AXONS, SCHWANN CELLS, AND DIABETIC NEUROPATHY*

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DISCUSSIONS of diabetic peripheral neuropathy have often had the implicit suggestion of a unitary process—a single disorder with a single underlying pathogenetic mechanism. This has led to the unresolved controversy between proponents of a vascular and a metabolic etiology. Surely the clinician cannot help but be aware that the postulation of a unifying mechanism of production of the peripheral neurological concomitants of diabetes is a naive oversimplification. Some disorders, as the isolated mononeuropathy of sudden onset, circumscribed duration, and complete recovery, must be of vascular origin. Others reflect the increased susceptibility of the peripheral nerves of patients with diabetes to focal trauma.[1] In each, large fibers are often preferentially affected, while signs and symptoms are restricted to the distribution of a major nerve trunk. The more usual peripheral polyneuropathy, characterized by a distal affection of overlapping terminals of long nerves, with decreased appreciation of pain and temperature—the modalities mediated by smaller fibers—is thought to be of metabolic origin. Perhaps a better understanding of the possibilities of metabolic derangement can be obtained by a review of the dynamic relations between a peripheral nerve and its environment.

Peripheral nerve trunks consist of large and small sensory and motor fibers collected in bundles. Longitudinal collagen fibers that have a diameter of 700 to 850 Å. surround these bundles as the epineurium.[2] Each nerve bundle is surrounded in turn by concentric lamellated, flattened endothelial type cells of the perineurium. Delicate fibers of the endoneurium extend into the bundles between the myelinated and unmyelinated nerves. The collagen of the endoneurium, 500 to 600 Å. in diameter, is arranged in two layers: an outer layer of longitudinal fibers is the sheath of Key and Retzius. An inner collection of

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longitudinal, oblique, and circular fibers corresponds to the sheath of Plenk and Laidlaw.[3] Endoneurial collagen is formed by endoneurial fibroblasts[4] and perhaps by Schwann cells.[5] All axons, myelinated or not, are in intimate relation with Schwann cells.[6,7] The Schwann cell is surrounded by a basement membrane that separates it from the endoneurium. The so-called neurilemma, or sheath of Schwann cells, should be distinguished from the axolemma, or true sheath of the axon.[8]

Normal myelinated fibers are interrupted at a regular interval by annular constrictions known as the nodes of Ranvier. Between the nodes, the internodal segment of myelin is formed by the spiral wrapping of an individual Schwann cell.[9] The length of the internode depends upon the "stretching" produced by the growth of the axon. Early myelination produces long nodes.[10] Internodal length varies directly as the diameter of the fiber,[11] although after the age of 65, irregularities of length are common.[10] Interruption in the internodal myelin is produced by the Schmidt-Lantermann incisures. Schwann cell cytoplasm lies in these clefts.[12] Immunologic studies[13, 14] indicate a distinction between myelin of the peripheral and central nervous system.

An axon, often extending thousands of times the diameter of the nerve cell body, is dependent upon the perikaryon for axoplasm, which is elaborated in the nerve cell body and flows into the fiber.[15] Following section of a nerve, outflow of axoplasm occurs at the cut end, which becomes covered by myelin. The myelin, distended by axoplasmic flow, ultimately bursts and the process recurs.[16] Apparently axoplasm can exist in a sol as well as a gel state.[17] Increase of axoplasmic mitochondria occurs at the node of Ranvier,[18] where the axon is constricted to less than one half its diameter at the internode.[8] The two opposed Schwann cells of adjacent internodes extend fingerlike processes of about 500 Å. in diameter which interdigitate at the node, leaving a 150 Å. gap as a possible pathway for ionic current.[19] Schwann cell mitochondria are concentrated at the node,[8,20] where the collar of the Schwann cell has a close apposition to the axolemma (of the order of 20 Å.) and an increase of electron density at the point of contact.[20] The dimensions of the proximal paranodal bulb are greater than those of the distal. Myelin in the paranodal region is crenated and the underlying axon fluted,[21] apparently increasing surface relations. The possibility of an intimate metabolic interrelation between Schwann cell and axon has been suggested,[21,22] with the node behaving as a point of

energy exchange. Schmitt[23] points out that an important evolutionary advance from unicellular to multicellular organisms, with the associated need for rapid communication over long distances, may have depended on solving the problem by local metabolic energy supplied by satellite cells. This intimate dependence between contiguous cells should not be surprising in light of transneuronal degeneration that occurs in visual,[24] auditory,[25] and other neuronal systems. Indeed, the outcome of the historical debate on continuity versus contiguity of cells may require some reinterpretation in light of the recent demonstration[26] not only of propagation of tracer elements from nerve cell body into axon but, more important, ultimate transsynaptic appearance in the muscle innervated by the nerves with tagged axoplasm.

The dependence of Schwann cells on the axon they surround is well demonstrated in Wallerian degeneration. Following section of the fiber, the distal axon degenerates, the Schwann cells remove axonal remnants and myelin debris,[27] and proliferate to form the bands of Büngner.[28] Widening of the incisures has been reported in states of deterioration.[17] Activity of the Schwann cell is prominent in the peripheral stump, with central activity confined to a few millimeters adjacent to the section and never exceeding 10 per cent of that in the peripheral stump.[28] The myelin internode proximal to the section degenerates if the Schwann cell nucleus has been involved by the section. When the nucleus remains proximal to the damage, retrograde degeneration does not occur, but the terminal internode is short.[29] The stimulus for nuclear proliferation induced by Wallerian degeneration may be the degenerating myelin, for the larger the fiber the greater the increase of nuclei.[30] Degeneration and regeneration, of course, go on actively and simultaneously.[31] Regenerated nerves have a higher cell population than normal,[32] and the normal linear relation between fiber diameter and internodal length disappears,[33] to be replaced by short internodes.[10] Not only do regenerating nerve fibers suppress the migration of Schwann cells,[34] but the nature of the peripheral stump has bearing on the final axonal diameter. Sectioned medullated spinal nerves sutured to a nonmedullated postganglionic autonomic trunk produce marked decrease in myelin formation.[35] Even connections with the periphery are influential, for the decrease in size of the fiber in the central stump —affecting axon proportionally more than myelin—remains present until peripheral connections are established.[36, 37] Finally, the plasticity of the

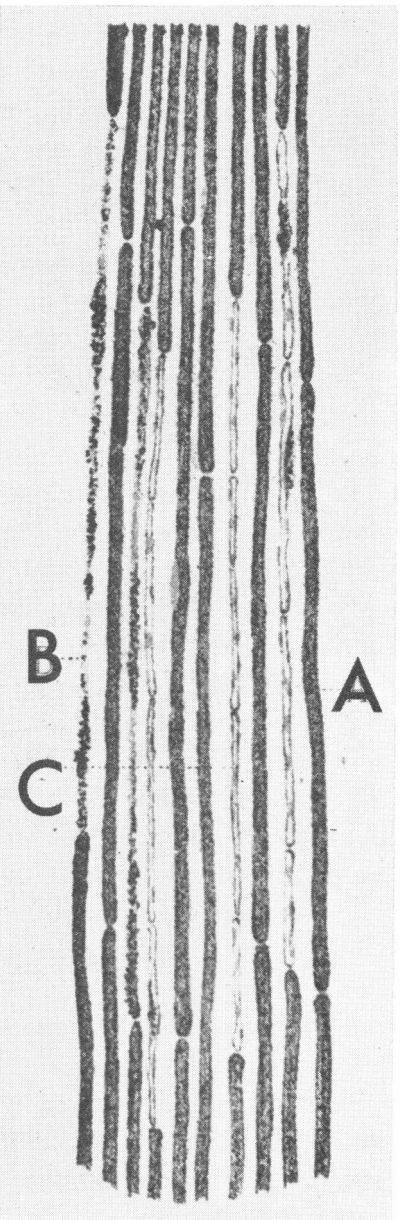

Fig. 1. Experimental segmental demyelination. Nerve stained with osmic acid and picrocarmine. *A*. Normal fiber; *B*. degenerating segment; *C*. internodal segment replaced by a series of short and narrow segments limited by well-marked nodes during the period of regeneration. Reproduced from Gombault.[42]

regenerative process is indicated by proximal collateral nerve sprouts that invade adjacent regenerating Schwann cell sheaths[38] in a manner reminiscent of the distal collateral regeneration in partially denervated muscles.[39]

A peripheral nerve, then, is not a simple structure vulnerable in only one way and with a single stereotyped reaction. The response of the soma, axon, and myelin to toxins differs.[40] Wallerian degeneration affects the axon primarily. Toxins, such as diphtheria, affect the individual Schwann cell. The demyelination associated with involvement of individual Schwann cells is designated segmental, with the implication of relative preservation of axon. "The occurrence of segmental demyelination suggests that individual Schwann cells are randomly attacked and that myelin degeneration occurs when the normal metabolic functions of the Schwann cell are disturbed."[41] This segmental demyelination of Gombault is discontinuous; it spares the axis cylinder, may be followed by recovery or by Wallerian degeneration, does not result from a tropic change in spinal centers, and in man "appears to play an important role in certain disorders of peripheral nerves where, until now, only the characteristic lesions of Wallerian degeneration have been described."[42] Fibers that have undergone segmental demyelination manifest marked variation of internodal length.[43] Although it has been argued that the conduction velocity of nerve action potential is related to myelin sheath thickness and not to internodal length[44] as had been previously claimed,[11] the fact is that in experimental segmental demyelination a decrease in conduction velocity is observed,[45] presumably because the decreased myelin thickness results in decreased resistance, increased capacitance, current leakage, and resultant decrease of current density at the node.[45, 46] This decreased density of current delays the regenerative action potential, decreasing the rate of saltatory conduction.

The usual suggestion for the mechanism of the peripheral distribution of signs and symptoms in diabetic polyneuropathy relates to the elaboration of axoplasm in perikaryon and propagation into the axis cylinder, with failure of function of axoplasm before it reaches the distal nerve terminals.[47] Demonstration by standard histological techniques of patchy demyelination in diabetic neuropathy[48] and delineation of segmental demyelination in single fiber preparations[49] raises the possibility that the site of abnormality is the Schwann cell rather than

the axis cylinder. The distal distribution of the abnormality would be attributed to the demonstrated decrease in lipogenesis and oxygen uptake from proximal to distal part of the nerve. "A depressing influence acting on the nerve as a whole might cause greater and earlier damage (i.e., demyelination) at the distal tip, where lipogenesis is lowest."[50] The difficulty of distinguishing the axonal and Schwann-cell vulnerability to metabolic impairment is emphasized by the slit sheath preparations in which, following extrusion of axoplasm, the respiratory rate is of the same order as that in the intact fiber. In addition, sheath cells maintained high potassium, low sodium, and similar enzymes to those of axoplasm.[23] Destruction of axis cylinders with attendant Wallerian degeneration in severe cases of diabetic neuropathy[51] is quite concordant with Gombault's original description, and the demonstration of large and small internodes correlates well with the reduction of motor nerve conduction velocity present in patients with diabetes even in the absence of overt manifestations of clinical neuropathy.[52]

Not only is the question of a vascular or metabolic etiology of diabetic neuropathy still unresolved, but the possible sites of metabolic impairment are not yet delineated. It appears with increasing knowledge that the mechanism of production of the disorder, like its clinical manifestations, is really multiple. Perhaps, then, it is best to speak of the neuropathies of diabetes.

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