OBSERVATIONS ON THE HOMOGENEOUS NATURE AND PATHOGENESIS OF DIABETIC NEUROPATHY

BY

D. GREENBAUM

(From The London Hospital, London, E.1)

Although the clinical features of diabetic neuropathy have often been described, its pathological basis and aetiology remain uncertain, nor is it known whether it consists of more than one entity.

It has been suggested that it has an ischaemic origin, either from occlusion of the vasa nervorum by atheroma (Woltman and Wilder, 1929) or by diabetic angiopathy (Fagerberg, 1959). Many authors consider that it is caused by a metabolic defect of unknown nature associated with poorly treated diabetes but this is disputed by others (e.g. Wilder, 1940; Ellenberg, 1959). The site of the lesion is also controversial, some localizing it in the peripheral nerves (Woltman and Wilder, 1929; Goodman et al., 1953) and others speculating on other sites (Garland, 1955).

Its clinical manifestations are varied and attempts have been made to divide it on a clinical basis. Jordan (1936) separated it into "true" and "degenerative neuritis," Sullivan (1958) into "asymmetric motor" and "distal symmetric neuropathy" and Fry et al. (1962) into "amyotrophy" and "symmetrical peripheral neuropathy." Root and Rogers (1930), Garland (1955), Bischoff (1959) and Isaacs and Gilchrist (1960) considered that patients with predominantly motor involvement warranted special description. The divisions of these and other authors appear largely to be variants of two contrasting syndromes—one of well-defined onset with pain and muscle weakness as prominent features, and another of insidious onset with clinical signs but few or no symptoms. It is uncertain whether such variants represent more than one disease process as has been suggested by Jordan (1936) and Sullivan (1958).

In the present paper an attempt is made to elucidate some of these problems. The paper is based on a study of 80 patients with clinical evidence of diabetic neuropathy.

Selection of Patients

All the patients attended The London Hospital and were seen and examined by the author. The criteria for the diagnosis of diabetic...
neuropathy were based on the descriptions in the large clinical surveys of Jordan (1936), Rundles (1945) and Martin (1953a) and included one or more of the following features occurring in diabetic patients: pain of a type to be later described, muscle weakness, tendon areflexia and sensory loss. The diagnosis of diabetes mellitus was, in general, based on a history of thirst, weight loss and polyuria in the presence of heavy glycosuria and supported by random blood glucose levels elevated above 200 mg./100 ml. In 4 patients, in whom polyuria was absent and glycosuria slight, the diagnosis was based on the standard glucose tolerance test.

Patients in whom the clinical manifestations may have been due to coincidental neurological disease (for example those with positive serological tests for syphilis) were excluded, as were those with isolated cranial nerve lesions without other evidence of neuropathy, since these are not peculiar to diabetes. Absent ankle-jerks alone were not accepted as adequate evidence of diabetic neuropathy, neither was foot ulceration in the absence of neurological signs. When pain was the only clinical manifestation, it was often difficult to exclude other conditions which might have caused it, and only 3 such patients were included.

An attempt was made to see all those diabetic patients presenting with pain or muscle weakness during the years 1958–60 inclusive. After exclusion of other diseases as a cause of these symptoms, 34 such patients were included in the study. It is believed that these represented most or all of the patients presenting in this way during the stated period and that they formed a largely unselected group. As this group did not include patients whose acute symptoms had subsided or who had neurological signs but no symptoms, a further group of 46 patients was selected by reference to the hospital diagnostic index of the preceding twenty years or to current case records and these were subsequently interviewed and examined. The method of selection of these patients limited the conclusions to be derived from their study. In all, 80 patients (41 men and 39 women) were included in the series.

Methods of Investigation

Information about past history and previously observed neurological signs was derived from hospital records. Information about near relatives was obtained when possible by personal interview and examination and in other cases by letter.

Electrodiagnostic tests were carried out on 47 patients. They included the determination of strength duration curves of muscles by the method described by Wynn Parry (1956) and concentric needle electromyography in each and the determination of motor nerve conduction velocity by the method described by Thomas et al. (1959) in 4.

Reflex skin temperature responses in the extremities were investigated in 42 patients by the method described by Martin (1953b) modified by the
use of a fan for cooling and of hot water bottles for heating the trunk. Failure of the toes to cool in response to trunk cooling when the thumbs did so normally was the only response accepted as evidence of vasoconstrictor nerve damage. Other responses which included failure to obtain adequate trunk cooling because of discomfort, failure to obtain a contrast in reflex cooling between thumbs and toes and persistently cold toes failing to respond to trunk heating were regarded as inconclusive.

**CLINICAL NEUROLOGICAL FEATURES**

For the purpose of description and subsequent analysis the patients are divided into two groups as proposed in the introduction: (1) a group of 54 (27 of each sex) who either presented with or gave a history of pain or muscle weakness, (2) a group of 26 (14 men and 12 women) who developed neurological signs insidiously. The first syndrome will be called the "subacute" neuropathy and the second the "insidious" neuropathy, but apart from pain and weakness, the occurrence of various neuropathic features was not markedly different in the two groups.

The incidence of neurological signs and symptoms is shown in Table I.

<table>
<thead>
<tr>
<th>TABLE I.—INCIDENCE OF CLINICAL FEATURES</th>
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<tbody>
<tr>
<td>(The figures in brackets refer to the 34 patients with the &quot;subacute&quot; neuropathy presenting during 1958–60)</td>
</tr>
<tr>
<td><strong>No. of patients</strong></td>
</tr>
<tr>
<td><strong>Subacute neuropathy</strong></td>
</tr>
<tr>
<td>54 patients</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Muscle weakness</td>
</tr>
<tr>
<td>Loss of tendon reflexes</td>
</tr>
<tr>
<td>Sensory loss</td>
</tr>
<tr>
<td>Autonomic disturbance</td>
</tr>
<tr>
<td>(diarrhoea or impotence)</td>
</tr>
<tr>
<td>Penetrating foot ulcers</td>
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</table>

The diagnosis of neuropathic pain was based on its clinical features. It was of a peculiarly disagreeable quality and often graphically described, for example "the skin feels as if it is being lifted with forks." It was worse at night in about four-fifths of the patients affected and was not aggravated by exertion, coughing or by moving the spine. Cutaneous hypersensitivity of a similar distribution was present in about one-third of the patients affected. Differentiation from other causes of pain largely depended on these features and was inevitably somewhat arbitrary. Muscle weakness varied from the slightest degree to a severity sufficient to prevent all ordinary activities. Sensory loss varied from the absence of vibration sense to the partial loss of all modalities; except in one case, it was not severe. Impotence and predominantly nocturnal diarrhoea
are widely regarded as evidence of autonomic nerve involvement in diabetes and have accordingly been listed as neuropathic manifestations, but there was no certainty that they were always of neuropathic origin. The assessment of the aetiology of foot ulcers presented similar difficulties in some cases.

The neuropathic manifestations were predominantly localized in the legs (sensory loss in their distal part). Pain and muscle weakness often occurred together (37 patients), and then shared a similar distribution, which, within the legs, was very variable (Table II). When severe,

<table>
<thead>
<tr>
<th>Predominantly</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>unilateral</td>
<td>proximal 17 (12)</td>
</tr>
<tr>
<td></td>
<td>distal 2 (1)</td>
</tr>
<tr>
<td></td>
<td>diffuse 10 (5)</td>
</tr>
<tr>
<td>Predominantly</td>
<td>proximal 12 (8)</td>
</tr>
<tr>
<td>bilateral</td>
<td>distal 4 (2)</td>
</tr>
<tr>
<td></td>
<td>diffuse 9 (6)</td>
</tr>
</tbody>
</table>

muscle weakness invariably affected both legs, even though it had been unilateral at its onset. Loss of tendon reflexes was predominantly unilateral in 21 patients, and bilateral in 45; sensory loss, unilateral in 12 and bilateral in 24. The symmetry or otherwise of these two signs did not appear to depend on the clinical syndrome of which they were a component, for example sensory loss was unilateral in 5 patients with the "insidious" neuropathy and symmetrical in 12 with the "subacute" neuropathy.

Apart from the frequent association of muscle weakness with pain and with loss of diminution of the corresponding tendon reflexes, clinical features occurred in apparently unpredictable combinations. Thus, bilateral distal sensory loss was seen in association with asymmetrical motor weakness and severe diffuse weakness in the complete absence of sensory loss. Pain occurred in association with weakness, with loss of tendon reflexes and with sensory loss, singly or together, and neither its quality nor its severity appeared to depend on these associations.

The clinical course of the two syndromes.—No patient in the present series was below the age of 30 when neuropathic manifestations were first recorded.

The progress of the "subacute" neuropathy was distinctive. Its symptoms were of well-defined onset, progressed during a variable period, then invariably improved and either disappeared or became stationary. In 6 patients, the symptoms were divided into two episodes separated by
no more than a few weeks; in the remainder they formed a continuous illness. The duration of symptoms which disappeared was less than three years; when continuing for longer they failed to regress completely and in 7 patients have persisted unchanged for between three and six years. Severe illnesses, as judged by disabling muscle weakness, lasted for not less than six months; there was no converse relation in respect of mild illnesses. The incidence of recovery of individual neuropathic components is shown in Table III. Once recovery or maximum improvement had occurred, no

Table III.—Incidence of Recovery of Individual Clinical Features

<table>
<thead>
<tr>
<th>No. of patients in whom clinical manifestations disappeared (Number initially affected in brackets)</th>
<th>Subacute neuropathy (1958–60)</th>
<th>Insidious neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>39 (47)</td>
<td>28 (33)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>33 (44)</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Loss of one or both knee-jerks</td>
<td>18 (31)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Loss of one or both ankle-jerks</td>
<td>4 (27)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>10 (19)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Autonomic disturbances</td>
<td>5 (16)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Penetrating ulcers</td>
<td>0 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

recurrence or relapse of symptoms took place in any of the 54 patients with the "subacute" neuropathy; the follow-up period on which this observation is based varied from one to seventeen years. Records of routine neurological examinations which preceded the onset of neuropathic symptoms were available in 31 patients; neurological signs—absent tendon reflexes or sensory loss—had been found in 5.

The time of onset of neuropathic symptoms in relation to the initiation of treatment in the representative group of 34 patients is shown in Table IV.

Table IV.—Time of Onset of "Subacute" Neuropathy in 34 Patients Presenting During 1958–60

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Before beginning diabetic treatment</th>
<th>0–1 year after treatment</th>
<th>1–2 years after treatment</th>
<th>2–5 years after treatment</th>
<th>5–20 years after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

In 17 of these patients, neuropathic symptoms preceded diabetic treatment and were, in fact, usually the presenting symptoms. Neuropathic symptoms which began after the initiation of treatment usually did so
within a relatively short period—of 17 patients presenting after beginning treatment during 1958–60, 13 did so within the first two years.

The time of onset of the "insidious" neuropathy could not be precisely determined, but in 6 patients neurological signs were found at the time of discovery of diabetes or of beginning its treatment. In the other examples of this syndrome, neurological signs had been first recorded between five and twenty-nine years after beginning treatment. In all but 2 patients with the "insidious" neuropathy, each physical sign, once recorded, altered little irrespective of its duration (eighteen years in one patient). In all but 3, all the signs which were noted were first recorded at the same time. Disappearance of signs occurred in 2 patients—distal sensory loss in 1 and loss of tendon reflexes in the other.

Time relations between neuropathic manifestations and diabetic treatment.—In those patients who developed symptoms or signs before beginning diabetic treatment, an attempt was made to assess the preceding duration and severity of diabetes by reference to weight loss which appeared to provide the only measurable indication of these factors (Table V). Marked weight loss was, in fact, usual in these patients, in contrast to the frequent mildness of thirst and polyuria. This was especially so when disabling muscle weakness occurred, all but one of 16 patients so affected having lost more than 20 lb.; there was no converse relation in respect of mild symptoms.

In 25 of the 54 patients of the "subacute" Group (17 of the 34 patients who present during 1958–60), neuropathic symptoms were already present when diabetic treatment was begun. The initial change in symptoms after beginning treatment was as follows; in 11 patients they continued to worsen, in 6 they improved temporarily and then worsened and in 8 they improved steadily. (The corresponding figures for the patients presenting during 1958–60 were 7, 6 and 4 respectively.) This variation did not appear to depend on the preceding duration and severity of the neuropathic symptoms, on the speed with which effective diabetic control was established nor on whether effective control was established at all.

Table V.—Preceding Weight Loss in Patients Who Developed Neuropathic Symptoms or Signs Before Beginning Treatment

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>No. of patients</th>
</tr>
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<tbody>
<tr>
<td>Less than 10 lb.</td>
<td>5 (2)</td>
</tr>
<tr>
<td>10–20 lb.</td>
<td>7 (7)</td>
</tr>
<tr>
<td>20–30 lb.</td>
<td>7 (3)</td>
</tr>
<tr>
<td>30–40 lb.</td>
<td>7 (2)</td>
</tr>
<tr>
<td>More than 40 lb.</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>31 (17)</td>
</tr>
</tbody>
</table>
Irrespective of their initial alteration, the symptoms eventually improved in all patients; in 5, this occurred in the presence of control which, judged by glycosuria and weight alteration, was continuously inadequate.

In 6 patients with the "insidious" neuropathy, neuropathic signs were present on beginning diabetic treatment. Satisfactory diabetic control was subsequently established in 4, in 1 of whom absent tendon reflexes later returned. In the others, little or no change in signs occurred irrespective of subsequent diabetic control.

In 29 of the 54 patients with the "subacute" neuropathy (17 of 34 presenting during 1958–60) and in 20 of the 26 patients with the "insidious" neuropathy, neuropathic manifestations began or were first observed during the course of treatment. In 8 (7 in the "subacute" group and 1 in the "insidious" group) diabetic control which preceded the onset of neuropathic symptoms or the first record of neurological signs appeared to have been adequate when judged by glycosuria and weight changes. In 7 of these patients this period of adequate control varied from two to twelve months; it shortly followed the initiation of treatment in 5 and a period of several years of persistent glycosuria or failure to maintain normal weight in 2. In 1 (who had the "insidious" neuropathy) the period of adequate control preceding the first record of neuropathic signs was several years. In the remaining 41 patients in whom neuropathic manifestations first appeared during the course of treatment, preceding diabetic control, judged by the foregoing criteria, had been inadequate (27 cases) or was uncertain because of failure to attend the diabetic clinic (14 cases). In the former, the period of inadequate control extended with little interruption from the time of initiation of treatment, and varied from a few weeks to several years. In all but one patient in the whole series, therefore, the onset of neuropathic manifestations was preceded by one of the following: (1) latent or untreated diabetes of uncertain duration; (2) a long period of inadequate treatment or of failure to attend the diabetic clinic; (3) a period of adequate treatment not exceeding one year which was preceded by (1) or (2).

Of the 29 patients with the "subacute" neuropathy whose neuropathic symptoms began during the course of treatment, diabetic control, judged by glycosuria and weight, was already adequate in 7, was made adequate in a further 14 and in 8 remained inadequate. The subsequent course of their neuropathic symptoms bore no general relation to these factors. For example, 3 patients fully recovered in the presence of persistently inadequate control, and 6 others became steadily worse in spite of the introduction of rigid control. However, of 22 patients in whom preceding diabetic control had been inadequate, 14 developed disabling illnesses; while of 7 patients, whose preceding control was adequate, none did so. Of 7 patients in the whole "subacute" group who developed permanent disability, satisfactory control was never established in 3, in 1, it was
established but not long maintained, and in 3 was established only after a substantial delay. Similar delay, however, occurred in other patients who fully recovered.

In 20 patients with the “insidious” neuropathy whose neuropathic signs were first noted during treatment, preceding control had been adequate by the foregoing criteria in 1, inadequate in 10 and (because of failure to attend regularly) uncertain in 9. Control remained inadequate or uncertain in 8 of these patients. Disappearance of previously recorded sensory loss occurred in one whose diabetic control had been made adequate; in the others there was no substantial change in signs irrespective of subsequent control.

In 5 cases of the “subacute” neuropathy, diabetic treatment was stopped for various reasons while neuropathic symptoms were still present. In 3 whose symptoms began or grew worse shortly after beginning treatment, insulin was withdrawn for periods varying from one week to two months. In each, there was no discernible alteration in the progress of the symptoms. Two patients stopped treatment of their own accord while their symptoms were improving. In each, the symptoms continued to improve and eventually subsided. In 12 patients with the “subacute” neuropathy diabetic control which had been adequate at the time of recovery or of maximum improvement, subsequently became inadequate for periods of six months or more. No relapse or recurrence of neuropathic symptoms occurred.

ASSOCIATED DIABETIC FEATURES

In 73 of the 80 patients, including the whole of the “subacute” group, diabetes had been first discovered after the age of 30. In 14 patients (4 of the “subacute” and 10 of the “insidious” group) there was a manifest tendency to ketosis. In both groups (especially the “subacute”) diabetes of gradual onset without tendency to ketosis was common. The various agents of treatment appeared to be randomly distributed amongst all the patients.

Both neurological syndromes occurred in the presence or absence of other diabetic complications. The number of unselected patients was too few to examine possible correlations but, in several, differences were observed between the progress of neuropathic manifestations and that of other complications. In 7 patients (2 of the “subacute” and 5 of the “insidious” group), retinopathy gradually progressed to virtual blindness after neuropathic manifestations had either subsided or become stationary. Progressive renal failure occurred in 2 cases of the “insidious” neuropathy, while neuropathic signs remained unaltered or disappeared. In 3 cases, (1 of the “subacute” and 2 of the “insidious”) similar contrasts were observed in respect of intermittent claudication.
Familial Observations

The "subacute" neuropathy group of patients included three pairs of siblings. Of these, one pair had another sibling (seen but not included in the study since she did not attend the London Hospital) who had suffered from the same type of neuropathy. The family trees are shown in the figure.

The time of discovery of diabetes in each of the affected siblings was similar—in middle or late middle age—and in each the onset had been gradual. The neuropathic manifestations preceded the discovery of diabetes in 5 siblings and began within fifteen months of beginning treatment in 2; they did not obviously differ from those occurring in other patients in the study. With the exception of sibling No. 2 in family B whose diabetes had been discovered during a routine examination, all the
known diabetic members of these families developed neuropathic symptoms. Serum pseudocholinesterase (estimated by the method of Kalow and Davies, 1958) was found to be within normal limits in each of the affected siblings.

Of the remaining patients in the "subacute" group, 6 had one or more diabetic siblings. One of these had had symptoms suggestive of the "subacute" type of neuropathy, but the details were too uncertain for a firm diagnosis. Further inquiry was made regarding the occurrence of symptoms suggestive of neuropathy in siblings not known to be diabetic of whom six were subsequently interviewed. In each, the symptoms appeared attributable to some other cause.

Of the 26 patients with the "insidious" neuropathy, 3 had a sibling who was known to be diabetic; each of these was seen and no evidence of neuropathy either in the form of signs or of symptoms, past or present, was found. One pair of siblings had developed diabetes at a similar age (11 and 15 years respectively) with similar insulin requirements. At the time of the study each had had diabetes for more than twenty years, but there had been a marked contrast in the efficacy of diabetic control, which, judged by heavy glycosuria and failure to maintain normal weight, had been uniformly poor in one, and by the same criteria, adequate in the other. Neuropathic signs had developed only in the first.

**Electrodiagnostic tests**

These were carried out in 47 cases (37 of the "subacute" and 10 of the "insidious" group). In the "subacute" group tests were carried out on muscles which were or had been weak and where possible on at least one other; in the "insidious" group tests were carried out on randomly selected leg muscles.

Abnormalities in one or more muscles were found as follows: discontinuous strength duration curves in 25 patients (20 in the "subacute" and 5 in the "insidious" group); profuse long duration polyphasic potentials in 44 patients (35 "subacute" and 9 "insidious"); reduced interference patterns in 19 patients (16 "subacute" and 3 "insidious"); and "giant" motor units of more than 15 m.v. potential in 4 (2 "subacute" and 2 "insidious"). Motor nerve conduction velocities were determined in the lateral popliteal median and ulnar nerves in 4 of the patients with the "insidious" neuropathy; velocities of less than 36 metres/second were found in one or more of these nerves in 3.

In the "subacute" neuropathy, one or more of the foregoing abnormalities was invariably found in muscles which were weak or within a painful area and occasionally in clinically unaffected muscles. In one patient they disappeared after three months and in another persisted for at least twenty months. In 9 patients tested several years after the "subacute"
neuropathy had subsided, one or more of these abnormalities were found in 4 in muscles which had previously been weak.

Of 14 patients without clinical evidence of neuropathy (of whom 9 had not yet begun treatment) discontinuous strength duration curves were found in one or more muscles in 2, reduced interference patterns in 3 and profuse long duration polyphasic potentials in 8.

**Tests of Reflex Temperature Control in the Extremities**

These were carried out in 42 patients (32 of the "subacute" and 10 of the "insidious" group). Failure of reflex cooling in one or both great toes was found in 15 patients with the "subacute" neuropathy (including 3 whose symptoms had subsided several years before) and in three with the "insidious" neuropathy. In 4 patients with the "subacute" neuropathy, normal reflex cooling returned after intervals of between three and seventeen months. In the other patients tested, either normal or inconclusive results were obtained.

In the "subacute" neuropathy, failure of reflex cooling showed the following relation to other neuropathic symptoms: in each of 4 patients in which it was unilateral, the clinical symptoms were largely restricted to the same side; it was found in each of 7 cases with disabling muscle weakness, but in only 2 out of 13 without such weakness.

In 14 patients without evidence of neuropathy (those mentioned in the previous section) failure of reflex cooling was found in one (in one great toe).

**Pathological Observations**

Material was obtained from 5 patients. Autopsies were performed on 4 who died from incidental diseases and, in one, a limb was amputated for intractable penetrating ulcers.

In each case, varying degrees of damage were found either in the peripheral nerves or spinal roots or both together. In one, marked loss of anterior horn cells in the lumbar spinal cord was found. Mild loss of cells in the lumbar dorsal root ganglia was found in one and minor changes in the same cells in each of the other 3 autopsy cases. In 4 of the 5 cases, neurogenic muscle atrophy was found—including the amputation case in whom the only clinical evidence of motor involvement was electromyographic. Most of the vasa nervorum examined appeared healthy and significant stenosis was observed in only one of these vessels.

These findings are described in detail in a separate paper (Greenbaum et al., 1964).

**Discussion**

One aspect of the course of diabetic neuropathy appeared common to all the patients of the present study—the absence of continued progression of clinical manifestations. No matter how severe, these were invariably
arrested and often reversed, either partially or completely. This applied to pain, muscle weakness, loss of tendon reflexes, sensory loss and the manifestations of autonomic nerve damage, and did not depend on the mode of clinical presentation. Thus the course of diabetic neuropathy contrasts with that of other diabetic complications.

The view that diabetic neuropathy may be due to more than one disease process depends on the possibility of dividing it into different clinical syndromes. Some of the divisions made by previous authors have been briefly reviewed; although broadly similar, they differ in detail and that made in the present study corresponds only approximately with any one of them. It would, in fact, have been difficult to satisfy fully the requirements of individual authors. For example, the syndrome of "diabetic amyotrophy" (Garland, 1955) is characterized by motor weakness in the absence of sensory loss, yet patients were observed in the present study whose clinical features closely resembled those described in Garland's case reports but in whom sensory loss was present; the same is true of cases reported in the papers of Jordan (1936), Rundles (1945) and Martin (1953a). Sullivan (1958) separated patients with asymmetrical motor involvement but in the present study all grades of symmetry of motor weakness were seen, as well as the transition from asymmetrical to symmetrical weakness; Isaacs and Gilchrist (1960) noted similar variations. Certain features could not have been satisfactorily separated no matter what division was made; these included the predominant localization of neuropathic manifestations in the lower limbs, and the occurrence of sensory loss, tendon areflexia and manifestations of autonomic nerve damage. Further, since reversal was not necessarily complete, all the clinical manifestations were potentially chronic and patients with widely differing modes of presentation were left, in the end, with similar physical signs. Contrasting clinical features in individual cases appear, in fact, to merge when a group of patients is reviewed.

Attempts have also been made to establish associations between different neuropathic syndromes and other diabetic features, and from them to draw conclusions about pathogenesis. Sullivan (1958), for example, considered that "asymmetrical motor neuropathy" occurred in mild diabetes and was, therefore, not due to a metabolic defect; with "symmetric distal neuropathy" he postulated the reverse. Gilliland (1951) amongst others, claimed to have demonstrated a significant association between neuropathy, retinopathy and nephropathy; and on the basis of such associations Fagerberg (1956) postulated a common vascular pathogenesis. The present findings do not support such views. Both clinical syndromes and their variants were frequently observed in association with "mild" diabetes and both occurred in patients who had a liability to develop ketosis, although the "subacute" neuropathy did not do so commonly. Divergences between the progress of neuropathy and that of other diabetic

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complications were observed in some patients and, as already mentioned, the clinical course of the former differed in general from that of other complications. If there are indeed correlations between neuropathy and other diabetic complications, they may only imply that the mechanisms for each are dependent on a common factor—for example, the duration of diabetes.

Electrodiagnostic techniques have been used by several investigators in the study of diabetic neuropathy. In general these have provided evidence of lower motor neurone damage both in the presence of overt muscle weakness (Gilliatt and Willison, 1962) and in its absence (Skillman et al. 1961). The present findings are in agreement, and such evidence of motor nerve damage in the absence of overt weakness throws further doubt on the validity of using the latter as a criterion for dividing diabetic neuropathy into different forms.

The principal observations derived from the reflex skin temperature tests in the present study were that vasomotor nerve damage may occur synchronously with other neuropathic manifestations and that it sometimes shares their distribution and reversibility. In contrast with Martin's (1953b) findings, defective skin temperature control was not found to be invariably present in diabetic neuropathy and his view that the autonomic nerves are the first to be involved was therefore not supported.

The occurrence of neuropathy in more than one diabetic sibling in each of three families, if not a haphazard occurrence, raised the possibility that neuropathy may occur only in diabetics who have some form of hereditary predisposition, for example a hereditary defect of the nervous system. One such defect considered (and excluded) was pseudo-cholinesterase deficiency. However, since all but one of the known diabetic siblings in these families developed neuropathy, this hypothesis would appear to require the linkage of two separate hereditary defects. It seems more likely, therefore, that the hereditary factor, if present, was simply the tendency to develop that sort of diabetes which is conducive to the production of neuropathy, and it will later be suggested that diabetes presenting in middle age provides the appropriate conditions. The fact that neuropathy may occur in diabetes due to pancreatitis (Duncan and MacFarlane, 1958) also suggests that it has only one aetiological factor.

The morbid anatomical findings are discussed in detail in a separate paper. They provided evidence of variable damage to the lower motor and primary sensory neurones, including the cells of the anterior horn and dorsal root ganglia, in the absence of significant occlusion of the vasa nervorum. This was in agreement with previous reports, notably those of Alderman (1938), Bosanquet and Henson (1957), Ellenberg and Krainer (1959) and Dolman (1963). The findings provided little support for the division of diabetic neuropathy into more than one entity, and the occurrence of sensory neurone damage in the absence of clinical sensory
loss and of neurogenic muscle atrophy in the absence of clinical weakness emphasized the difficulties to be encountered in basing such divisions on clinical manifestations alone. Nothing was found to support suggestions (e.g. Garland, 1951) that muscle involvement might be due to other than denervation.

The principal postulated mechanisms of the production of diabetic neuropathy are occlusion of the vasa nervorum and a metabolic defect caused by inadequate diabetic treatment. It has also been suggested (Hirson et al., 1953; Ellenberg, 1959) that, because it may precede the discovery of diabetes, neuropathy is not a complication but an integral part of the disease. The observations of the present study appear to require that the neuropathic process is not continuously progressive, that it may be arrested or reversed even when it has produced severe and widespread damage, and that it may remain reversed for many years. Neither atheroma nor the specific angiopathy postulated by Fagerberg (1956 and 1959) appear able to fill all these requirements except in unusual circumstances. Whether vascular occlusion may play a subsidiary part, as suggested by Fry et al. (1962), is uncertain, but on the basis of the present findings even this appears unlikely.

The metabolic hypothesis, although widely held, has not obtained general acceptance because the onset and progress of neuropathic manifestations do not always bear a clear relation to concurrent diabetic control. For example, Ellenberg (1959) states that neuropathy may be the first manifestation of diabetes unattended by symptoms of uncontrolled glycosuria, that it may occur during good control and that it may develop soon after the initiation of treatment; Wilder (1940) stated that its duration and severity do not appear to be affected by rigid control. These observations were confirmed in the present study, and two others not apparently according with the metabolic hypothesis were also made; that neuropathy may develop during inadequate diabetic control and subside without improvement in such control and that once reversed it need not relapse when control becomes inadequate.

In fact, none of these observations is incompatible with the metabolic hypothesis. In the present study as in others (e.g. Ellenberg, 1958a), neuropathy as a presenting diabetic feature was seen in middle-aged patients in whom the preceding duration of diabetes was quite uncertain and whose effects, when judged by weight loss (Table V), had not necessarily been mild. Indeed, Martin (1953a) suggested that latent diabetes may be especially conducive to the development of neuropathy because of the possibility of its long duration without treatment. The onset of neuropathy during good diabetic control was observed in the present study in similar patients who had been treated only for a short time or in patients who had previously been treated inadequately for long periods, and the duration of adequate control may have been insufficient to reverse
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the preceding harmful effects of the disease. The development of neuropathy during inadequate treatment and its reversal without improvement in treatment was also observed only in patients whose diabetes had been recently diagnosed and whose treatment although inadequate was presumably an improvement on what had gone before. Finally, the worsening of neuropathy in spite of rigid diabetic control need only mean that it is not readily reversed.

In Table IV it is shown that the “subacute” neuropathy presented most commonly before beginning treatment, fairly often during the first two years of treatment and thereafter only rarely. This suggests not only that conditions favourable for its development are to be found in latent diabetes but that such conditions tend to disappear after beginning treatment. If lack of treatment is the etiological factor, it may well be that the requisite duration is only readily obtained in latent diabetes. If so, it would not be expected that neuropathy would readily relapse after arrest or reversal—as was observed in the present study.

The remaining difficulty in the metabolic hypothesis is the occasional onset of neuropathic symptoms very shortly after beginning treatment (Caravati, 1933; Ellenberg, 1958b) which has usually been regarded as evidence that treatment may be a precipitating factor. However, no satisfactory explanation of the mechanism has been given nor is it clear why neuropathic manifestations developing in this way should eventually improve in spite of continuing treatment. An alternative suggestion is that the sequence of events is coincidental; that neuropathy would have developed at the same time even if treatment had not been begun. Since it often develops before beginning treatment, this would, in fact, be expected to occur occasionally.

Most of the foregoing discussion is of necessity based on observations derived from patients with symptoms of well-defined onset, since only in these could the time relations be adequately defined. However, with one exception, the other patients in the study presented no contradictory data. Further, in two siblings with diabetes of closely similar characteristics and duration, the development of the “insidious” neuropathy occurred only in the one whose diabetic control had been persistently inadequate.

Thus, the present observations are compatible with the hypothesis that the neuropathic process in diabetes is produced by inadequate treatment and reversed by adequate treatment and some appear readily explicable in no other way. The requisite inadequacy of treatment is not necessarily shown by high blood glucose levels nor by severe symptoms of uncontrolled glycosuria; and these should be regarded as related to neuropathy only in that they may be reversed by the same agents.
Summary

The results of an investigation of 80 patients with clinical evidence of diabetic neuropathy are presented.

The principal observations were the following:

(1) Clinical features occurred in many different combinations; contrasting pictures in individual patients tended to merge when the group as a whole was considered.

(2) Each of the principal components of diabetic neuropathy appeared potentially reversible, and, once reversed, did not readily relapse. Chronic manifestations showed no tendency to further progression.

(3) The onset of neuropathic manifestations, with one exception, followed (a) latent untreated diabetes in middle-age, (b) a long period of inadequate treatment, or (c) a period of adequate treatment which was relatively short and preceded by (a) or (b).

(4) Contrasts between the progress of neuropathic manifestations and that of other diabetic complications were observed.

(5) Electrodiagnostic tests suggested that motor neurone involvement commonly occurs in the absence of overt muscle weakness.

(6) Limited pathological material showed changes which varied from peripheral nerve damage alone to involvement of the whole of the lower motor and primary sensory neurone in the absence of significant occlusion of the vasa nervorum.

Conclusions

There appears to be no satisfactory basis for a general division of diabetic neuropathy into separate clinical syndromes; this throws doubt on suggestions that more than one process is concerned in its pathogenesis.

The present observations are compatible with the possibility that diabetic neuropathy is caused by a reversible metabolic defect produced by inadequate diabetic treatment and do not support the view that it is caused by occlusion of the vasa nervorum.

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