Special Article

Neurologic Disorders of Diabetes Mellitus

Part I of a Two-part Review

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SUMMARY

Neurologic disorders are a common and often disabling aspect of diabetes mellitus. Pain and sensory disturbances, weakness and paralysis and symptoms of autonomic dysfunction may be experienced by the diabetic patient.

Although neurologic disorders have been noted in association with diabetes mellitus for many years, knowledge concerning this group of disorders is quite incomplete. Terminology used in discussing them is often vague and inconsistent. There is no accepted method of classification. Pathologic studies are incomplete and inconclusive. A great variation in clinical manifestations creates difficulties in diagnosis as well as in pathophysiologic interpretation. Numerous papers have discussed the theories of pathogenesis of these disorders, yet none has answered the basic question.

This report is a review of a major portion of the literature on the subject. Emphasis is placed on the theoretical as well as practical aspects of these disorders, as their relationship to the disease state of diabetes mellitus is unique and important. These disorders must be explained in a final analysis of diabetes mellitus. Deficiencies exist in the present state of knowledge, but a solid basis for future study has been established. DIABETES *14*:424-29, July 1965.

A. INTRODUCTION

Neurologic disorders represent important practical and theoretical facets of diabetes mellitus. From a practical standpoint, they are a common source of morbidity in diabetes. Severe pain, distressing visceral symptoms, paralysis and invalidism may be suffered by the diabetic patient. From a theoretical standpoint, diabetic neurological disorders must be accounted for in any discussion of the nature and pathogenesis of diabetes mellitus.

Although diabetes has been described for some 3,500 years,[1] neurologic disorders associated with diabetes were not recorded until 1798, when John Rollo[2] mentioned them in his book *Cases of Diabetes Mellitus*. Confusion as to which disorder caused the other was resolved in 1864 when Marchal di Calvi[3] stated that diabetes caused the neurologic disorders. Thorough accounts of the history of these disorders have been given by Goodman et al.,[4] Jordan,[5] Martin,[6,7] Rundles,[8,9] Woltman and Wilder,[10] Garland[1] and Johnson.[11]

There has been a persistent lack of understanding of the neurologic disorders in diabetes. Protean clinical manifestations, misuse of common neurologic terminology, a paucity of pathologic studies and incomplete knowledge of diabetes contribute to our ignorance. There is no diabetic neurologic syndrome, but rather a heterogeneous array of mononeuropathies, polyneuropathies, myelopathies and possibly encephalopathies, which vary in type, nature of onset, relationship to diabetic control, severity, prognosis and susceptibility to various therapeutic programs. The vagaries of diabetic neurologic disorders are so numerous that their recital leads to discouraging confusion.[12] Apparent and real contradictions in the literature are commonplace. Inconsistencies in the use and definition of such terms as "neuropathy" and "control" cloud interpretation and comparison. Yet the subject is not one of total confusion. A solid nidus for more cohesive and economic study of these disorders has been established. Future work will hopefully add the depth and clarity that is presently lacking.

This paper is a review and analysis of a major portion of the literature on the subject. Certain disorders which might justifiably be included under the broad title are wholly or partially excluded from this survey. They are cerebral vascular disease and diabetic retinopathy.

B. DEFINITION OF TERMS

The term "diabetic neurologic disorder" denotes any dysfunction or pathologic change in the nervous system, central or peripheral, which coexists with and can be attributed to no etiologic factor other than diabetes mellitus.

A lack of consistency in the terminology used on the subject is evident. The term "neuropathy," which refers to a pathologic alteration of one or more peripheral nerves, has often been mistakenly used when structures other than peripheral nerves may be implicated.[13] "Neuronopathy" implies involvement of spinal roots while "myelopathy" implies involvement of spinal cord. "Encephalopathy" and "myopathy" refer to disease of the brain and muscle, respectively. "Amyotrophy" infers atrophy of muscle. This atrophy may or may not be neural in origin. Disease of one nerve is "mononeuropathy." "Mononeuropathy multiplex" is the simultaneous dysfunction of several single, major nerves. "Polyneuropathy" implies a more diffuse process which affects multiple systems.

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It is often bilateral and symmetric.[14,15] The term "neurologic disorder" may be used when the damaged structure is in question. It must be stressed that the term "neuropathy," as it has been used by certain authors, has frequently connoted dysfunction which may involve more than peripheral nerves.

C. CLASSIFICATION

Presently there is no universally accepted classification. Classification of neurological disorders in diabetes has been based on location of the lesions,[6,16,17] pathogenesis,[5,18-21] and clinical manifestations.[1,4,11,22-24] The brain, spinal cord, spinal roots, peripheral nerves and autonomic nerves have been listed in an anatomical classification. Pathogenic factors mentioned are hyperglycemia, vascular disease, nutritional disturbance and a "specific" effect of diabetes. Logothetis and Baker[25] presented a classification of clinical types. They listed:

A. *Peripheral nervous system syndromes (diabetic neuropathies).*
   1. Symmetrical peripheral neuropathy (diabetic polyneuropathy)
   2. Asymmetric neuropathy (mononeuropathy, mononeuropathy multiplex)
   3. Radiculopathy
   4. Autonomic visceral neuropathy
   5. Cranial neuropathy and retinopathy

B. *Spinal cord syndromes*
   1. Diabetic myelopathy, diabetic pseudotabes
   2. Diabetic amyotrophy
   3. Acute vascular syndrome; myelomalacia

C. *Cerebral syndromes.*
   1. Cerebrovascular accidents and chronic cerebrovascular disease
   2. Diabetic coma

D. *Neurologic abnormalities in infants of diabetic mothers.*

D. PATHOLOGY

Pathologic studies of the neurologic disorders associated with diabetes are few and not definitive. Contradictions are noted from one author to another. Specimens are difficult to obtain because many patients recover, and many studies have been done on patients with severe forms of disease who may have had concomitant disorders affecting the nervous system.[26] A poor delineation of the patho-physiologic processes involved is evident.

1. *Brain*

A study of the brain of thirty-six diabetics was done by Dolman.[27] He examined microscopic sections from the cerebral cortex, white matter, lenticular nucleus, internal capsule, thalamus, hypothalamus, midbrain, pons, medulla and cerebellum. He found no evidence of damage. Courville[28] noted chromatolysis in the motor nuclei of the brain stem. Garland[1] doubts the existence of a diabetic encephalopathy if diabetic coma is excluded. Cerebral vascular disease, hypertension, diabetic coma and hypoglycemia are major factors in the development of pathologic alterations in the brain of diabetics.

2. *Spinal cord*

Grossly, the cord may appear normal[1,29,30] or it may be shrunken and rubbery.[31] Lesions may be found anywhere in the spinal cord. Dolman[27] and Greenbaum et al.[204] observed the lesions to be more severe caudally but others[29,30,32] observed changes in the cervical and thoracic regions more frequently. The dorsal columns are most commonly involved[27] but the anterior horn cells, ventral posterior columns and right posterior columns may be affected.

Several pathological processes have been noted and one or more processes may be observed in a given specimen. Dolman[27] noted a reduction in number of myelin sheaths and a thinning of both myelin sheaths and axons. Heavy fibrous gliosis was seen in extreme cases. Alderman[31] observed an almost selective attack on anterior horn cells with atrophy and replacement by fat. He proposed the term "neuronopathy." This finding was verified by Greenbaum et al.,[204] however, Dolman[27] reported no pathologic changes in anterior horn cells. Gill[33] stated, "The characteristic lesion appeared to be a mild, diffuse gliosis of the dorsal columns with vacuolization, rarefaction and loss of substance. Some cells showed an increase in lipoid material and eccentric nuclei. There were also numerous corpora amylacea present." Griggs and Olsen[30] saw "... myriads of compound granular corpuscles which were filled with fat," and also observed new blood vessel formation. Muri[34] noted anterior horn cell degeneration with disintegration of Nissl granules and peripheral nuclei.

3. *Spinal roots*

Spinal root involvement is usually associated with spinal cord changes. The posterior roots may be atrophic and demyelinated in severe cases.[27,29,33] Ellenberg and Krainer[35] observed marked fibrosis in the lumbar roots. Muri[34] reported that the spinal roots were normal in the presence of severe anterior horn cell destruction.

4. *Peripheral nerves*

All sizes of nerves may be affected. Small, unmyelinated fibers may be affected first,[1,7,36] however, Greenbaum et al.[204] report damage to large myelinated fibers as the earliest change. The sciatic, femoral, posterior tibial, anterior tibial, tibial and sural nerves have displayed evidence of damage on histologic section. Dolman[27] found no histologic mononeuritis although clinical evidence of mononeuritis is documented.[37] The relative frequency of individual nerve involvement was reported by Dolman.[27] Among thirty-five sciatic nerves which he examined, eleven had severe changes and ten had slight changes. One of twenty-five femoral nerves examined was badly damaged and twelve were slightly damaged. Fourteen of thirty-one anterior tibial nerves were severely damaged, and eight were slightly damaged.

Four pathologic processes are described: myelin degeneration, axonal degeneration, fibrosis and swelling of motor end plates. Dolman[27] believed that the principal lesion was a patchy myelin degeneration with axonal degeneration. Greenbaum et al.[204] assert that the basic pattern is primary neuronal degeneration rather than demyelinization. Ellenberg and Krainer[35] reported the major process to be endoneural thickening and patchy fibrosis. Muri[34] noted no fibrosis of the posterior tibial nerve but observed myelin degeneration. Zucker and Marder[32] and Forster and Bassett[38] noted both processes occurring together.

A conflicting report is that of Woolf and Malins.[39] They were amazed at the rarity of degeneration of nerve fibers in diabetic neuropathy and they presented biopsy studies of muscle which demonstrate a lesion in the motor end plate.

They believe that the lesion is quite specific for diabetes, "... only in diabetic neuropathy have we seen this almost universal transformation of the end plates into a single large element." They state that the end plate may take the form either of an irregular or a regular swelling of the terminal expansions which may fuse to form a single balloon or soap-bubble structure. They conclude from this that the terms "peripheral neuritis" or "neuropathy" are misleading labels and suggest that the lesions noted represent a disease of the entire neuron manifesting itself by a dying back from the end organ. This dying back, or abiotrophy may be similar to the spinocerebellar degenerations described by Greenfield.[40] Swelling of terminal nerve fibers with motor endplate degeneration in diabetes is discussed by Zachs in his recent book on the motor endplate.[206]

5. *Cranial nerves*

Dreyfus et al.[41] examined a paralyzed oculomotor nerve. It was swollen to twice normal size with extensive destruction and disappearance of both myelin sheaths and axis cylinders. The nerve they studied was from a patient with acute paralysis. No other studies of cranial nerves are available.

6. *Autonomic nerves*

Berge et al.[42] examined the entire thickness of large and small intestine from patients who had suffered diabetic diarrhea. Ganglion cells in the plexuses of Auerbach and Meissner were noted to display varying degrees of chromatolysis, vacuolization of cytoplasm and pyknosis. Fibrosis was prominent in one specimen. Auerbach's plexus was more frequently involved. An unexplained finding was that in thirty-two specimens, intact nerve fibers and ganglion cell processes were associated with ganglia that were abnormal.

7. *Muscles*

It is uncertain whether muscular atrophy in diabetes is primary or secondary to a neural lesion. Dolman[27] and Greenbaum et al.[204] reported neurogenic atrophy of muscle on histologic section. Garland[1] observed neurogenic atrophy yet detected no lesion in the peripheral nerves or spinal cord. Locke et al.[43] and Bischoff[44] noted a histologic pattern of normal and atrophic fibers side by side. This single fiber muscle atrophy is in distinct contrast to the unit muscular atrophy of a neurogenic disorder. Diabetic angiopathy was not believed to cause the observed histological picture. Therefore a primary lesion of muscle must also be considered.[43]

8. *Relationships to surrounding blood vessels*

Occlusive vascular disease has been found in association with neuropathy. Woltman and Wilder[10] are frequently quoted for having demonstrated a definite cause-effect relationship between the two. It must be noted that eight of ten of the patients studied by them had gangrene of the legs, and it was these structures that were examined. Their findings of severe myelin degeneration associated with severely damaged vessels were identical to the findings of Priestly[45] who studied the nerves in legs with arteriosclerotic gangrene not associated with diabetes. Gill[33] examined blood vessels in the spinal cord from a patient who suffered from diabetic myelopathy and found no evidence of vascular occlusion. Greenbaum et al.[204] found no evidence of occluded vasa nervora in their recent study. Dolman[27] made particular note of the vessels associated with involved nerves. A common feature was cellular hyperplasia in the intra- and perineural arterioles with reduction of the lumen. PAS staining of the internal elastica and vascular reticulum of arterioles and the entire walls of capillaries could be effected; however, staining was much less intense in neural vessels than in those of the pancreas and kidney in diabetic subjects. Goldenberg et al.[46] and Fagerberg[47] present evidence for a specific diabetic vascular disease which might affect nervous tissue. This process, detected by PAS positive substance in the vessels and intimal swelling and proliferation of endothelium, was found to be present in the vascular supply to nerves (see section on pathogenesis).

9. *Clinical pathological correlation*

Attempts to correlate pathologic and clinical findings have revealed paradoxes. Woltman and Wilder[10] stated, "Although in cases 1 and 8 the neurologic complications were sufficiently complex to justify a diagnosis of pseudotabes diabetica, few of the other patients exhibited more than mild pain or paresthesia and none had any ataxia or motor weakness. The extent of degeneration in the peripheral nerves in all ten cases is the more remarkable, in view of the mildness of the nerve symptoms. It would appear that accurate correlation does not exist between the degree of degeneration of the nerves and the symptoms." Hutchinson and Liversedge[48] reported similar findings. In contrast to this Dreyfus et al.[41] reported that the extra-ocular paralyses possibly were due to a disorder of function rather than an irreversible structural change as the paralysis was much more severe than the pathological picture would indicate and patients recovered long before regeneration could be expected. Berge et al.[42] could not correlate intestinal dysfunction with changes in the neurons of the enteric ganglia. They stated that their study did not give direct pathologic confirmation for a neurogenic basis for diabetic diarrhea. Minimal nerve damage may be associated with severe neurogenic atrophy of muscles.[1,27] However, Fagerberg[49] reported good correlation between the clinical and the pathological, as determined by sural nerve biopsies.

Goldenberg et al.[46] correlated the presence of clinical neurologic signs with histologic evidence of vascular derangement. In his study, twenty-two of twenty-four patients had clinical signs with evidence of vascular damage. Six of thirteen had questionable clinical signs with evidence of vascular damage and one of eight had no clinical signs with evidence of vascular damage.

E. CLINICAL CHARACTERISTICS

Clinical manifestations of diabetic neurologic disorders are extremely variable. There is no specific syndrome. Dividing diabetic patients into neurologically normal and pathologic groups is often difficult.[38] Any combination of structures may be involved and considerable overlapping of involvement may be seen.[50]

1. *Incidence*

Neurological disorders are common in diabetics although agreement on a precise statement of incidence is lacking. Variability of diagnostic criteria, continued refinement in diagnostic technics and the degree of awareness of the disorders account for differences of reported incidence. Mulder et al.[37] using objective evidence such as definitive electromyographic changes, reflex changes and muscle weakness recorded involvement in forty-three of 103 patients. Goodman et al.[4] recorded an incidence of 62 per cent when subjective complaints such

as pain and paresthesias were accepted. Others have reported the incidence to be from zero to 93 per cent.[4] Garland[1] stated that in England there were 400,000 patients suffering from diabetic neuropathy as compared to 30,000 patients with Parkinson's disease.

2. *Signs and symptoms*

(a) *Peripheral nerves.* Polyneuropathy affecting chiefly the lower extremities is the most common neurologic disorder in diabetes. Typically the disorder is manifested by diffuse, symmetrical sensory disturbances of the distal portions of the legs.[23,25] Although not as common as the diffuse sensory disorders of the legs, mononeuropathy and mononeuropathy multiplex are seen in diabetes. Any peripheral nerve may be damaged.[51,6] The femoral, sciatic, median, ulnar, peroneal, radial and lateral femoral cutaneous nerves are commonly involved.[35,51,6,53] Paralysis of the long thoracic nerve,[6] the recurrent laryngeal nerve and superior laryngeal nerve[5] has been reported. Clinically, nerves may be involved singly or in combination. In a series of forty-three patients, twenty-seven had a diffuse polyneuropathy, twelve had a mononeuropathy and four had a combination of both.[37] Involvement may be purely sensory, purely motor or mixed sensory and motor.

Sensory disturbances and pain are the most common complaints.[8,20,21,54,55] The pain may be deep-seated, as if in the bone marrow,[55] cramplike with tenderness, or it may have a burning quality. Legs have been amputated for relief of pain. The pain is often nocturnal, appearing a few hours after the patient has gone to bed. Walking often gives relief.[23,56] Numbness is a frequent complaint. Paresthesia, hyperesthesias and dysesthesias may be so severe as to make the touch of bed clothing excruciating and require construction of special cradles. Weight loss may be severe. Anorexia is an infrequent complaint.

The loss of tendon reflexes is the most common sign.[9] In one group of diabetics,[57] 64.9 per cent had diminished or absent achilles reflexes, 50 per cent had diminished or absent knee jerks and 39.2 per cent had diminished reflexes in the upper extremities. Ellenberg[58] reported that diminished or absent tendon reflexes are not a manifestation of old age, as Critchley[59] had stated. The mean vibratory perception threshold is significantly increased in diabetics.[60] Areas of anesthesia in the extremities are common. Muscle weakness is not as common but diabetic amyotrophy has been thoroughly described.[1,23,43,61,62] Locke et al.[43] observed twenty patients with the disorder; twenty had weakness of the pelvic girdle with all displaying weakness of the psoas muscles. The glutei, hamstrings, quadriceps and other thigh muscles were weak. Five of twenty had weakness of the shoulder girdle with the triceps, biceps, deltoid, supinator longus and sternocleidomastoid being involved. Weakness was always bilateral and often asymmetric. Fasciculations were noted in four of twenty patients. Janda and Kozak[202] recently reported electromyographic evidence of muscular dysfunction occurring independently of a peripheral nerve abnormality. This observation was more apparent in a younger group of diabetic patients.

Diabetic Charcot joints and neuropathic ulcers of the lower extremities may be associated with peripheral neuropathy.[38,63-66] These lesions are caused by minor and constant trauma, infection, decreased deep and superficial pain sensation and decreased proprioception.[38,63,65,67] Vascular insufficiency may be present but is not necessary for the development of these lesions. The joints most commonly involved are those of the small bones of the foot in the tarsal region. Involvement of ankle and knee has been reported. The process may be unilateral or bilateral. The first sign is painless swelling without heat or redness. With further degeneration a tendency to eversion and external rotation is noted. These joints differ from true Charcot joints by (1) their location, (2) the lack of fluid and (3) the slow onset. Neuropathic ulcers must be differentiated from ischemic ulcers as the treatment differs considerably.

b. *Spinal cord and spinal roots.* Rudy and Epstein[54] noted signs of myelopathy in twenty-six of 100 patients with neurologic disorders attributed to diabetes. Diabetic myelopathy may simulate tabes dorsalis and posterolateral sclerosis.[17] The term "pseudotabes diabetica" has been given to the cord syndrome. The gait may be broad based and unsteady, requiring the patient to look at the ground when walking.[43,67] Loss of position sense and a positive Romberg may be observed.[67] Atonic bladders and impotence are reported. Weakness and muscle wasting, particularly of proximal musculature of the legs, constitute part of the cord syndrome. This is usually bilateral and asymmetric.[1,23,43] The patient may be unable to mount stairs or rise from a chair unassisted.[67] Diffuse pain,[13] loss of deep tendon reflexes[13,43,67] and fasciculations[43] may be seen in cord lesions as well as peripheral neuropathy and indeed the two may often coexist.

c. *Autonomic nervous system.* Functional disturbance of the autonomic nervous system in diabetes is common and may be particularly distressing to the patient. Martin[7] noted small vessel dysfunction in all patients with peripheral neuropathy. Absent circulatory reflexes were present in sixty-nine of 337 patients studied by Sharpey-Shafer and Taylor.[68] The autonomic lesion is post-ganglionic[36] and may affect one or more anatomical areas. Martin[6] noted paralysis of peripheral vessels similar to that seen in sympathectomy in half the patients studied; the other half retained the capacity for vasoconstriction. Handelsman et al.[84] observed a decrease in skin vessel dilatation after Priscoline injection when no peripheral vascular disease or peripheral neuropathy could be detected.

Symptoms resulting from altered sudomotor and vasomotor activity may assume two discrete syndromes; one is similar to surgical sympathectomy and the other is a symptom complex simulating overactivity of the autonomic nervous system.[7] The sympathectomy syndrome consists of temperature elevation, absence of sweating, and redness associated with hyperemia at the affected area. Orthostatic hypotension, syncope and a compensatory tachycardia may be noted in severe cases. Peripheral pulses are often intact. Opposite effects such as pale, cold extremities, inability to increase skin temperature and increased sweating are noted in the other group of patients. Autonomic dysfunction is often observed in the legs, but any part of the body may display these disorders. Pavy,[55] in 1885, reported a patient who had an absence of sweating on one side of the body with normal sweating on the other side.

Impotence has been noted to affect from 43 per cent[69] to 51 per cent[70] of male diabetics. Autonomic dysfunction has been considered important in the development of impotence,[59] but the disorder may be present without other signs of autonomic disturbance.[71] Schoffling et al.[70] reported decreased urinary

excretion of pituitary gonadotrophin in male diabetics and concluded that diabetic impotence may be caused by hypogonadotrophic hypogonadism. Atonic bladders,[6,72] urinary incontinence and prostatism[8] have been attributed to diabetic autonomic dysfunction. Retrograde ejaculation of semen into the bladder has been observed.[52,201] This autonomic disturbance may effect sterility in male diabetics.

Gastrointestinal disturbances include gastric atony (gastroparesis diabetacorum,[72-74] segmental hypomotility of the small intestine,[72] intractable constipation,[6] fecal incontinence[8] and diarrhea. Diabetic diarrhea is the most common of these disorders. It is often intermittent and nocturnal; however, it may be chronic and unrelenting.[6,7,50,72,75] Abdominal cramps may precede an episode of diarrhea, but pain is unusual.[75,76] Malabsorption and steatorrhea occasionally complicate the disorder. The severity of the steatorrhea parallels that of the diarrhea.[77-80] Recovery is very slow. Gastric atony may produce nausea, vomiting, unexplained weight loss, worsening of diabetic control and ill-defined, vague, abdominal pain. Upper gastrointestinal symptoms may be absent, however, with the condition.[72] X-ray studies reveal nonspecific dilation, residue and sluggish or absent peristalsis,[72,74,81] similar to the gastric findings in vagotomized patients.

Martin[6] noted pupillary changes in 9.0 per cent of patients with diabetic neurologic disorders. Sluggish or true Argyll-Robertson pupils may be seen.[6,82] Pupillary disturbances often exist independently of optic or oculomotor neuritis. Other disorders attributed to autonomic dysfunction are ankle edema and malformed and pigmented toenails.[6]

d. *Cranial nerves.* Dysfunction of ten of the twelve cranial nerves has been reported: II,[4,5,85] III,[41,86-88] IV,[41,86] V,[89,90] VI[41,89,90] VII[5,6,89] VIII,[5,6] IX, X and XI.[89] One or more cranial nerves may be affected in a patient. The most commonly involved are the III and VI nerves.[41] Skillern[85] reported fourteen cases of diabetic optic neuritis. Loss of vision was the main complaint and a few patients noted pain. Eight had bilateral involvement. The optic disk revealed papillitis or definite optic atrophy. Seven patients had a central scotoma and eleven had peripheral contraction of the visual fields. Pain is a common feature of III, IV and VI nerve palsies. The third nerve may be affected without concommitant pupillary disturbance.[88,91] Acute onset with recovery in a few months is typical for this condition. Facial nerve palsy and nerve deafness are infrequently reported and their relationship to diabetes is questioned.[5,6] Larson and Auchincloss[89] reported three cases of multiple, bilateral symmetrical cranial nerve palsies which affected from five to seven cranial nerves including the III, V, VI, VII, IX, X, XI nerves.

e. *Cerebrum.* Rudy and Epstein[54] reported encephalopathy in nine of 100 patients with diabetic neurologic disorders. Symptoms of irritability, inner tension, disturbing thoughts, nervousness, hypochondriasis, delirium, suicidal tendency, hallucinations, ideas of persecution, difficulty in concentration, emotional lability, psychic aberrations and severe depression have been reported.[5,17,50,92,93] The existence of diabetic encephalopathy has been questioned by Garland.[1] A high coincidence of hypertension and arteriosclerosis and the stresses and tensions associated with adapting to a chronic disease add difficulty to an evaluation of the patients.[93,94] Diabetic coma, hypoglycemic episodes[95] and cerebral vascular disease must be considered in the evaluation of cerebral symptoms in diabetics.

3. *Relationship to various factors*

a. *Rapidity of onset.* Neurological disorders in diabetes vary in rapidity of onset from acute, within hours, to extremely insidious. The most notoriously acute cases are those involving the nerves to extra-ocular muscles.[5,41,86,96] Peripheral neuropathies may also have an acute onset.[97] Ellenberg[98] and Dolger[99] noted acute neuropathies which occurred after stress situations, with a latent time of approximately ten days to two weeks. However, some neurological disorders are subtle and are detected only by a decrease in vibratory sense,[60] lack of peripheral vasodilation[7] and loss of deep tendon reflexes.[100] Many autonomic disorders are slowly progressive. Gastric atony may have either an acute or insidious onset.[72,81] The loss of vision in diabetic optic neuritis is usually slowly progressive.[85]

b. *Age.* Diabetic neurological disorders are rare under the age of ten years,[16] but occur at all ages over ten. The frequency increases with age,[37,96,101,102] but neurological disorders are not uncommon in the younger groups.[6] Lawrence and Locke[103] report an incidence among diabetic children which is considered higher than previously suspected. They noted that eight of twenty-five randomly selected diabetic children had neurological disorders.

c. *Sex.* The frequency of diabetic neurological disorders varies little between the sexes. Martin[6] noted 47 per cent of the cases to be males. Rundles[9] reported an incidence of 55 per cent for males.

d. *Severity of glucose intolerance.* Several authors report no correlation of neurologic disorders with the severity of glucose intolerance, as measured by insulin requirement[50,69,86,104,105] although Pirart[203] presents recent data which demonstrate a positive correlation. The most severe forms of neurological disorders may occur in diabetics who have normal fasting blood sugar values.[1,15,23,100] Ophthalmoplegia,[41,86] gastric atony,[72] impotence,[69] myelopathy,[13] amyotrophy,[43] and sensory disturbances may occur in mild diabetics.

e. *Duration of diabetes.* The relationship between the duration of known glucose intolerance and the occurrence of neurologic disorders is disputed. Although statistical evidence pointing up a positive correlation is reported,[203] neural mechanisms may be grossly and permanently altered long before carbohydrate tolerance is greatly affected.[15] Patients with unrecognized diabetes may present with a neurological disorder as a chief complaint and others with severe diabetes for decades may have no neurological disturbance.[37] Two cases of "diabetic" neurologic disorders have been observed before detectable glucose intolerance.[54]

Perhaps any correlation of a complication of diabetes with the "duration" of diabetes is only a correlation of that complication with the age of the patient, as diabetes is considered to be an hereditary disorder which begins at birth[106] and glucose intolerance is preceded by a "prediabetic state."[107,108]

f. *Control.* Although arbitrary criteria have been suggested,[16,22,109,203] the word "control" denotes no standard quantitative definition. The importance of the relationship of diabetic control to the diabetic neurological disorders lies both in the theoretical aspect of causality and in the practical aspect of therapy.

Certain authors state that well controlled diabetics rarely

develop neurological disorders[4,102,110,203,205] and others note that certain symptoms, namely the sensory complaints of aching pains, cramps, tenderness, burning and numbness, occur during periods of poor control and are relieved by good control.[5,19,20,22,111-113] Pirart[203] in evaluation of 1,175 diabetic patients, reported poor control to be a major factor in the development of these disorders. A growing number of authors, however, regard control as a minor factor in the development of neurological disorders.[37,49,96,104,105,114-117] Aring[116] stated, "It is disheartening again and again to bump into a lighthearted and somewhat mesmeric statement that 'control' of the diabetic state will in some manner prevent or ameliorate diabetic neuritis (neuropathy) and lack of 'control' foster it."

g. *Cerebrospinal fluid protein.* Increase in cerebrospinal fluid protein has been noted with varying incidence in diabetic neurological disorders.[9,13,43,67] The significance of elevated values is unknown. Ives[119] noted that 69 per cent of patients with peripheral neuropathy had elevated cerebrospinal fluid protein levels, but no obvious correlation with vascular disease, pathologic studies, co-existing retinopathy, or duration of diabetes was found. There was an increased tendency for the values to be elevated in older groups. Patients with outstandingly good control had a slightly higher incidence of increased protein and institution of therapy changed the levels very little. Kutt et al.[120] studied cerebrospinal fluid protein levels in diabetics with both vascular disease and neurological disorders and found protein elevation in patients who had either of the two disorders singly or in combination; however, some patients who had both disorders had normal values. The more acute disorders were generally associated with higher values. Electrophoretic studies revealed no typical "diabetic" pattern.[120]

h. *Severity of neurological disorders.* A spectrum of disability may be found. Mild pains, cramps and paresthesias are common. Conversely, cases of extreme disability have been presented. Blindness, deafness, chronic malnutrition from diarrhea, impotence and severe weakness are reported. Amputation of an extremity for the relief of pain has been performed. The severity of the neurological disorder reveals no apparent relationship to the severity or duration of the diabetic state, age, sex, or cerebrospinal fluid levels.

4. *Neurologic abnormalities of infants born to diabetic mothers* Infants of diabetic mothers have increased mortality rates and a higher incidence of malformation.[25,121-128] Neurologic abnormalities contribute to these statistics. Congenital cerebral diplegia, severe malformation of the brain, mental deficiency, hydrocephalus, meningocele, monsters, stillbirth, deafness associated with mutism, spinal malformation, microcephaly, anencephaly, and intracranial hemorrhage are reported. Hormonal imbalance, hypoglycemia and hyperglycemia with its associated ketosis are factors which have been considered important in the development of these disorders.

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