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THE PATHOLOGY AND PATHOGENESIS OF DIABETIC NEUROPATHY*

C. L. DOLMAN

Pathologist, Vancouver General Hospital
Clinical Associate Professor of Pathology
University of British Columbia
Vancouver, Canada

THE earliest accounts of the pathology of diabetic neuropathy go back to the turn of the century when Auché[1] and Fraser and Bruce[2] described degeneration of the peripheral nerves, and Pryce,[3] Leichtentritt,[4] and Williamson[5] described demyelination and gliosis of the dorsal columns of the spinal cord in diabetics. In 1929, in an often quoted article, Woltman and Wilder[6] published their findings in 10 cases of diabetic neuropathy (4 postmortems and 6 amputated limbs), and summarized the literature. Subsequently only sporadic case reports appeared, until the last decade, when several systematic investigations of the lesions were attempted, with the particular objective of elucidating the pathogenesis.[7-10] Newer tools such as the electron microscope, which are just beginning to be applied in this field, are hampered by the difficulty of obtaining suitable biopsy specimens. A full review of the whole subject of diabetic neuropathy with 206 references was published last year by Colby.[11]

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First I propose to discuss the lesions on an anatomical basis in the light of my own observations and of reports from the literature. Then I shall review current hypotheses bearing on the pathogenesis of these lesions. Let me here interject that, in order to appraise the whole picture, it is necessary to integrate the experiences of many authors. The fact that one worker has not been able to find lesions of a kind noted by another does not necessarily refute the latter's claim, but is more likely due to the chance selection of material, or sometimes to the methods of study.

The Lesions

Brain. There is no specific encephalopathy. Diabetics are often hypertensive and tend to have severe atheroma. They are therefore more prone to suffer cerebral infarcts and hemorrhages, and to do so at an earlier age than the average person. These lesions do not differ in any respect from those incurred by nondiabetic subjects and therefore need not be discussed further.

Cranial nerves. The majority of the cranial nerves have shown dysfunction clinically. Unfortunately, pathological observations are almost nonexistent. I have never seen any lesions myself. The only relevant pathological report in the literature is by Dreyfus *et al.*[12] In a patient who died during an attack of oculomotor paralysis, one of the third nerves showed a fusiform swelling with destruction of myelin sheaths and axis cylinders, and retrograde changes in the proximal portions of the nerve and its nucleus.

Spinal cord. The spinal cord, like the brain, may be the seat of infarcts due to vascular insufficiency. An example of this change was described by Ellenberg and Krainer.[13] The spinal cord may also undergo a variety of more specific degenerations, of which the most frequently encountered involves the dorsal columns. As already noted, this was one of the earliest to be described pathologically. It is probably the form that gives rise to the clinical picture of pseudotabes. In the majority of such cases the most extensive damage is found in the lumbosacral region where the dorsal columns, with the exception of the funiculi proprii, are diffusely demyelinated. This degeneration either does not rise to higher levels or is confined there to the funiculi graciles. Occasionally the upper segments of the cord are selectively affected. In some such instances, the changes undoubtedly represent a

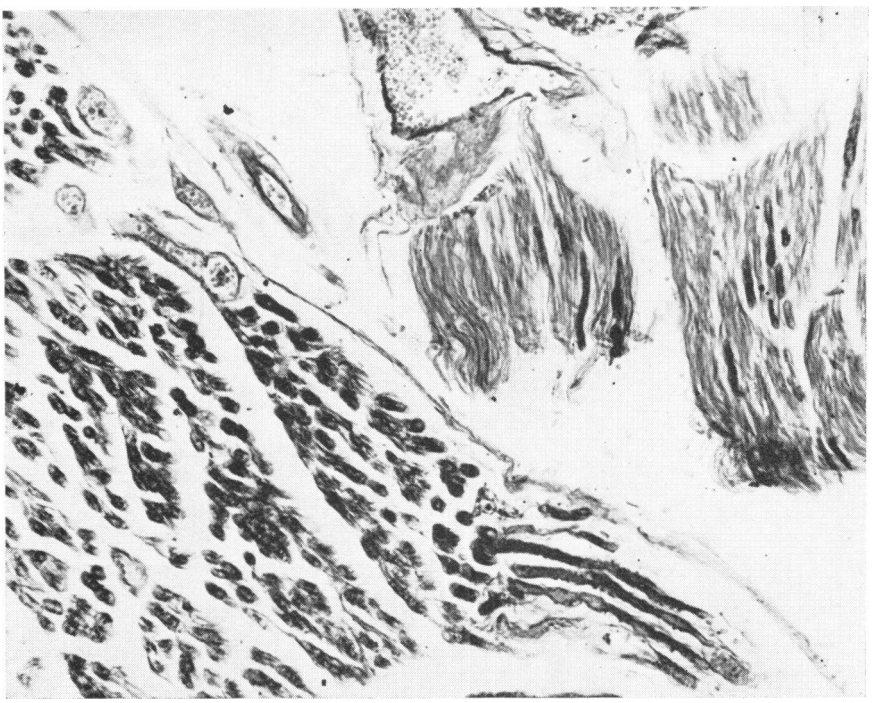

Fig. 1. Severely demyelinated posterior roots to right, in contrast to fully myelinated anterior root at left. The intraneural vessels are normal in both. Luxol-fast-blue—periodic acid Schiff. ×167.

Wallerian degeneration from foci of myelomalacia below; in others, they appear to be primary lesions. In the portion of the dorsal columns involved, myelin sheaths are lost as well as, to a lesser extent, axis cylinders. Frequently large numbers of fine unmyelinated axons persist. The process must be a slow one since, in contrast to what is found in infarcts, macrophages and catabolic products are usually absent; but in severe cases astrocytes proliferate and fibrous gliosis results.

The dorsal roots not only participate in this process but are often more severely demyelinated. Axis cylinders again are less affected. Occasionally, fibrosis has been noted, but it is usually not prominent. The severely demyelinated dorsal roots may provide a striking contrast to the normal anterior roots (Figure 1). The dorsal horns are normal. In the dorsal root ganglia, various degenerative changes varying from peripheral vacuolization to complete dissolution of neurons has been reported, with resultant loss of axons and proliferation of the capsule cells. These lesions are minor and they are greatly overshadowed by the root lesions.

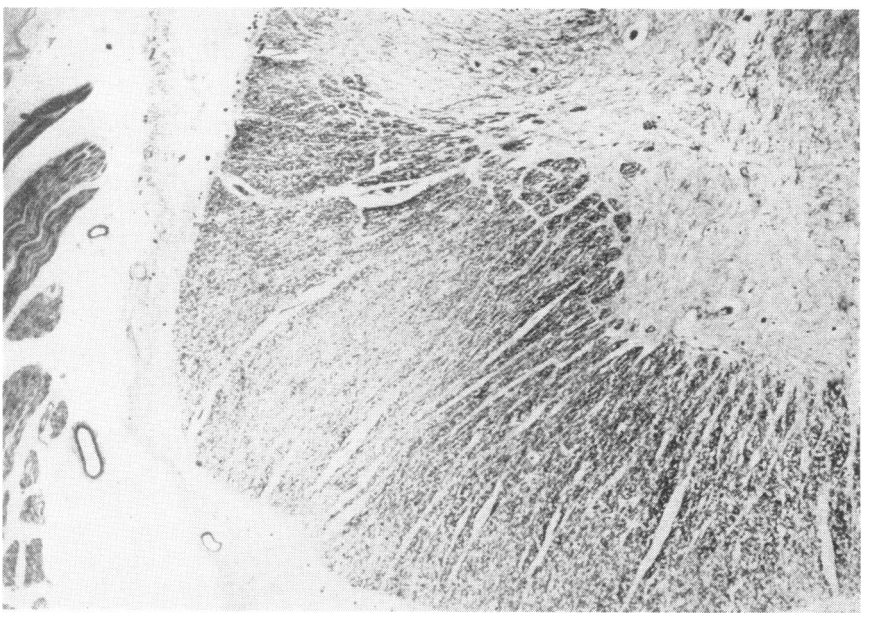

Fig. 2. Spinal cord. Degeneration of lateral column. This was bilaterally symmetrical and combined with degeneration of the dorsal columns. Luxol-fast-blue—periodic acid Schiff. ×34.

Less common than dorsal column degeneration is dorsolateral sclerosis of the cord.[14] The pathological features here are identical with those in the dorsal columns (Figure 2). Causes other than diabetes for the degeneration have not always been excluded with certainty.

Diabetic amyotrophy has formed the basis of many clinical investigations. One of the chief authors in this field is Garland, who considered initially that at least part of the lesion was situated in the spinal cord.[15] Marked loss of ventral horn cells has indeed been reported in one instance,[9] but usually only the occasional nerve cell is lost or may show an axon reaction.[8,16]

Peripheral nerves. The most frequently noted and severest damage is found in the peripheral nerves. The lesions are usually fairly symmetrical, are often most extensive in the distal portions, and particularly affect the sciatic nerves and their branches. The descriptions and interpretations of these lesions have varied. For example, Greenbaum *et al.*[9] felt that large fibers suffered most and that axons degenerated to the same degree as myelin sheaths, and concluded that the process was essentially a primary neuronal degeneration. My own observations led me to believe that patchy demyelination was the major feature, although

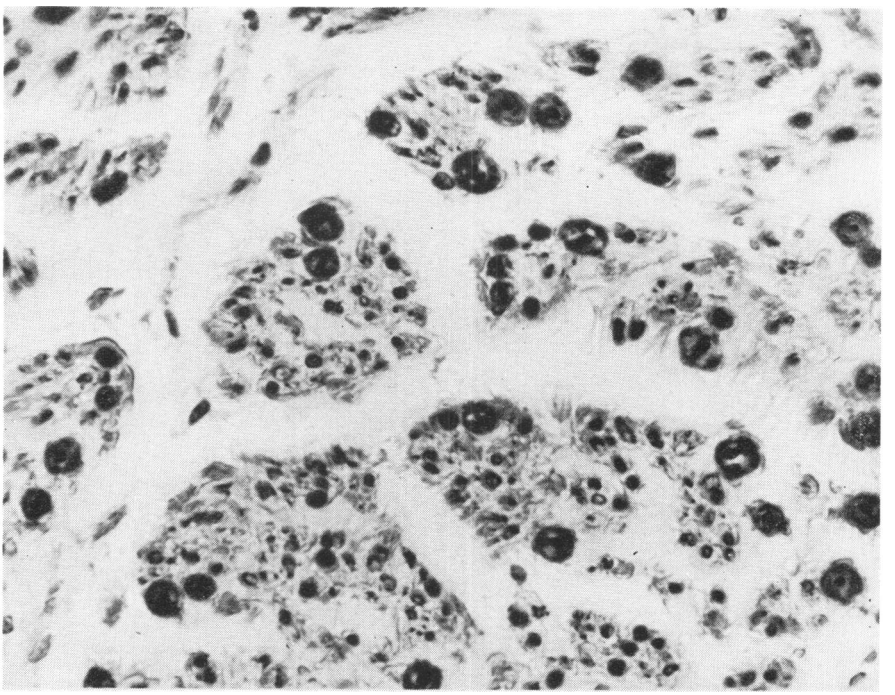

Fig. 3. Sciatic nerve. Naked axis cylinders persist between large and smaller myelinated fibers. Luxol-fast-blue—Holmes. ×585.

undeniably axons also were lost (Figure 3). Thomas and Lascelles[10,17] confirmed this claim by finding segmental demyelination and remyelination in teased-out isolated fibers of diabetic sural and radial nerves. In a few fibers, axonal degeneration had occurred. Many fibers, however, were intact and showed only myelin loss, some only at the nodes of Ranvier, others over one or more internodal segments. Frequently the internodal lengths were shortened.

Electron microscopic studies by Sarah Luse[18] also demonstrated focal segmental demyelination. In addition to this, Luse observed loss of unmyelinated axons, revealed by an accordionlike folding of the Schwann cytoplasm after disappearance of the "C" fibers. Peripheral nerve conduction studies tend to support the importance of demyelinization in diabetic neuropathy.[19] The presence of motor fiber degeneration was established by means of the intravital methylene blue technique by Woolf and Malins,[20] who noted transformation of the normal petaled, flowerlike terminal arborizations of motor end plates into single "balloons" and "soap bubbles." Further, Coërs and Hildebrand[21] found

marked collateral sprouting of motor fibers in both diabetics and alcoholics, the sprouting being a regenerative phenomenon after axonal damage. Schwannian proliferation, sometimes very marked, accompanies the degeneration of nerves, while true fibrosis is seen less often.

Autonomic nervous system. The autonomic nervous system, which is clinically so often severely affected in diabetes, is unfortunately a difficult field to investigate pathologically. Berge[22] examined postmortem bowel specimens and was unable to notice any difference between the ganglion cells and vessels of three groups of patients—diabetics with diarrhea, diabetics without diarrhea, and normal controls. In a recent peroral jejunal biopsy studied with the electron microscope,[23] the vessels were reported as normal, but no mention was made of the nerves and ganglion cells. In my own series of 20 sympathetic trunks and ganglia, I was not convinced of any definite pathological changes.[8] However, Appenzeller and Richardson[24] recently described giant neurons, about twice the normal size, exhibiting severe degenerative changes and even dissolution in the sympathetic ganglia of four out of five diabetics and three out of four alcoholics. These cells did not display the conventional axon reaction. No lesions were seen in postganglionic fibers. Such observations are difficult to interpret since, according to Herzog,[25] swelling and degenerative changes in the neurons of sympathetic ganglia are found not only in a great variety of diseases, but are encountered occasionally in ganglia of apparently healthy subjects. Further studies are needed, and it is hoped that electron microscopic examination of surgically excised sympathetic ganglia and of postganglionic fibers may shed some light on this field.

Muscles. Small foci of typical neurogenic atrophy are often seen in the muscles, particularly of the foot and leg, of diabetics. These exceed in frequency those found in normal controls and tend to occur at an earlier age. Clinically, weakness and atrophy have often been most pronounced in proximal muscles, particularly in the thighs, and in the pelvic and shoulder girdles.[15, 26, 27] But Feller and Szyrynski[28] described 14 patients with distal muscle involvement, often in the hands, and Ellenberg[29] had previously reported a similar case. Locke *et al.*[27] studied 17 biopsies of muscles of diabetics. They drew attention to "single fiber atrophy"—i.e., single small fibers scattered among healthy ones—that preceded the usual unit pattern of neurogenic atrophy (Figure 4). This placed the lesion at the level of the single fiber and its end plate.

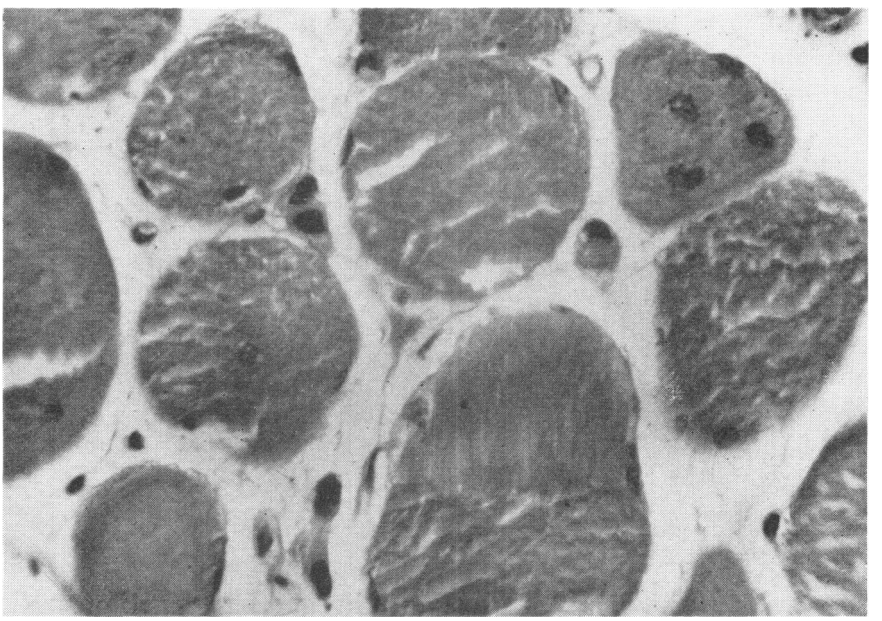

Fig. 4. Muscle. Small atrophic fibers lie between large normal ones. One fiber contains several central nuclei. Hematoxylin and eosin. ×585.

Coërs and Hildebrand[21] emphasized that this single fiber atrophy, which they also found in alcoholics, is not myopathic, but is due to degeneration of single terminal motor fibers that later spreads to the main axon and results in the familiar picture of neurogenic atrophy. Many so-called myopathic features, such as swelling and centralization of nuclei, are undoubtedly characteristic of the early phases of neurogenic atrophy.

Joints. Charcot joints, particularly affecting the tarsal and proximal metatarsal joints, but occasionally the ankles, knees, and spine, may be a troublesome complication of diabetes. In x-ray studies of one series,[30] the overgrowth of bone has been notably absent, but in other cases studied histologically, fibrosis, granulation tissue, and overgrowth of bone were present, sometimes to a very marked degree.[31-33]

Summary of pathological changes. Except for obvious vascular accidents, the most commonly encountered lesions are degeneration of the peripheral nerves, with segmental demyelination, some loss of axons (probably both "A" and "C" fibers), and degeneration of terminal motor axons and end plates. The cell body takes comparatively little part in this process. Demyelination of sensory roots and tract degen-

eration may occur in the spinal cord, mainly in the dorsal columns, sometimes as combined dorsolateral sclerosis. Denervation phenomena are found in joints and muscles.

Pathogenesis

The hypotheses about the pathogenesis of diabetic neuropathy can be divided into two broad groups; one postulates an underlying angiopathy and the other a metabolic defect.

Diabetics have always been known as subject to severe premature arteriosclerosis. Woltman and Wilder,[6] who found marked sclerotic changes in the leg arteries of all their cases, attributed the lesions in the nerves to vascular insufficiency. Objections were raised to this conclusion on the grounds that neuropathy may exist in the absence of appreciable peripheral vascular disease while, on the other hand, persons with nondiabetic atherosclerosis or even thrombosis of the leg arteries, had healthy nerves. Attention then shifted to vessels of smaller caliber. Goldenberg *et al.*[34] found, in the amputated legs of diabetics, lesions that differed from those usually encountered in ordinary arteriosclerosis. In small arteries there was thickening of walls and endothelial proliferation, whereas the arterioles and capillaries showed hyaline thickening of the walls, with marked affinity for the periodic acid Schiff reagent. Agenaes and Moe[35] described changes in dermal capillaries in diabetes, comparable to the vascular lesions found in the kidneys and in the eye. Despite many investigations in this field, the facts are not yet indisputably established. For example, during the past year three electron microscopic studies were published. One group reported significant thickening (by measurement of the basement membrane) of diabetic dermal capillaries;[36] a second claimed that the lesions consisted of collagen deposition rather than basement membrane thickening;[37] and a third was unable, in a blind study, to distinguish diabetic capillaries from normal controls.[38]

Fagerberg[7] examined histologically a large number of diabetic sural nerves, mainly obtained by biopsy. He was impressed by the arteriolar thickening in the nerves, which was present in both young and old subjects. Further, he found a high correlation between the presence of diabetic disease in the nerves, kidneys, and eyes. He concluded that arteriolar disease was responsible for the demyelination. This is a unifying and therefore attractive theory. However, there are several points

against its acceptance. If one examines larger areas of the nervous system, it becomes apparent that very often it is not possible to relate abnormalities in the vasa nervorum to the state of the nerves. In other words, normal arterioles and capillaries may be in badly demyelinated segments while, by contrast, hypertensive patients whose arteriolar lesions closely resemble those of diabetics may have almost obliterated intraneural vessels accompanying normal nerves. Moreover, occlusion of vasa nervorum with resulting nervous damage, as exemplified by periarteritis nodosa, usually leads to infarcts of the nerves rather than demyelination. Again, the lesions of diabetic neuropathy follow a definite anatomical pattern, e.g., the posterior roots may be severely damaged while the anterior ones are spared, which is easier to explain by selective vulnerability to a general metabolic disorder than by a structural alteration of vessels. Furthermore, the lesions resemble those encountered in metabolic disorders and intoxications. For example, in investigations such as those by Coërs,[21] findings have run parallel for alcoholics and diabetics; and, in plumbism, the lesions consist of segmental demyelination with isolated axon degeneration and destruction of end plates.[39]

We do not yet know the exact nature of the metabolic derangement in diabetic neuropathy. Nutritional disorders have been ruled out by the lack of response to therapy. Recent work by Field and his coworkers[40, 41] has demonstrated abnormalities in the fat and carbohydrate metabolism of diabetic nerves and spinal cord. Greenbaum[42] believes that symptoms are due to poor diabetic control, but this opinion is not shared by others.[43, 44] Thomas and Lascelles[10, 17] suggested as the basic fault an abnormality of the metabolism of Schwann cells that leads to myelin breakdown.

Conclusion

There is one very large gap in knowledge of the pathology and the pathogenesis of diabetic neuropathy. All the lesions described are those seen in patients with a chronic, usually mild, clinical neuropathy. Such patients characteristically display amazingly slight neurological disabilities in view of the severe degrees of degeneration of the nerves. The really troublesome neurological manifestations, particularly those associated with pain, are often transient, so that there is little opportunity for histological study of the nervous system. Greenbaum[42]

claims that there is one single diabetic neuropathy, which may show many clinical variants. The only pathological report available on a transient mononeuropathy, that by Dreyfus *et al.*[12] on an oculomotor nerve, showed a lesion that differed from that usually seen in nerves by being focal and by producing a swelling. Although the authors attributed it to vascular insufficiency, no occluded vessels were seen. Careful histological studies of further cases of this kind must be awaited before any definite conclusions can be drawn about the uniformity of the neuropathies.

Finally, I draw your attention to a penetrating comment by Theobald Smith, the famous American microbiologist and comparative pathologist. In a letter sent to Simon Flexner nearly 50 years ago, after criticizing a paper which had been submitted for publication in a well-known journal, Smith writes as follows: "Pathology, being practically the last synthesis of a large number of coordinated and subordinated factors, must actually be studied before these other factors have been cleared up, and as a result pathology must be more or less descriptive; but insofar as it is descriptive it must not claim more for that description than the evidence warrants."[45]

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