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Diabetic Neuropathy Complex

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Summary. Pathological data obtained from a comprehensive general and neuropathological post mortem examination of ten unselected cases of diabetes mellitus are reported. The findings suggest that the "diabetic neuropathy" is a multifaceted disorder, affecting primarily the sensory, and autonomic peripheral nervous systems, involvement of the former leading secondarily to degeneration of the related intraspinal systems. The relationship between the autonomic neuropathy and "diabetic angiopathy" is discussed and the evidence indicating that the former may be a factor in the pathogenesis of the diabetic vascular disease presented.

Inspite of the fact that the diabetic neuropathy has continuously attracted attention of the clinician since its recognition more than one hundred years ago, its pathogenesis and interrelation with other pathologic manifestations of the diabetes remain largely obscure or controversial. The wealth of clinical and laboratory investigations pertaining to various aspects of diabetes mellitus is contrasted by a relatively few pathological studies. Although the disturbances in the sensory sphere rank first among the clinical manifestations of diabetic neuropathy, examination of sensory ganglia has been done but infrequently (Bosanquet and Henson, 1957; Dolman, 1963; Greenbaum *et al.*, 1964). Furthermore, in contrast to the ever growing awareness on the part of the clinician of the frequency and extent of the involvement of the autonomic nervous system in a diabetic, pertinent pathological studies are likewise few (Appenzeller and Richardson, 1966; Berge *et al.*, 1956; Dolman, 1963; Martin, 1953; Olsson and Sourander, 1968).

In this paper, the results of a combined pathological examination of the central and peripheral (somatic and autonomic) nervous systems of ten unselected diabetic patients will be presented, and a concept of diabetic neuropathy as a "primary neuronal degeneration ... independent of vascular disease" (Greenbaum *et al.*, 1964) will be expanded to include peripheral sympathetic system. Hitherto unreported changes in the post-ganglionic subdivison of the peripheral sympathetic will be described, and their possible relation to some other systemic manifestations of diabetes mellitus, especially to "diabetic angiopathy", discussed.

Material and Methods

Ten patients with diabetes mellitus were studied (Table). In each case, the brain, spinal cord, sensory and prevertebral and/or paravertebral sympathetic[1] ganglia and peripheral

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1 Sympathetic chains were not available in Cases 1 and 10.

Table

Case no.	AGE and sex	Known duration	Severity	Control	Autonomic PNS	Somatic PNS	CNS	Nephropathy	Retinopathy	Blood pressure	Absent peripheral pulses
1	37, ♂	14	++	F	Orthostatic hypotension; diarrhea	NR	NR	Yes	Yes	170/190 (sitting) 120/100 (supine)	NR
2	29, ♂	21	++	F	NR	hyporeflexia	NR	Yes	Yes	160/108	NR
3	29, ♂	16	++	G	NR	NR	NR	Yes	Yes	100/75	NR
4	55, ♂	17	+	G	NR	NR	Lumbar transverse myelitis	NR	Yes	130/70	Aa. dorsales pedis
5	49, ♂	31	NR	F	NR	areflex — ia	coma; Babinsky	NR	Yes	cardiac arrest	NR
6	74, ♂	"long standing"	++	F	NR	NR	stupor	Yes	NR	210/80	NR
7	53, ♂	24	+++	P	constipation and diarrea; impotence; atonic bladder	"shooting pains" and numbness in extremities; fasciculations	NR	Yes	Yes	150/80	Bilateral below knee amputation
8	62, ♀	10	++	G	NR	NR	left hemiparesis	Yes	NR	100/60	Post. tibial arteries

9	72, ♂	5	+	G	NR	decreased touch and pinprick sensation in legs	NR	NR	Yes	180/96	NR
10	55, ♂	3	+	G	atonic bladder; urinary incontinence	absent knee and ankle jerks; decreased sensation in legs	nuchal rigidity	Yes	NR	194/102	NR

P = poor; F = fair; G = good; NR = not recorded.

nerves were examined. Samples of skeletal muscles were available for study in some cases. All protocols of gross pathologic findings as well as histologic preparations from general autopsies were reviewed, and a search for alterations in the visceral nerves and autonomic ganglia was made. All neuropathological material was embedded in paraffin and the sections were routinely stained with hematoxylin and eosin. Special stains used included Romanes' and Bielschowsky's silver methods for axons, Nissl, Luxol-fast Blue and periodic acid-Schiff, phosphotungstic acid hematoxylin, Holzer and azocarmine stains.

For the sake of brevity, pertinent clinical data are presented in the Table; major findings at general autopsies are summarized in the Appendix.

Neuropathological Findings and Comment

It is generally recognized that disturbances of the sensory modalities represent one of the early and most characteristic clinical manifestations of diabetic neuropathy (Bischoff, 1963; Goodman *et al.*, 1953). In this series, the anatomical findings in the sensory ganglia were essentially similar to those reported (Bosanquet and Henson, 1957; Greenbaum *et al.*, 1964) while being at variance with those of Dolman (1963), who examined spinal ganglia in "13 instances" and found that "the majority were normal" and "only occasionally a ganglion cell seemed to have been lost". The changes in sensory ganglia, both spinal and cranial, represented a consistent, though variable in degree, finding, and were purely degenerative and reactive in nature, the inflammation lacking completely. In the earliest recognizable phases of degeneration only the capsule cells appeared to be affected, showing hypertrophy and hyperplasia, while the nerve cells themselves were not appreciably altered. In more advanced stages, swollen capsule cells seemed to "erode" the ganglion cell bodies and, upon complete dissolution of the latter, to form residual nodules. Woven into the clusters of the proliferating capsule cells about many degenerating neurons there often appeared, in increasing numbers, very fine non-myelinated, regularly beaded nerve fibers which eventually formed dense cocoon-like tangles about severely injured nerve cells and within residual nodules. Many of these fibers terminated in relatively large bulbous swellings; similar swellings were seen on non-myelinated nerve fibers pervading

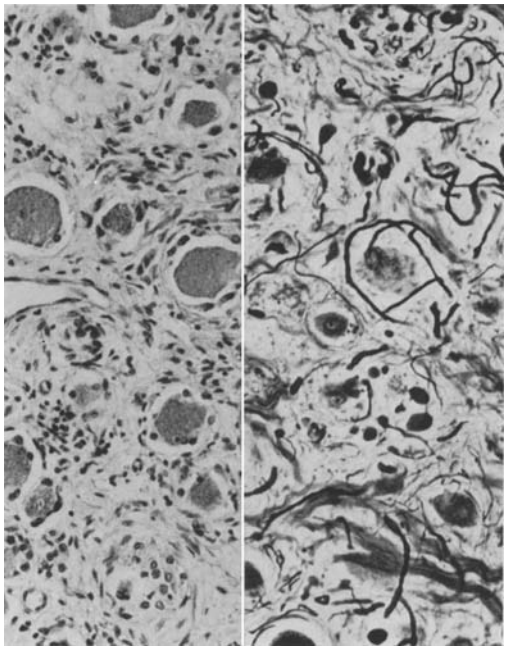

Fig. 1. Case 1. Spinal ganglion. There is degeneration and loss of neurons, and formation of residual nodules of Nageotte (left). Many retraction bulbs are seen (right). H and E and Romanes' stains. × 150

the stroma of a ganglion (Fig. 1). In no instance were we able to demonstrate a continuity between these fine fibers and the ordinarily much thicker processes of the sensory ganglion cells. Previous workers (Scharf, 1958) have interpreted such fibers as periganglionic terminals of other sensory or sympathetic neurons either establishing synaptic contact with sensory nerve cells, or exercising "trophic" influences upon their capsular cells necessary for maintenance and proper functioning of the neuron (neurono-neuroglial symbiosis of Cajal; Cajal, 1928; Knoche, 1961; Kornmüller, 1950). It seems possible that at least some of the fine axons may indeed represent terminal portions of some distant (possibly sympathetic) neurons, connections with which have also been suggested by several workers (Cajal, 1928; de Castro, 1951; Dogiel, 1908). More recently, presence of these fibers within the cytoplasm of capsule cells of normal sensory neurons (Andres, 1961 a), and their multiplication following posterior rhizotomy and neurectomy have again been demonstrated electron-microscopically (Andres, 1961 b). Nageotte (1906) has considered such newly formed fibers as regenerative, and postulated their origin from the injured sensory nerve cell bodies or their processes (collateral regeneration). This theory, however, while applicable to axonal regeneration in general, does not explain an increase in these fine, non-myelinated axis cylinders paralleling the degree of neuronal degeneration and being most prominent in association with fully developed residual nodules, since death of a ganglion cell would, by necessity, be accompanied by degeneration of all its processes, both normal and regenerated. Be it as it may, the origin and nature of these fine

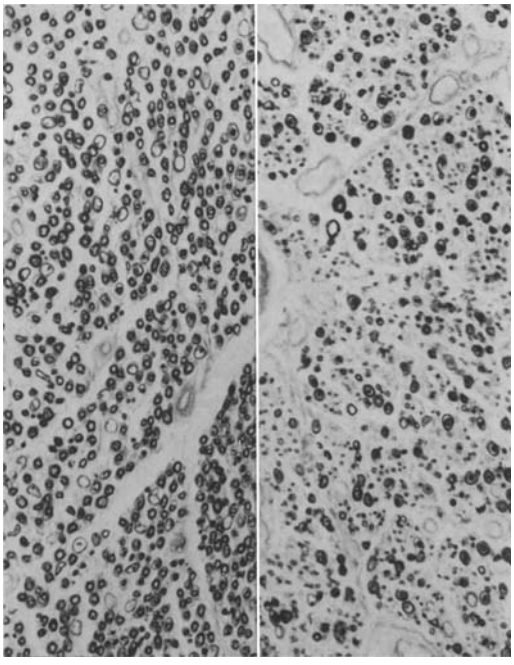

Fig. 2. Case 6. Anterior (left) and posterior (right) spinal nerve roots. There is a marked loss of large caliber fibers and swelling of many remaining ones in the posterior root. The anterior root is only slightly rarified. Luxol Fast Blue-PAS stain. × 150

stromal and especially pericellular fibers which are so consistently and conspicuously increased in the sensory ganglia of this series still remain obscure.

Pathological changes in the posterior roots were chiefly characterized by degeneration of the large myelinated fibers and preservation and, possibly proliferation of fine, non-myelinated fibers, whose prominence paralleled the degree of the large fiber loss (Fig. 2). These changes were present in seven of our ten cases and were in a striking contrast to the relative preservation of the anterior roots where degeneration could be discerned only in two cases. These observations are in general agreement with those of Bosanquet (1957), Dolman (1963) and Greenbaum *et al.* (1964). Such discrepancy in the degree and extent of degeneration of the posterior and anterior roots speaks strongly for a preferential involvement of a particular, in this instance, sensory system not unlike that observed in man and experimental animals in some nutritional deficiency states (Swank and Adams, 1944), or occurring spontaneously and without a known cause (Denny-Brown, 1951).

Within the spinal cord the posterior columns were involved in eight cases, thus being the most consistently and severely affected long tracts. The main changes comprised varying degrees of depletion of the nerve fibers and fibrillary gliosis. The pattern of involvement was similar to that reported recently (Dolman, 1963; Greenbaum, 1964), the degeneration being more severe in the distal segments of the cord, and more pronounced in the fasciculus gracilis, while being only slight or not detectable at all in the fasciculus cuneatus.

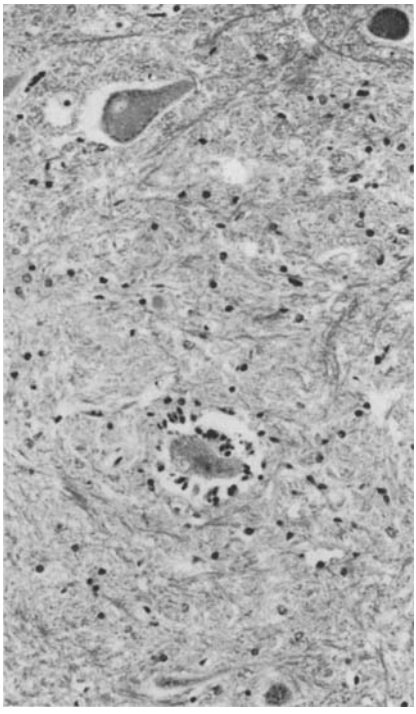

Fig. 3. Case 3. Spinal cord. Neuronophagia in the column of Clarke. H and E. × 150

It is well established at present that an injury to certain neuronal systems can induce a secondary (trans-synaptic) degeneration in other neuronal systems which form close functional links with the primarily affected ones (Becker, 1952). In the context of this discussion the work of several investigators who have studied the spinal cord of primates (rhesus monkey) following a dorsal rhizotomy in both acute and chronic experiments is of particular interest. In the former (Foerster *et al.*, 1933), degenerating fibers passing to and chromatolytic ganglion cells within the dorsal sensory nuclei, columns of Clarke, intermediatemedial and anterior horn grisea were observed. The other group of workers (Stein and Carpenter, 1965), in addition to demonstrating degeneration of the intramedullary collateral branches of dorsal root fibers, found an "unquestioned ascending degeneration seen in the position of the posterior spino-cerebellar tract" and raised "the question of possible transneuronal degeneration in the cells of Clarke's nucleus".

Considered in the light of these experimental studies, our findings of neuronal depletion and of such changes as central chromatolysis, disintegration of perikaria with or without neuronophagia and attendant fibrillary astrocytosis in the dorsal sensory nuclei (Cases 1, 3), columns of Clarke (Cases 1, 3, 4, 6—10) (Fig. 3), intermediate-medial griseum (Cases 1, 4) and anterior horns (Cases 1, 3, 4, 6—10) of our series, may be interpreted similarly, i.e. as indicating a prograde trans-synaptic degeneration of the neuronal systems which are closely linked with the sensory neurons of I order. Furthermore, distinct loss of fibers in both spino-cerebellar

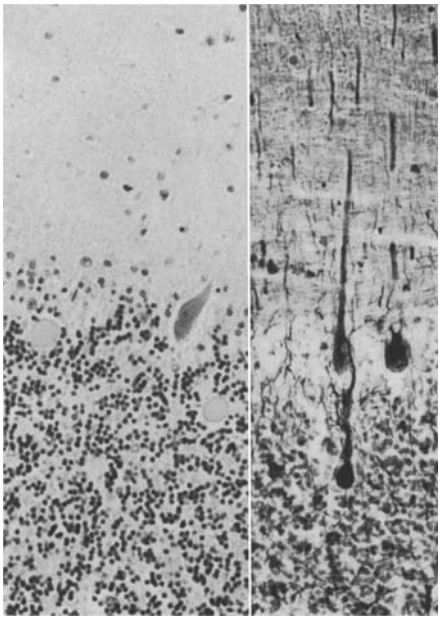

Fig. 4. Case 1. Cerebellum. Focal loss of Purkinje cells and formation of axonal "torpedos" in the granular cell layer. H and E and Romanes' stains. × 150

tracts of Case 1 and dorsal spino-cerebellar tracts in Case 10 as well as relatively slight cortical cerebellar degeneration (drop-out of Purkinje cells, formation of axonal "torpedoes" and proliferation of Bergmann's glia) involving predominantly the superior vermis (Fig. 4), but also affecting the hemispheres in Cases 1, 7, 9 and 10, serve to further complete the pattern and extent of the involvement of the secondary and tertiary sensory neurons. The seeming discrepancy between the changes in the cerebellum and those in its afferent tracts is perhaps best explained by the technical difficulties in demonstrating slight changes in the long tracts of the spinal cord, while degenerative cerebellar changes of similar degree are more readily recognized.

While the above noted changes within the intraspinal afferent neuronal systems can be looked upon as a result of the antegrade transneuronal degeneration, this "chain reaction" being initiated by an injury to the primary sensory neuron, similar pathological changes in the motoneurons of the anterior horns, which were observed in Cases 1, 3, 6—10 deserve further comment. While it is admittedly difficult to exclude a direct injury to the spinal motoneurons, a mechanism which has been suggested by Alderman (1938), Dolman (1963) and Greenbaum *et al.* (1964), certain observations tend to make this mechanism rather unlikely for the following reasons. The degenerative changes and loss of motoneurons were either negligible or not detectable at all at the higher levels of the spinal cord, in the brain stem or cerebrum, but were prominent in the lumbar-sacral segments of the cord. Such a localized involvement would argue strongly against a uniformly acting noxa. Furthermore, the relatively good preservation of

the anterior roots would tend to rule out any significant degree of retrograde degeneration of motoneurons due to an injury to their peripheral fibers. On the other hand, a good correlation between the severity of degeneration of the spinal sensory ganglia and the changes in the motoneurons of the corresponding segments of the spinal cord would again suggest a trans-synpatic degeneration of the latter as a most likely pathogenetic mechanism responsible for the lower motor neuron involvement at these levels. In addition, relative mildness of the degenerative changes in the anterior roots contrasted by the presence of large zones of "neurogenic" atrophy in the skeletal muscles of some cases would indicate that the site of the injury to the motoneuron is, in many instances, the anterior horn itself.

Several examined spinal nerves and vagi in Case 3 were essentially normal. Only slight and focal loss of myelin was noted in the major peripheral nerves of Cases 1, 2 and 4. A diffuse, but moderate demyelination was observed in the lumbar-sacral plexuses of Cases 5, 6 and 10, the brachial plexuses being essentially normaly in Case 5 and showing relatively slight changes in Cases 6 and 10. Although the unsystematic fashion of sampling of the major somatic peripheral nerves in this series does not permit drawing of final conclusions as to the relative importance of their involvement in the complex of diabetic neuropathy, there are some points deserving comment. The obvious discrepancy in the severity of degenerative changes in the posterior nerve root (pure sensory) and in the corresponding peripheral nerve (mixed) is best explained on the premise that the true loss of the sensory fibers in a mixed nerve may not be fully appreciated because of their intimate intermingling with the motor ones, which, as judged by the degree of preservation of the anterior roots suffer much less. The generally known greater vulnerability of longer nerves of a diabetic (Colby, 1965), as again illustrated by our Cases 5, 6 and 10, could perhaps be explained by hypothesizing that, if a series of functionally similar (sensory) neurons is equally affected, it is likely that those nerve cells, which are endowed with the longest processes, will be among the first ones to become unable to maintain the integrity of the entire length of their fibers, with resultant "dying back" type of neuropathy

Since the classical studies of diabetic neuropathy by Rundles (1945), an involvement of the autonomic nerves in a diabetic has increasingly been appreciated as an integral part of the diabetic neuropathy and held responsible for disturbances in the vasomotor and sudomotor activity as well as for dysfunction of the lower urinary, and gastrointestinal tracts (Bischoff, 1963; Goodman *et al.*, 1953; and Keen, 1959). It is of special interest, that in a few, more recently reported cases the "autonomic neuropathy" was the most prominent and disabling manifestations of the neurologic disturbance (Cohen, 1959; Odel, 1955).

In the papers dealing with pathology of autonomic ganglia and nerves in diabetics, absence of pathological changes was reported in two (Berge, 1956; Dolman, 1963), while degenerative changes similar to those observed in our material were reported by Olsson and Sourander (1968). Appenzeller and Richardson (1966) described "abnormal giant sympathetic neurons" containing PAS-positive material in the ganglia of patients with diabetic and alcoholic polyeneuropathies and suggested that the changes "might be related to the vasomotor disturbances which occur in patients with diabetic and alcoholic polyneuropathy". In another study, an early and predominant degeneration of the "non-myelinated

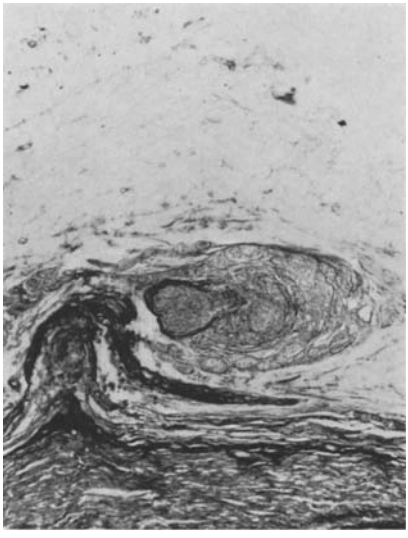

Fig. 5. Case 4. A neuroma arising from a gray ramus. Note an almost complete lack of myelinated fibers. Luxol Fast Blue-PAS stain. × 30

small-calibre fibers", interpreted by the author as autonomic, was found in biopsies of the sural and tibial nerves of patients with diabetic polyneuropathy, leading the author to the conclusion "that non-myelinated nerve fibres may be the first to suffer from the pathological process responsible for the nervous complications of diabetes" (Martin, 1953).

The pathological changes in the sympathetic ganglia in the present series were slight to moderate in degree and were characterized by chromatolysis, swelling, and vacuolation of the nerve cells and their processes. Many of these vacuoles contained a "mucoid" material which stained metachromatically with cresyl violet and gave positive reactions with mucicarmine and Alcian blue stains. This change was observed in the paravertebral sympathetic ganglia of Cases 2, 3, 5, 7, 8, 9, being most severe in Case 7. Neuronophagia was occasionally seen. Some degenerating neurons were surrounded by a dense meshwork of very fine nerve fibers. Terminal axonal retraction bulbs were seen in some ganglia.

In contrast to these relatively non-specific changes in the ganglia proper, distinct lesions were present in the gray rami of all cases (Figs. 5, 6), perivascular nerves in the subarachnoid and Virchow-Robin spaces of the spinal cord (Cases 1, 3, 4, 6, 7, 9, 10) (Figs. 7, 8) and lower brain stem (Cases 3 and 9) (Fig. 9) and in some visceral (Cases 4 and 9) nerves (Figs. 10, 11). Morphologically, these lesions closely resembled "traumatic" neuromata providing, in our opinion, a clear cut evidence of a focal injury to and a subsequent attempt at regeneration of the nerves involved. It should be noted at this point that the changes like those observed in the subarachnoid and perivascular spaces of the spinal cords and brain stems of our patients have previously been reported under various designations: nevrome de régénération (Raymond, 1893), angioneuroma (Staemmler, 1939), schwannosis (Russell and Rubinstein, 1959), heterotopia of peripheral

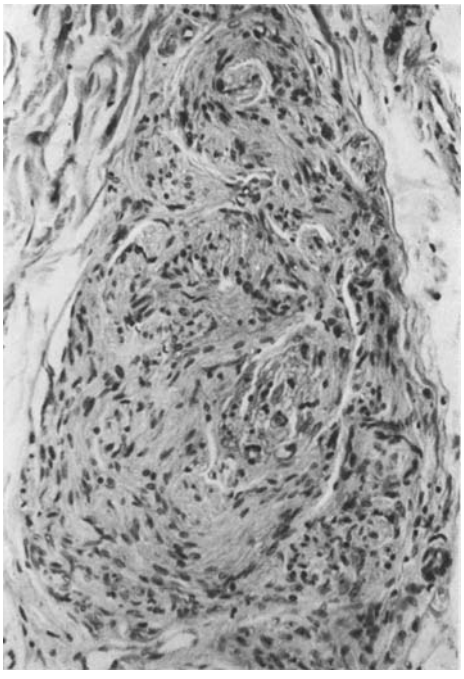

Fig. 6. Case 4. Gray ramus neuroma. Same as in Fig. 5. H and E. × 150

nerves (Feigin and Cravioto, 1961), neuroma (Klintworth, 1964), central neurinoma (Payan and Levine, 1965), intramedullary sheath cell tumor (Riggs and Clary, 1957) and in many instances were associated with various pathological states including syringomyelia, mechanical trauma, neurofibromatosis, etc. The literature on the subject has recently been fully reviewed (Klintworth, 1964). While some authors favored developmental factors in the formation of these structures (Russell and Rubinstein, 1959; Feigin and Cravioto, 1961) the notable frequency of their association with focal destructive lesions of the spinal cord or brain stem, such as traumatic myelopathy or infarcts, led others (Klintworth, 1964; Payan and Levine, 1965) to liken them to ordinary "traumatic" neuromata. It may be added that in the cases under discussion their relationship to a "chemical trauma" inherent in the diabetic state must be considered. It is this author's belief, that in the spinal cord and brain stem the changes under discussion occur in mixed (sensory and vasomotor) vascular nerves, whose existance in the central nervous system appears to be well established (Dahl *et al.*, 1965; Grigor'eva, 1962; Humphreys, 1939; Klosovskii, 1951; Lassmann, 1965). A conspicuous prevalence of the non-myelinated fibers in the majority of these lesions seems to confirm a greater degree of vulnerability of these fibers as has already been suggested by Martin (1953). Of particular interest, especially in view of the degree and extent to which the autonomic functions may be deranged in a diabetic, is the demonstration of similar neuromata in the gray rami, as well as along the course of some visceral nerves. It should be noted at this point that a lesion involving the postganglionic subdivision of the peripheral sympathetic system has, indeed, been

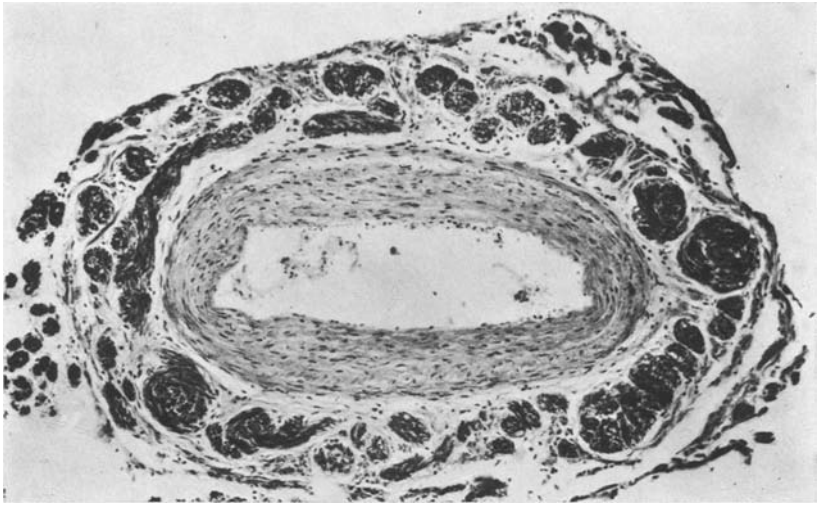

Fig. 7. Case 10. Anterior spinal artery. Whorles of fine (non-myelinated) nerves are present in the adventitia. Paraffin. Bielschowski method. × 100

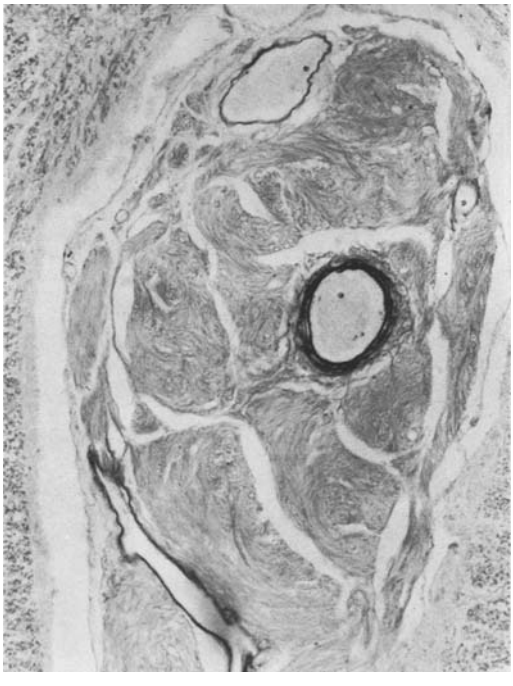

Fig. 8. Case 9. Ventral sulcus of spinal cord is occupied by a large neuroma which is composed almost exclusively of non-myelinated fibers. Luxol Fast Blue-PAS stain. × 150

predicted, and held responsible for the autonomic disturbances in diabetic subjects (Barany and Cooper, 1956).

The interrelation between the diabetic neuropathy and arteriosclerosis has continuously attracted much attention. While many of the earlier and more recent

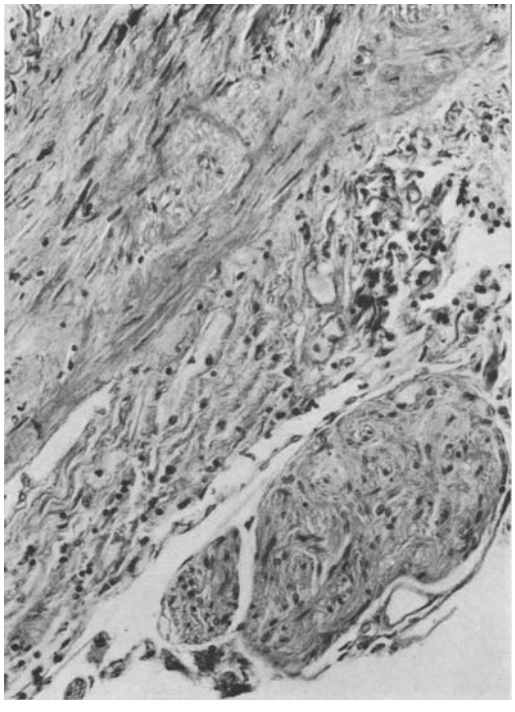

Fig. 9. Case 3. Basilar artery. Note a neuroma in the outer zone of the adventitia. H and E. × 150

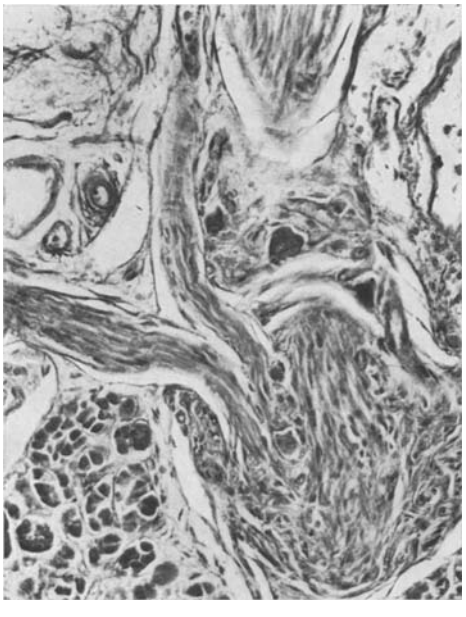

Fig. 10. Case 4. Pancreas. A neuroma in the interstitial tissue. Note ganglion cells (parasympathetic) within and outside of the lesion. H and E. × 150

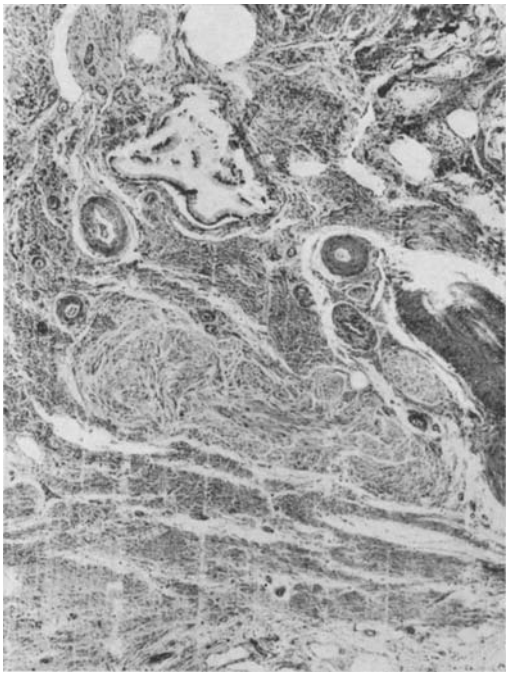

Fig. 11. Case 9. Gall bladder. A large mixed neuroma is seen in the lower portion of the illustration. H and E. × 60

writers believed that the neural lesions are secondary to the affection of either the large and medium-sized arteries (Woltman and Wilder, 1929), or arterioles (Fagerberg, 1959), or even capillaries (Bárány, 1955), the majority of recent authors contested the above views (Bischoff, 1963; Bosanquet and Henson, 1957; Chopra *et al.*, 1969; Dolman, 1963; Goodman *et al.*, 1953; Greenbaum *et al.*, 1964; Hirson *et al.*, 1953; Keen, 1959; Martin, 1953; Pickering, 1959; Pirart, 1965; Rundles, 1945). Of particular interest is one study in which the peripheral nerves of diabetic patients were compared with those of subjects with hypertension but without diabetes, the latter having been found to have "particularly excellent nerves" despite "gross lesions in the intraneural arterioles" (Dolman, 1963). Our findings regarding the state of the vasa nervorum and of the corresponding peripheral nerves are, on the whole, in support of the views of the latter workers.

Nevertheless, a distinct susceptibility of diabetic subjects to develop earlier and more severe arteriosclerosis than the general population is generally recognized, and concurrent hypertension, hyperglycemia, and hypercholesterolemia all have been implicated as the factors responsible for this vulnerability (Warren, 1938). On the other hand, careful analysis of the pertinent data led others to a conclusion that "the exact nature of the mechanisms that promote the development of atherosclerosis in diabetic patients" has not been clarified, and that "some unidentified factors inherent in the diabetic state" (Edit. N.E.J. Med., 1965) may chiefly be responsible for the accelerated development and relative severity of the diabetic vascular disease.

In this context, the demonstration in this series of a rather consistent and at times quite extensive involvement of the peripheral sympathetic nerves not only provides a firm anatomical basis for the clinical concept of "autonomic neuropathy", but also permits a completely different approach to the problem of "diabetic angiopathy". The latter, in our opinion, may be not a cause of the neuropathy, as it still is widely held, but rather a consequence, at least in part, of a primary damage to the autonomic (vasomotor) nerves leading to a partial or complete denervation of the blood vessel wall and resulting in the development of denervation supersensitivity (Bárány, 1955). Subsequent functional derangement of the vascular smooth muscle (spasm) and disturbances in the metabolic transport capacity of the vessel wall may provide favorable conditions for development of vascular disease in a diabetic (Snyder and Campbell, 1958). In support of this hypothesis, reports dealing with enhancing influences of sympathectomy alone or in combination with an atherogenic diet on the development of vascular disease in an animal can be cited (Harrison, 1939; Kerper and Collier, 1926/27; Lapinsky, 1900; Murphy *et al.*, 1957). Similarly, the degenerative vascular changes occurring in v. Recklinghausen's disease (Feyrter, 1949) and those observed in the limbs of the soliders who suffered peripheral nerve injuries (Krücke, 1955), may serve to further substantiate the above views regarding the suggested role of the autonomic neuropathy in the pathogenesis of the "diabetic angiopathy".

With regard to the formal pathogenesis of the "diabetic neuropathy complex" as outlined in this paper, it is our belief that it is a multifaceted neurological disorder which is chiefly characterized by a primary affection of the peripheral nervous system, both somatic (sensory) and autonomic. Segmental demyelination of the somatic peripheral nerves has been clearly shown to occur in diabetes and was interpreted as an evidence of a direct, presumably metabolic, injury to the Schwann cell (Chopra, 1969; Thomas and Lascelles, 1965; Thompson, 1965). However, an injury to the Schwann cell by itself could not account for the formation of the neuromata in the post-ganglionic division of the sympathetic nervous system since this presupposes interruption of the entire nerve fiber and a serious damage to its endoneurial sheath as well. Furthermore, the identity of the Schwann cells of the motor and sensory somatic nerves which often are discrepantly involved in diabetes would speak against an assumption that their Schwann cells are the sole point of attack by the postulated noxa. The extent of degenerative changes in the sensory roots and ganglia as demonstrated in this series as well as by others (Bosanquet and Henson, 1957; Greenbaum *et al.*, 1964) clearly demonstrates that the sensory neuron suffers as a whole. Therefore, a simultaneous damage to the sensory (and autonomic) ganglion cells either via a direct injury to their perikarya (Greenbaum *et al.*, 1964) or through an injury to their capsule cells (satellites), which were shown to be closely related to the Schwann cells (Cervós-Navarro, 1960), must be considered. It may further be conjectured that the above postulated adverse effects upon anatomically "exposed" sensory and autonomic neurons can significantly impede their metabolic functions seriously affecting their ability to maintain the integrity of their processes, and thus secondarily facilitating degeneration and retarding regeneration of the sheath cells. In contrast, the motoneurons, which by virtue of their position, are "protected" from the noxious metabolic influences by the blood-brain barrier

would retain that ability to maintain, and in the case of a damage, to facilitate regeneration of their peripheral processes to a much greater degree.

Direct or trans-synaptic extension of the degenerative process to the intraspinal neuronal systems which have close functional connections with the primary sensory neurons is thought to be responsible for the changes in those systems, rather than a direct metabolic injury as has been suggested by Greenbaum *et al.* (1964).

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Appendix
Major Findings at General Autopsy

Case 1. Atherosclerosis of coronary, cerebral and systemic arteries, moderate; arteriolar nephrosclerosis; hypertrophy of heart (520 g); atrophy and fibrosis of pancreas, moderate to severe; subacute interstitial pancreatitis; diabetic glomerulosclerosis, severe, nodular and diffuse type; uremic "frost" of skin; calcification of vasa deferentia; atrophy of testes; hyperplasia of parathyroids.

Case 2. Focal necrosis and fibrosis of myocardium; cardiac hypertrophy (530 g); arterial and arteriolar sclerosis, moderate to severe; diabetic glomerulosclerosis, diffuse and nodular type; hyperplasia of parathyroid glands; diabetic retinopathy; diffuse interstitial fibrosis of pancreas; decrease in numbers of (otherwise normal) islets of Langerhans; necrotizing lobular pneumonia.

Case 3. Occlusion of right coronary artery by atheromatous embolus; recent infarct of myocardium; atherosclerosis of systemic arteries, moderate, and coronary and cerebral arteries, marked; arteriolar sclerosis (hyalinization) of viscera; diabetic nephrosclerosis; diabetic retinopathy; hyalinization of islets of Langerhans.

Case 4. Atherosclerosis of the aorta and major arteries, mild, with recent thrombosis of left popliteal artery; atherosclerosis of coronary arteries, severe, with old and recent occlusions; hypertrophy of heart (420 g); old and recent infarcts of myocardium; arteriolar sclerosis of viscera; diabetic glomerulosclerosis; thrombophlebitis of femoral and popliteal veins; thromboemboli in pulmonary arteries.

Case 5. Generalized arteriosclerosis, moderate; arteriosclerosis of coronary arteries, marked; hypertrophy and dilatation of heart (480 g); pulmonary thrombo-emboli with recent infarcts; recent thrombosis of right popliteal vein; diabetic glomerulosclerosis; calcification of vasa deferentia; atrophy of testis; interstitial fibrosis of pancreas.

Case 6. Atherosclerosis of coronary arteries, slight to moderate; aorta, severe; major systemic and cerebral arteries, slight to moderate; generalized arteriolar sclerosis, severe; interstitial fibrosis of myocardium; hypertrophy of heart (520 g); diabetic glomerulosclerosis, slight, diffuse and nodular type; interacinar and perilobular fibrosis of pancreas.

Case 7. Hypertrophy of heart (410 g); atherosclerosis of coronary arteries, aorta and major systemic, moderate; and cerebral arteries, slight; interstitial fibrosis of myocardium, slight; focal necrosis of myocardium; arteriolar nephrosclerosis; acinar atrophy of pancreas, severe; hyalinization of islands of Langerhans, focal; diabetic glomerulosclerosis, nodular type; status post amputation of both legs; status post suprapubic prostatectomy and cystotomy.

Case 8. Atherosclerosis of coronary and major systemic arteries, slight to moderate; myocardial fibrosis, focal; hyalinization of islands of Langerhans; diabetic nephrosclerosis, diffuse type; lobular pneumonia.

Case 9. Chronic duodenal ulcer, perforated; purulent peritonitis; hypertrophy of heart (440 g); atherosclerosis of coronary arteries, severe, and of aorta and systemic arteries, moderate; infarcts of heart, recent and old; acinar atrophy and fibrosis of pancreas; diabetic glomerulosclerosis, slight, membraneous type.

Case 10. Subacute bacterial endocarditis; abscess in mediastinum; reactive splenitis; atherosclerosis of coronary arteries, slight; aorta and major systemic arteries, moderate; hypertrophy of heart (610 g); fibrosis of myocardium, slight; diabetic glomerulosclerosis, diffuse and nodular type, severe; acinar fibrosis and paucity of islands of Langerhans; lobular pneumonia.

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