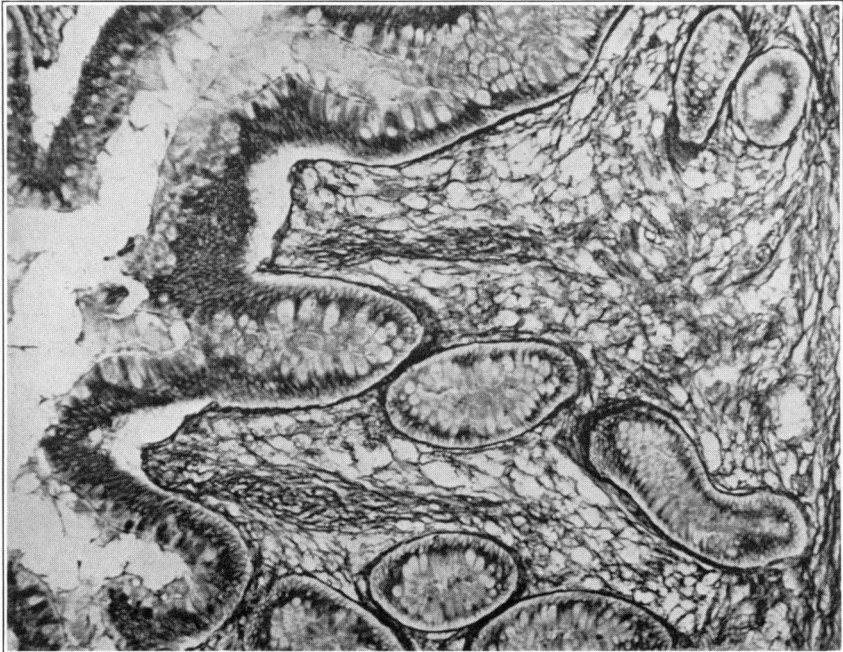
Two neuromas in pendulum form, their summits reaching the basal epithelium of the appendix. Here again only the contours of the nerve fibers are outlined by the reticulin which is continuous with that of the stroma.



90  
7

J.C. CONSTANTIN

12



13

PLATE 52

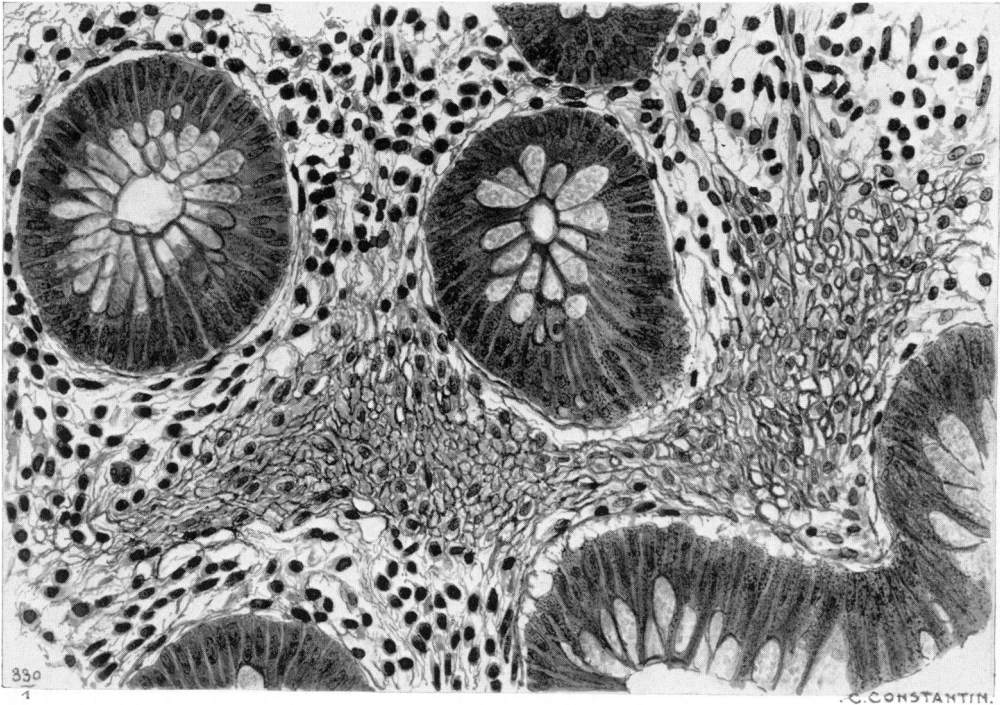
FIG. 14. (Obs. 68 M.) Trichrome.

Section of the mucosa near the surface and almost parallel to it. Note the considerable hypertrophy of the epithelial cells. Between them is a neuroma cut through the swollen portion. Note its irregular form, its compact texture, the thickness of the collagen sheath around each nerve fiber, the relative pallor of the nuclei of Remak and the continuity of these fibers with those which form an important part of the reticulated framework of the adjoining stroma.

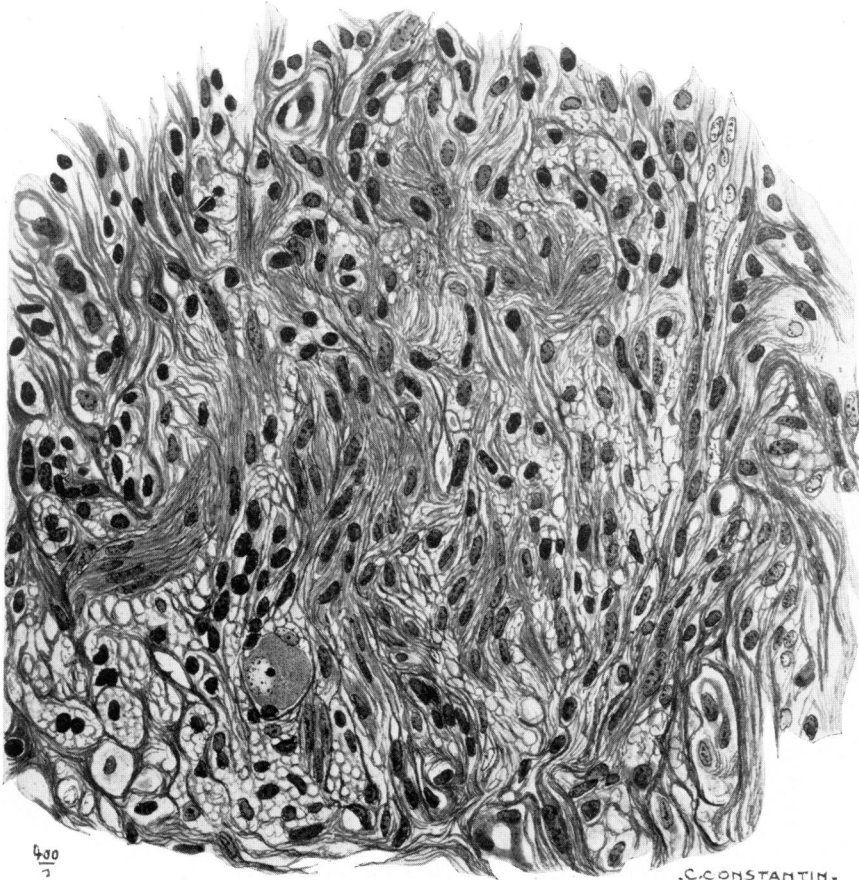
FIG. 15. (Obs. 126 M.) Trichrome.

Hyperplasia of the musculonervous complex of the submucosa. Submucosa in the neighborhood of the muscularis mucosae. Confused interweaving of non-medullated nerve fibers recognizable by their spongy aspect, and muscle fibers oriented in every direction and sketching here and there small bundles. Fine nerve fibers are seen in the interstices between the muscle cells. A ganglion cell.





14



15

PLATE 53

FIG. 16. (Obs. 126 M.) Trichrome.

Submucosa in the vicinity of the circular muscle. A muscle bundle in a longitudinal direction in the neighborhood of a bifurcation. This bundle is surrounded by a continuous nerve sheath of longitudinal fibers. A large ganglion cell in the nerve sheath.

FIG. 17. (Obs. 126 M.) Trichrome.

The same musculonervous bundle after its bifurcation. Each branch has its own nerve sheath. A small sympathetic ganglion in the nerve sheath.

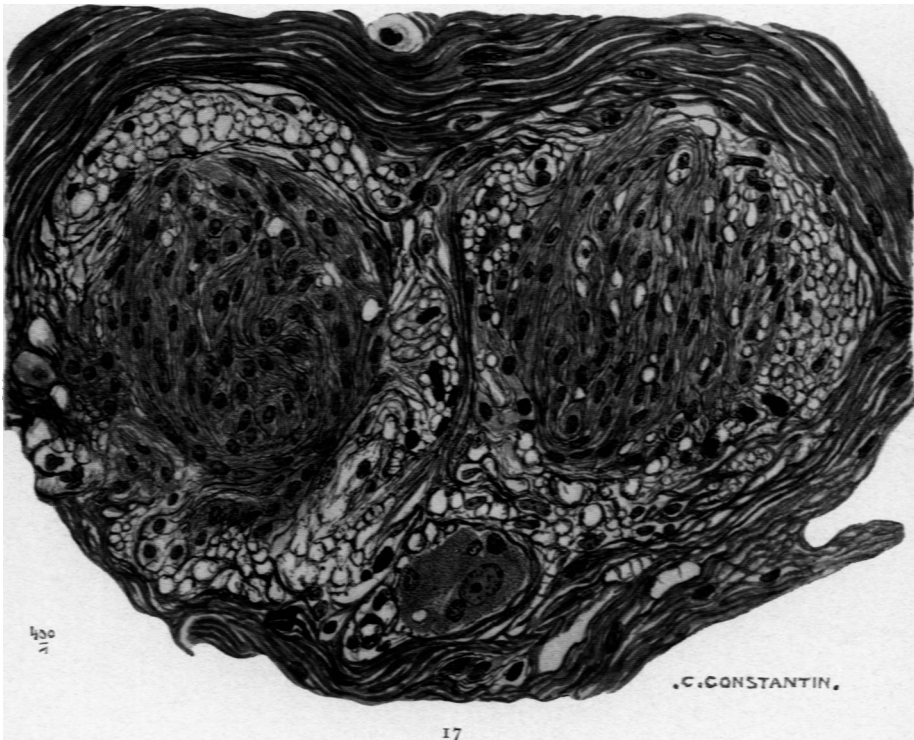
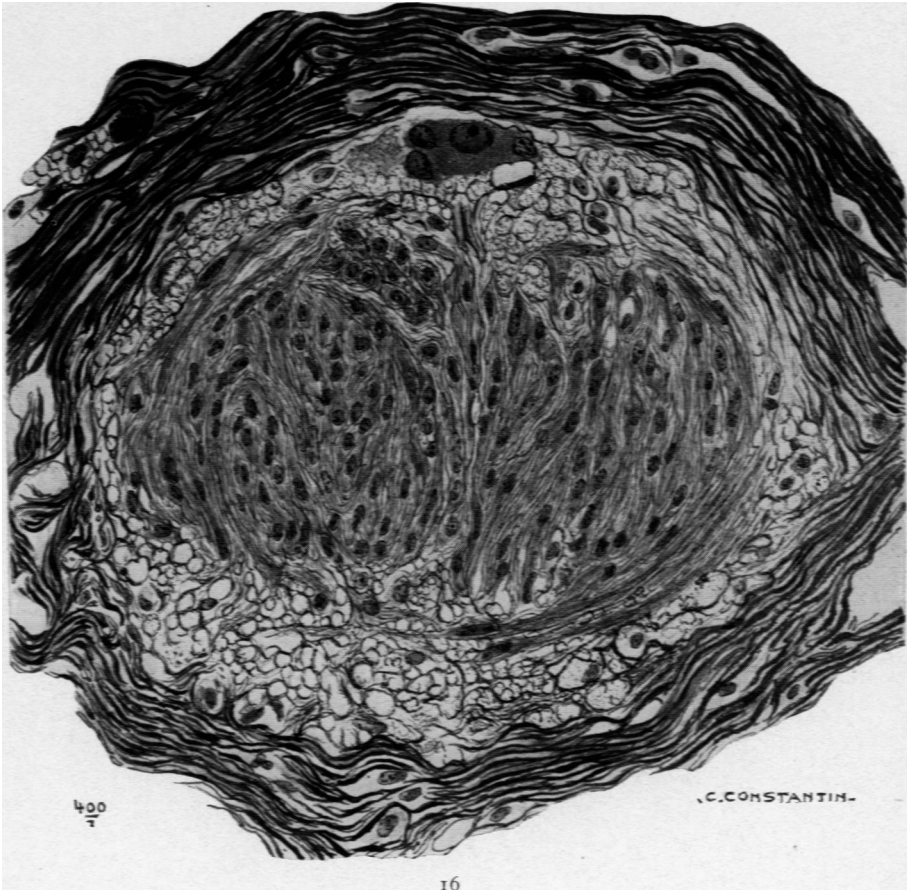


PLATE 54

FIG. 18. (Obs. 118 M.) Trichrome.

Intramucous argentaffin cell neuroma forming a clear mass between the tips of the crypts and the muscularis mucosae which is crowded into the submucosa.



PLATE 55

FIG. 19. (Obs. 126 M.) Trichrome.

Association in the same region of the mucosa of a small, argentaffin cell neuroma (above), developed between the tips of the crypts and the bulging muscularis mucosae, and a pendulum-shaped neuroma connected with hyperplasia of the musclonervous complex of the submucosa (below).

