

Some Nervous Lesions of the Vermiform Appendix

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THE existence of very thickened patches in the wall of the appendix is a well-known fact to all pathologists. Very often, in describing post-acute appendicitic lesions, they speak of cicatricial sclerosis of the submucosa invading the muscular walls and dissociating its bundles, so that many of them appear to lose themselves in the fibrous connective tissue of the submucosa. No doubt, some of these phenomena can be explained as post-inflammatory changes; but a great many of them are definitely non-inflammatory in origin. This non-inflammatory hypertrophy led Masson and his co-workers to make an exhaustive study of the appendix, normal and pathological. In 1924 he evolved the idea of a submucous musculonervous complex in the appendix, which by its variations caused marked changes in that organ, always of the same character, and often affecting the muscosal and muscular coats.

Even in the appendix of the newborn with no evidence of inflammation one sees small muscle bundles leaving the circular muscle layer and running centrally into the submucosa. At the same time, some fibres are seen leaving the thin muscularis mucosae and anastomosing with the other oblique muscle layer in the submucosa. This thin sheet of muscle has been designated by Masson as the *muscular complex* of the submucosa. It has been noticed that arterioles travelling to the submucosa are always accompanied by muscle bundles from the muscularis mucosa, and that Meissnerian nerves are always present between the bundles of a complex.

In the adolescent appendix where one finds a great increase in lymphoid tissue the muscularis mucosae is deficient or entirely lacking, but we can still make out little bundles emanating from the muscular layer and travelling centrally in the submucosa. After some attacks of appendicitis, there may be a disappearance of the lymph follicles and one can then distinguish these complexes quite readily.

In the study of adult appendices, one is confronted with many types. In the appendices with numerous lymph follicles one finds the muscular complexes only in the parts underlying the crypts, where the lymphoid tissue is absent or rarefied. Then there are the appendices which probably have had one or more attacks of appendicitis, and there is a decrease in the number of lymph follicles. Here the complexes are more in evidence, not because of any increase in number, but because of their greater size and the greater number of Meissnerian nerves mingled with them. Lastly, there are the appendices almost wholly denuded of lymph follicles, and usually with histories of repeated attacks of appendicitis. These are somewhat larger than the normal appendix, and have enormously thickened walls, with a very small lumen.

The changes met with in this last type are so striking that they merit some further discussion. A. The mucosa may show nothing further than an extreme dearth of lymph follicles, and may not contain an excessive number of nerves. The stroma is oedematous and thickened. Often, however, one notices a great increase in the nerves of the region. These nerves are very thin, containing one to four neuroglial fibres abreast, as contrasted with the argentaffin cell hyperplasia to be described later. Sometimes these nerves form multiple neuromata of the following types:

1. In the deeper part of the mucosa, one may see large neuromata with thin, closely approximated fibres. They run more or less parallel and often form whorls, around the lower half of the crypts. Their borders are ill-defined and continuous with the plexus of the mucosa.

2. In the middle of the mucosa numerous small circumscribed neuromata present light blue spots (with trichrome stain) located between contiguous crypts. These may be divided into two types:

- a. One group consists of many anastomosing non-medullated fibres pressed closely together. Each fibre of the tumor is enclosed in a thick collagen sheath, which is pierced by many fibres which are continuous with the mucosal reticulum.

- b. Little pendulum-shaped neuromata stretch between two contiguous crypts. These are similar to the rounded neuromata mentioned above, and often one can detect the continuity of their pedicle with Meissnerian nerves. They never contain argentaffin or ganglion cells.

B. It is in the *submucosa* that one detects the most prominent changes. This layer becomes greatly thickened and very fibrous. The muscular mechanism and Meissner's Plexus become very prominent. The nerves of the muscular mechanism, studded with tiny ganglia, run among the muscle bundles and come into intimate contact with the individual fibres. In the inner half of the submucosa are many muscle bundles, running parallel to and frequently connecting the muscularis mucosae with the circular muscle. The interstices of this plexus are crowded by many nerve fibres containing numerous ganglion cells, and arteries going to the mucosa. In many cases, the strands coming off the circular muscle and running in a longitudinal direction are separated from the submucosal connective tissue by a continuous sheath of non-myelinated nerve fibres, possessing some small sympathetic ganglion cells. In addition to these neuro-muscular changes, the arteries show hypertrophy of their walls, enlargement of their lumina, and an increase in their nerve supply.

C. *Muscularis and Auerbach's Plexus*—The circular muscle coat shows some hypertrophy, as does Auerbach's Plexus.

These lesions do not form an isolated group but really can be shown to be related to the normal appendix by many intermediate types. The gigantism often found in these appendices has been ascribed to various causes. Many authors have described ganglioneuromas, neurofibromas, Rankenneuromas, and neurinomas; but Rossle is inclined to believe it a mere work hyperplasia, due to the appendix undergoing powerful contractions to rid itself of some foreign substance, and he would thus regard

the musculonervous mechanism as the motor apparatus of the appendix. Pick and Oberndorfer, on the other hand, view these submucous neuromata as congenital malformations. Masson, while agreeing with the latter in part, is of the opinion that most of them are acquired lesions, probably associated with inflammation and involving nerve regeneration following ulceration, plus a new growth of the mucous plexus adapted to the new crypts which have replaced the lymph nodules.

There is still another type of nerve hyperplasia in the appendix, which occurs in the subglandular portion of the mucous plexus. These growths were first reported by Masson and Maresch, who found neuromatous tumors in obliterated appendixes and at first believed them to be of the nature of amputation neuromata. They thought the tumours were caused by a division of the sympathetic nerves of the mucosa by an ulcerative process, or by injury to the nerves, by an inflammatory process. One year after the appearance of their paper Schweizer described them again, but thought they were analogous to the neurinomas of Verrey (Schwannoma). At a later date, however, Masson disproved this "neurinoma" theory by pointing out these tumours really arose from the Kultschitzky cells (chromaffin, entero-chrome argentaffin cells) of the appendiceal mucosa, and did not possess the characteristics of the authentic neurinomas of Verrey. Much of the discussion as to the character of these tumours has arisen from difficulties encountered in staining them. Using the ordinary silver stains (Cajal, etc.) one is very often unable to stain these nerve fibres, but Masson is of the opinion that silver impregnation is at best a very "capricious and the least reliable of all techniques", and he points out that he has been able to detect these argentaffin cell neuromata using his trichrome stain when others have failed with their silver impregnation methods.

These argentaffin cells occur to some extent throughout the whole gastro-intestinal tract, but the great majority of them are found in the appendix and the distal portion of the small intestine. They may be seen chiefly (1) at the bases of the crypts of Lieberkuhn and (2) in the periglandular plexus of nerves. The glandular argentaffin cells are scattered among the columnar cells lining the glands of the mucosa, 90% being found at the bottom of the crypts. These cells are usually shorter and wider than the epithelial cells lining the glands. Their cytoplasm is clear and homogenous, but it contains many granules (usually at the basal portion of the cell) which reduce silver.

As regards the periglandular type of argentaffin cell, Masson distinguishes four types.

(1) *Neurocrine cell*—these cells are usually polygonal or rounded in shape, with a granular cytoplasm which contains lipoids. The granules here may be bi-polar in arrangement.

(2) *Schwannian cell*—the nucleus of this cell is enclosed in a neuroglial syncytium and the cytoplasm contains but few granules.

(3) *Ganglion cell*—this cell has the clear contour of a ganglion cell, with a vesicular nucleus and rounded nucleoli.

(4) *Intestinal cells*—these are cylindrical or cuboidal cells arranged in rosette fashion around a cavity filled with a substance of colloid appearance; only their basal portion contains cytoplasm. Other workers have been unable to detect these “gland-like” cells and there is some doubt as to their nature.

Masson, in a study of obliterated appendices, finds a constant prominent muscular sheath in the axial connective tissue, formed by the persistence of the smooth muscle fibres of the muscularis mucosae. Inside this sheath there are always large non-medullated nerves, often clustered together to form neuromata nerves which are accompanied by cells whose protoplasm is dotted with argentaffin granules. These cells appear to have migrated into the nerves, while epithelium was still intact, in the following way:

The process is supposed to be initiated by a “budding” of the “indifferent cells” at the tip of Lieberkuhn’s glands. The nuclei of these cells divide amitotically and arrange themselves in several layers at various parts of the cell. The basal ends of two or three adjoining cells now elongate, unite to form a projection which pushes before it and then bursts through the basement membrane, and at last finds itself in contact with a nerve filament of the periglandular plexus. Several nuclei may now migrate into the bud which buries itself in the nerve. If it grows, it becomes rounded and remains for a time attached to the tip of the gland by a pedicle. At about this time, the appearance of the cell undergoes some change—the nucleus become bigger and the chromatin becomes finely reticulated. Soon the cells become cut off from the gland and they send their projections into the nerve sheaths. After their separation from the intestinal epithelium these argentaffin cells may remain near the gland; but more often they migrate into the filaments of the subglandular plexus and burrow deeper into the mucosa. This is usually preceded by a disintegration of the bud, the individual cells insinuating themselves between the nerve-fibres. Occasionally, when the budding has been very active, the argentaffin cells pile up as if they had been obstructed in their passage, and form rosettes with a lipoid substance in the center.

The presence of argentaffin cells in the nervous plexus causes a hyperplasia of the nerves. This process may involve the subglandular plexus, or may remain localized to form a small neuroma growing down to the muscularis mucosae and even pushing it aside. Using the trichrome stain, one sees the neuromata as strands of non-medullated nerve fibres or as red islands of compact interlacing bundles in a field of deep blue. As mentioned above, they rarely break through the muscularis mucosae and are often connected to each other by many nerve strands. These neuromata may survive and even increase in obliterated appendices; but they recede with the disappearance of the argentaffin cells.

In permeable appendices, neuromata are formed in a similar manner, often from the periglandular nerve plexus. The nerves then become broadened, hypertrophied, and increased in number. They are often

multiple, situated beneath the gland tubules, and are connected with Meissner's Plexus.

In certain cases, the argentaffin cells continue to multiply, invade the different nerve plexuses, then the muscle coats, and the connective tissue, at the same time collecting a comparatively thick muscular stroma, thus forming the "Carcinoid tumour" of the appendix.

These neuro-muscular and neuro-argentaffin hyperplasias may coexist, the appendices often showing argentaffinomas in the mucosa together with submucous neuromata. But on the other hand, each may exist independent of the other.

Clinical Significance:

Simard of Montreal, includes the following under the term "Neuro-appendicopathy":

- (1) muscosal nerve hyperplasia containing numerous argentaffin cells.
- (2) mucosal neuromas containing a few argentaffin cells.
- (3) axial neuromas in obliterated appendices.
- (4) musculo-nervous hyperplasia, with or without mucosal neuromas.
- (5) combined argentaffin cell and sympathetic nerve tissue hyperplasia.

This author points out that 51.77% of "chronic appendicitis" cases show nervous lesions, and the percentage of neuromas in obliterated appendices is as high as 87-88%. Hosoi of New Orleans finds that 86% of obliterated appendices show neuromata. Simard also reports that 9.27% of "acute appendicitis" cases show only these nervous changes without any evidence of inflammation.

These nervous lesions may not be the only cause of symptoms, but their constant presence with appendicitic attacks leads one to believe that they have some bearing on the symptomatology of the "appendicitis syndrome", and perhaps even in obscure right-sided pelvic pain in women. According to Hosoi, these lesions may simulate acute appendicitis, acute exacerbation of chronic appendicitis, or chronic appendicitis. Simard states that where the clinical signs and symptoms point to acute appendicitis but where the leucocyte count is near normal and disease of the kidney, ovary or bladder can be excluded, the diagnosis of neuro-appendicopathy can be made with some degree of certainty.

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"Are you ever short of wind?" inquired the physician engaged in examining the patient's chest.

"Oh, no, doctor," was the reply, "I pass lots of wind."