A Cause for Optimism in Diabetic Neuropathy

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The hypothesis is that the majority of the symptoms of diabetic neuropathy are due to multiple peripheral nerve entrapments. This hypothesis assumes that the underlying metabolic problem—hyperglycemia—makes the peripheral nerve more susceptible to compression at normal anatomic areas of narrowing, such as the carpal, cubital, and tarsal tunnels. If this hypothesis were true, then there would be a cause for optimism in the treatment of diabetic neuropathy. Although the surgeon cannot operate upon the metabolic neuropathy itself, he or she can release superimposed compression neuropathies.

Diabetic neuropathy is a major national health concern, conservatively estimated to affect 10% to 25% of the 6 million diabetics in the United States. The traditional teaching is that diabetic neuropathy is progressive and irreversible. Treatment has been directed at achieving control of the hyperglycemia and prophylactic care of soft tissue at risk of sensory loss, such as the feet. The diabetic neuropathy patient is referred to the surgeon usually to treat secondary infection, amputate necrotic tissue, and resurface ulceration in these insensitive tissues. If this hypothesis were true, then ideally patients will be referred to restore sensation and strength, preventing the long-term consequences of diabetic neuropathy, muscle atrophy, and soft-tissue loss.

The assumption that the diabetic is predisposed to nerve entrapment syndromes is commonly held. All surveys of diabetic populations have shown, for example, a high incidence of carpal tunnel syndrome. Conversely, the large series of patients with carpal tunnel syndrome have an incidence of diabetes of 7% to 14% compared with the incidence of diabetes in the general population of 2% to 4%. The experimental models of diabetes provide the basis for this increased susceptibility to compression. In both streptozotocin-induced diabetes and spontaneously occurring diabetes in rats and primates, the earliest histopathological finding is edema: subperineurial and endoneurial edema. The experimental model for galactosemia has the same finding. The mechanism is conversion of increased intraneural glucose (or galactose) to polyol (sorbitol), requiring the enzyme aldose reductase. The polyols are hydrophilic, drawing water into the nerve. Thus, the diabetic nerve is swollen. Although the mechanism is less well understood, axoplasmic flow is reduced for both the fast and slow component in diabetes. The experimental models of nerve compression as described by Mackinnon and co-workers are also characterized by subperineurial and endoneurial edema. Decreased axoplasmic flow has been documented in other models of nerve compression. Thus, hyperglycemia establishes in the nerve the same pathophysiological conditions that exist in compression neuropathy, supporting the assumption that the diabetic nerve is susceptible to compression. Direct experimental evidence demonstrating this susceptibility is reported in this issue of the *Annals*.

The most common form of diabetic neuropathy may be the one most appropriate for surgical intervention. This form is characterized by a diffuse, symmetrical, mainly sensory, but also motor, polyneuropathy. There is a "glove and stocking" distribution of sensory loss. The glove pattern can result from the concurrent compression of the median nerve at the wrist, ulnar nerve at the elbow, and radial sensory nerve in the forearm. Entrapment of the radial sensory nerve at this location was described in German in 1932 by Wartenberg, but not well documented in English until 1986 by Dellon and Mackinnon. If this hypothesis were true, then decompression of these three nerves would result in sensory recovery in the glove distribution and improved pinch and grip strength. This approach could be applied to the stocking pattern. Entrapment of the common peroneal nerve at the fibular head is well described. Entrapment of the posterior tibial nerve in the tarsal tunnel was described in 1972, and sites for entrapment of the lateral sural nerve, lateral cutaneous nerve of the calf, and deep peroneal nerve have been identified recently.

The "multiple crush" concept provides the framework for diagnosis and treatment of the patient with symptomatic diabetic neuropathy. Multiple sites of nerve compression, none of which alone may be sufficient to produce clinical symptoms, summate (e.g., by progressive diminution in axoplasmic flow, to create paresthesias, dysesthesias, and weakness. The symptoms may not be classic, and because each site alone is insufficient to produce symptoms, the physical examination may not be classic. The electrodiagnostic findings may not be classic for the classic nerve entrapment syndromes. A metabolic abnormality, in this example diabetes—but alcoholism, thyroid disease, uremia, or vitamin deficiency may produce the same susceptibility—is considered as the first, albeit universal, "crush." Then any one or more anatomic sites along the course of the peripheral nerve contributes to progressive neural dysfunction. The most proximal anatomic site of narrowing is probably the neural foramina. At surgery, the area of decompression may not have created the classic narrowing with proximal swelling in the nerve, because this one site may not be the sole site of the problem. If the surgical approach is being used early in the natural history of the patient's symptoms, simple decompression of the nerve may be sufficient treatment. In the experimental models of diabetes, alterations in electrical activity occur early, accompanied by little more histological than neural edema. Thus, clinical symptoms caused by the metabolic neuropathy may be minimal. The swollen nerve, when compressed by the normal anatomy, will have further increased intraneural pressure, decreased blood flow, and clinical complaints of neural ischemia. These can be corrected predictably and quickly by nerve decompression.

When the majority of the symptoms of diabetic neuropathy are associated with muscle wasting, persistent sensory dysfunction, and loss of two-point discrimination, structural changes such as segmental demyelination and wallerian degeneration have occurred in the nerve sufficient to produce loss of nerve fiber function. With the exception of the plantar nerves (distal tarsal tunnel) in caged diabetic guinea pigs, none of the experimental models of diabetes produce such changes. All the models of chronic nerve compression, however, do produce such changes. There is also interfascicular fibrosis. Thus, the patient with advanced symptoms and signs of diabetic neuropathy most likely has the histopathology of chronic nerve compression plus that of the diabetic axonopathy. The hypothesis presented here suggests that the majority of the symptoms are due to the chronic nerve compression. Experimental studies by Mackinnon and Dellon have demonstrated that microsurgical intraneural neurolysis can be performed in this plane of increased interfascicular connective tissue without creating more ischemia or fibrosis. The surgical approach in this setting should include an internal neurolysis in addition to the traditional nerve decompression. This approach should permit partial remyelination and neural regeneration, with recovery of motor and sensory function over a longer period of time. The effect of this surgery upon postoperative electrodiagnostic testing, which was probably markedly abnormal before surgery, cannot be predicted reliably. Most likely, postoperative electrodiagnostic testing will continue to demonstrate a diffuse polyneuropathy of the distal axonopathy type. The postoperative clinical improvement may not correlate with electrical changes in the patient with an advanced, diffuse neuropathy.

This hypothesis explains why the recent biochemical treatments for diabetic neuropathy have not been successful clinically. Although the experimental models of diabetes demonstrated decreased nerve myoinositol levels and increased aldose reductase activity, and although feeding myoinositol and aldose reductase inhibitors corrects the early electrophysiological abnormalities in these models, clinical trials with these agents have not proved valuable. As discussed previously, these early biochemical alterations represent the metabolic neuropathy, and may not be responsible for the clinical symtomatology. For example, many patients have electrodiagnostic findings compatible with diabetic neuropathy at the time of their being diagnosed as having diabetes, yet they are asymptomatic in terms of a neuropathy. With time, these biochemical alterations render the nerve susceptible to compression, at which time, if the hypothesis presented here were correct, clinical symptoms thus will become manifest. Since nerve compression can be treated, there is cause for optimism in diabetic neuropathy.

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