Section of Neurology

President—DENIS BRINTON, D.M.

Meeting
November 5, 1959

MEETING AT THE NATIONAL HOSPITAL FOR NERVOUS DISEASES, QUEEN SQUARE, LONDON

THE following cases were shown:

? Vogt-Koyanagi Syndrome.—Dr. F. CLIFFORD ROSE (for Dr. DENIS WILLIAMS).

Three Cases of Familial Swelling of Optic Discs with Visual Failure.—Dr. K. J. ZILKHA (for Dr. J. St.C. ELKINGTON).

Raeder's Syndrome (Paratrigeminal Paralysis of the Ocular Sympathetic).—Dr. J. B. FOSTER (for Dr. J. MARSHALL).

Glioma of the Optic Chiasm.—Dr. R. BROWN (for Mr. HARVEY JACKSON).

Hyperostosis Frontalis Interna.—Dr. K. L. GRANVILLE-GROSSMAN (for Dr. W. GOODDY and Dr. D. EDWARDS).

Collagen Disease with Myelopathy.—Dr. G. S. WAKEFIELD (for Dr. J. MARSHALL).

Spinal Schistosomiasis.—Dr. J. D. CARROLL (for Dr. J. MARSHALL).

External Carotid Angioma.—Dr. D. G. POTTS (for Dr. J. W. D. BULL and Dr. DENIS BRINTON).

Meeting
December 3, 1959

THE NEUROLOGICAL COMPLICATIONS OF DIABETES

Neurological Complications of Diabetes Mellitus: Clinical Aspects

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Introduction.—According to the Papyrus Ebers, diabetes was known about 3,500 years ago, in the days of Moses, but the neurological complications were probably not recognized until 1864 (Goodman *et al.*, 1953; Joslin *et al.*, 1959) when it was concluded that diabetes itself was neurogenic, though this idea was soon abandoned.

In 1959 the total picture of the neural complications of diabetes is confused and the many publications are contradictory. There may be several reasons for this confusion. Diabetes appears to be a very common disease in all races, and it has been estimated that there are 3 million diabetic patients in the United States (Joslin *et al.*, 1959). In Great Britain there has been no extensive survey of the problem, but a careful study of a small community (Walker, 1959*a*, *b*) has shown an incidence of about 1·3% in the population, and if this were true of the whole of Great Britain there would be about 650,000 such cases. The prevalence of neurological complications has been estimated at every figure from none to nearly 100% (Goodman *et al.*, 1953), but the general view is that about 60% of diabetics have such complications, which means about 400,000 in Great Britain. This must be compared with an estimated incidence of about 30,000 examples of Parkinsonism or disseminated sclerosis at any given time (Garland, 1952), and I think any clinical neurologist would find this high figure difficult to accept. Further, if the incidence of neurological complications of diabetes is 60% or more it would seem that these syndromes are not really complications but are part of the total picture of diabetes, and perhaps as frequent as polyuria, polydipsia, or loss of weight. Before discussing the reasons for the very variable incidence claimed we must first approach the problem of terminology, which in this context (as is equally true of epilepsy or head injury) is now inadequate and often inaccurate. In the earlier writings most of the neurological accompaniments of diabetes seem to be included under the titles of polyneuritis or peripheral neuritis. In the next phase the term diabetic neuropathy was introduced, and clearly some workers, both past and present, have used this term to cover all neural involvement at any anatomical level (Goodman *et al.*, 1953). By comparison with the terms encephalopathy, myelopathy, and myopathy, the use of "neuropathy" should be restricted to lesions of peripheral nerves. But here difficulties arise immediately; if the nerve roots are included as

part of the peripheral nerve then neuropathy must include lesions of posterior root ganglia, and if the sensory ganglion cells are to be included why not the motor? If motor or sensory ganglion damage is to be called neuronopathy this term will have to be qualified by the appropriate functions. If diabetic coma is excluded there seems to be no diabetic encephalopathy, either acute or chronic, and the incidence of strokes is probably not higher in diabetics than others, when allowance is made for age and hypertension (Joslin *et al.*, 1959). No acute form of diabetic myelopathy is known.

Some authors include as neurological complications of diabetes a variety of symptoms without physical signs—of which the commonest is pain—and it may be that such symptoms, which are easily reversed by diabetic control, are essentially neurogenic, but this is not proved. Others have added various isolated nerve palsies—I think incorrectly—though these have never been claimed to be frequent, and in the past decade repeated references have been made to signs and symptoms said to result from diabetic degeneration in autonomic nerve fibres, with or without involvement of medullated fibres. It is often impossible to tell from the name either of the author or of the journal whether published material is neurologically valid.

Nearly all diabetics are under the care of general physicians, and many attend a diabetic clinic. Because such physicians often have no neurological training and little interest in neurology, they may, and do, overlook neurological abnormalities in the diabetic, or, having found them, they may rightly label them as complications or wrongly attribute them to some other nosology.

Muscle and nerve biopsies have been made over the years but the histological interpretation is likely to have been inaccurate in the past. Moreover the important methylene-blue vital staining technique for end-plates was only discovered seven or eight years ago and is not applicable to post-mortem studies. When changes are found in peripheral biopsy material we know nothing of what is happening in the ganglion cells at the same time. Although diabetic damage may affect the whole neuron it has been suggested, on the basis of histology of biopsy specimens (Woolf and Malins, 1957), that there is a "dying-back" process starting in the end-organ, which would explain why symptoms usually start in the periphery. Unfortunately very few post-mortem studies seem to have been made of diabetics with neurological abnormalities, but in one very important report (Bosanquet and Henson, 1957) extensive degeneration in central and peripheral sensory pathways was thought to have started probably in root ganglion cells; although this patient was 70 there was little histological evidence of arterial disease. Finally, it is generally agreed that most neurological syndromes are reversible and therefore they are rarely available for post-mortem study. For these and probably other reasons our knowledge is still sketchy and contradictory.

Clinical Syndromes, Terminology and Ætiology

Diabetic sensory neuropathy.—Much the commonest neurological complication of diabetes is a purely sensory syndrome, comprising pain in the legs (often only nocturnal), muscle tenderness, loss of ankle-jerks, and loss of vibration sense in the feet and ankles. The signs and symptoms tend to spread upwards, other sensory modalities are involved later, and sometimes the arms may be affected. The syndrome is almost invariably bilateral and symmetrical, and commoner in the second half of life, often (but by no means always) being seen in diabetics of long standing who have not been under full diabetic control. Despite a long history of poorly controlled glycosuria, diabetes in these patients is often mild (Rundles, 1945). Perhaps the earliest sign of this syndrome is loss of vibration sense which is so slight that it can only be detected electrically. I have already mentioned that pain may occur without physical signs, and the converse is equally true. Sometimes there is a fairly close clinical resemblance to tabes dorsalis, and Argyll Robertson pupils have been described, though it has been suggested that this pupillary anomaly has never been demonstrated by a neurologist (Martin, 1953*a*). One of the difficulties in assessing the frequency of sensory neuropathy is that identical signs and symptoms are often found in elderly non-diabetics (Critchley, 1931). In the early stages the diabetic syndrome is easily and rapidly reversible by full diabetic control, and this is perhaps the only important contribution to knowledge in about a hundred years. As already pointed out the anatomical level of the earliest lesions of the syndrome is by no means certain, but since nobody has suggested that they are within the spinal cord I can see no objection to the term diabetic sensory neuropathy, and indeed I cannot suggest a more appropriate title.

Diabetic amyotrophy.—In a series of papers since 1953 (Garland and Taverner, 1953; Garland, 1955, 1957) I have described a purely motor diabetic syndrome. At first I thought this was a new clinical discovery, but it was in fact a re-discovery of an old and forgotten observation. Originally I regarded this as a

diabetic myelopathy on the basis of the distribution of muscle weakness, electromyographic changes, and the presence of extensor plantar responses. But I later found that the plantar response is often flexor, and in the absence of post-mortem confirmation I felt that the syndrome was better described as diabetic amyotrophy, since of all the manifestations weakness and wasting of muscles are the only constant features. That this is in some way determined by diabetes seems to be generally accepted. I have now seen 30 examples of this condition. The reactions of others to my first papers varied; many thought that this was only a product of my Leeds imagination but most neurologists soon found one or more examples, and recently 12 have been recorded in Zürich (Bischoff, 1959) and others in Boston (Sullivan, 1958).

Apart from being a purely motor syndrome this condition shows many differences from diabetic sensory neuropathy. The signs and symptoms are almost invariably asymmetrical, and often almost unilateral. As with the sensory form the legs are always affected first, and indeed the arms are rarely involved, but the proximal muscles tend to be most involved. Fasciculation is seen occasionally. The appropriate tendon-jerks are depressed or absent, and the plantar responses are sometimes extensor. Pain is usual, always being felt in the region of the affected muscles; in one example of mine the pain was abdominal and related to changes in the rectus abdominis. The protein content of the spinal fluid is sometimes considerably raised, as in sensory neuropathy. The history of diabetes is usually short and occasionally amyotrophy is the presenting symptom, but this is not always true and I have seen amyotrophy suddenly complicate diabetes of over twenty years' duration. Amyotrophy usually appears in the less severe examples of diabetes and no patient of mine has previously been in diabetic coma. The syndrome is known to relapse, and recovery from amyotrophy may be followed by sensory neuropathy (Sullivan, 1958). In my experience this syndrome is totally reversible, though muscle atrophy and electromyographic changes may be the last features to return to normal. The only treatment necessary is full diabetic control, and for this I think a desirable though arbitrary figure for the blood sugar two hours after a meal is 150 mg%. I am not prepared to defend myself on this point if attacked by a diabetician, but I am satisfied that such control will prove adequate, although the use of the insulins is almost invariably essential. In establishing a diagnosis of diabetes I have always relied on the glucose tolerance test, and I have sometimes accepted as evidence abnormally high levels (over 200 mg%) in a "lag" curve after a normal fasting level; some will no doubt say this is not diabetes, and I may have to change the nomenclature to hyperglycæmic amyotrophy.

The differential diagnosis of diabetic amyotrophy lies largely in laboratory tests. The imitators are polyarteritis nodosa, syphilitic amyotrophy, hypoglycæmic amyotrophy, or motor neuron disease in those examples that are painless. The majority of my cases had previously been given an incorrect neurological label—usually either sciatica or motor neuron disease—but I have not seen these errors committed by a neurologist, although before 1953 we must all have overlooked this condition.

The underlying pathology of diabetic amyotrophy has not yet been established, and the scanty evidence is conflicting. In one recorded example, in which I would accept the diagnostic criteria (Alderman, 1939), post-mortem studies showed gross changes in anterior horn cells, with appropriate asymmetry and little else. In the only post-mortem study made in Leeds (Harriman, 1959), where again I would accept the diagnostic criteria, virtually no histological changes were seen in the spinal cord or nerves though the muscles showed striking changes, apparently of neurogenic atrophy. This observation raises the possibility of a purely biochemical neural lesion, at any anatomical level, which, though not producing neurohistological change would, at any rate in its early stages, disturb function sufficiently to produce serious disability and even secondary histological changes in muscle. But this theory would not conform with the previously described changes starting in end-plates. At the moment, therefore, we must accept the entity of reversible diabetic amyotrophy, with the possibility of a lesion at any point from anterior horn cells to muscle end-plates, or at several levels, and with clinical and electrical evidence that the spinal cord is sometimes involved even without histological change.

Mixed sensory and motor diabetic syndromes.—It has always been recognized that diabetic polyneuritis, though largely sensory, might from time to time show minimal motor involvement. I have never seen, or heard of, a florid example of diabetic sensory neuropathy in combination with diabetic amyotrophy, and it may be that for some ætiological difference these syndromes have only the common denominator of diabetes. But even though the syndrome appears to be purely sensory on clinical grounds biopsy study may still show changes in motor end-plates

(Harriman, 1959). The clinical picture of diabetic sensory neuropathy is usually very different from that of other forms of polyneuropathy and rarely has to be considered in the differential diagnosis of "polyneuritis", except when the latter is carcinomatous.

Diabetic autonomic syndromes.—Involvement of the autonomic nervous system in diabetic degeneration has had frequent reference in the past ten years (Metcalfe, 1949; Martin, 1953*b*; Keen, 1959) though similar suggestions had been made long before this. If true, this group of signs and symptoms is extensive, and not very generally recognized—certainly not by myself. Many disabilities are said to result from diabetes and, in particular, from diabetic degeneration in the autonomic system, whether or not diabetic sensory neuropathy is associated. One of the commonest is paroxysmal diarrhœa, which is usually nocturnal, with very frequent fluid stools, and sometimes with fæcal incontinence. Impotence may appear as an isolated symptom—which may mean failure of erection, loss of libido, or failure of ejaculation (more properly then termed sterility). Paralysis of the bladder, with loss of sensation and a sizeable amount of residual urine, and even retention, may occur without peripheral sensory loss, but often in association with impotence. Other signs and symptoms include loss of sweating (usually in anæsthetic areas), postural hypotension, postural tachycardia, neuropathic joints (especially in the feet), perforating ulcers, possibly pupil changes, and even gastric retention. Dependent œdema without cardiac or renal cause has always been known to accompany peripheral neuritis on occasions, and is also said to result from autonomic degeneration. Impotence is said to occur in 75% of male diabetics between the ages of 60 and 65 (Keen, 1959), though without a control series this figure is not impressive; more important is the incidence of impotence in 25% of diabetics between the ages of 30 and 35. An assessment of the precise relation between nocturnal diarrhœa and any neurological accompaniments of diabetes is very difficult, because the diarrhœa is paroxysmal and is said to have been reversed by the use of antibiotics (Keen, 1959). But it is claimed that most of these autonomic disturbances can be reversed by diabetic control, though impotence may only be relieved if it be of fairly recent and sudden onset. I have not seen any of these symptoms in combination with diabetic amyotrophy.

It is suggested that non-myelinated nerve fibres are the first to suffer in diabetes (Martin, 1953*b*), and that perception of pain and extremes of temperature, as well as tendon areflexia, may all be determined by non-myelinated afferent pathways. These views are of importance in regard to ætiology in general, because it seems that non-myelinated fibres are less vulnerable to ischæmia than the larger myelinated fibres, suggesting that diabetic degeneration is more likely to be determined by metabolic than ischæmic changes.

It may be pertinent to draw an analogy with the known sequelæ of extensive sympathectomy, which has been done in many patients who have now been under observation for years. Postural hypotension is a well-known sequel, but retention of urine, nocturnal diarrhœa, neurogenic arthropathy, and perforating ulcer have not been seen. Sweating is never totally and permanently abolished after sympathectomy, except below the knees, and though impotence in all its forms often results it is by no means a certain hazard (Shucksmith, 1959). We can only conclude that diabetic involvement of the autonomic nervous system presents formidable and at present insoluble problems. This has always been true of all autonomic disorders, and our lack of knowledge is not helped by the variable behaviour of the autonomic system in experimental animals.

Cranial and other isolated nerve palsies.—Diabetes has often been claimed as the cause of palsies of isolated peripheral nerves, and particularly the oculomotor nerves. The largest number of diabetic ocular palsies seen by one observer seems to be 30 (Collier, 1930); in this series the VI nerve was most frequently affected but all three oculomotor nerves were sometimes involved on one or both sides. All these patients were in the second half of life, and all the ocular palsies recovered. I find it very difficult to accept this hypothesis especially as there was no reference to blood sugar studies or details of treatment. Sudden ocular palsies frequently appear in non-diabetics in middle and old age, and these usually make a complete recovery; their precise ætiology has always been a matter for speculation, but there has been one very important study of a III nerve palsy, in a diabetic, in whom opportunity for post-mortem study arose (Dreyfus *et al.*, 1957). A sizeable fusiform swelling of the nerve was found in its intracavernous course, and histological studies suggested that the essential lesion was occlusion of one of the vasa nervorum. Such occlusion was not identified but this might have been the result of damage at the time of removal of the brain. It was admitted that the diabetes might well have been fortuitous. However, this theory stimulated interest in the blood supply of the III nerve, about which little was previously known. Although the blood supply of the distal and

proximal parts of the III nerve was established in a series of post-mortem studies, that of the intra-cavernous portion eluded demonstration.

Other cranial nerve palsies, especially of the VII, have been ascribed to diabetes, and so have palsies of isolated nerves in the limbs; these are said to have a sudden onset and to be irreversible (Collier, 1930). I have never seen these myself, and I doubt their validity (cf. Goodman *et al.*, 1953). I am prepared to concede that bizarre areas of anæsthesia, with no acceptable anatomical substratum, may be evidence of diabetic sensory neuropathy, but in assessing any neurological syndrome it must always be remembered that diabetes is common, and that the association with neurological syndromes may be accidental.

Ætiology of the diabetic neurological syndromes.—Three explanations for the neurological complications of diabetes have been advanced in the past—namely, vitamin deficiency, hyperglycæmia or some intermediate disturbance of metabolism, and ischæmia resulting from arterial changes consequent on or aggravated by diabetes. There is little support for the first concept (Martin, 1953*a*; Keen, 1959), but the other two are intertwined and the evidence is more than contradictory. It has often been suggested that peripheral neuropathy in diabetes is determined by vascular occlusion from atheroma or medial thickening at various arterial levels, which is proved to operate in the neuropathy of polyarteritis nodosa. Against this theory are the facts that many such diabetics show no clinical evidence of arteriopathy or hypertension, that the neurological syndromes are totally reversible by diabetic control alone, and that these syndromes are often absent in gross arteriopaths whether or not they be diabetics. Certainly such a concept would not be acceptable when the lesion is in the spinal cord, since spinal arteriosclerotic syndromes do not seem to exist—which is very remarkable in view of the frequency of cerebral arteriosclerotic disorders. Of recent years an attempt has been made to establish the entity of a specific diabetic angiopathy, which is reversible by diabetic control. This theory turns largely on the application of special staining techniques to nerve biopsy material, and a case seems to have been established, though further study is required (Fagerberg, 1959).

The same basic pathology has been ascribed to the neurological, retinal, and renal complications of diabetes, and they are said to be clinically associated. Diabetic gangrene, retinopathy and probably nephropathy are thought to have a vascular rather than a primarily metabolic basis, and it is now suggested that this may be a specific diabetic angiopathy. The frequent association of sensory neuropathy, retinopathy, and nephropathy may be established (Joslin *et al.*, 1959), but I have not encountered diabetic amyotrophy in association with retinal or renal lesions, although diabetic angiopathy has been claimed as the basis of this amyotrophy (Sullivan, 1958). It is a curious fact that the microaneurysm which is so characteristic of diabetic retinopathy has not been seen in any other organ, except perhaps the kidney (Ashton, 1959).

All we can say to-day is that on the basis of histological studies there are those who think the neurological complications of diabetes are usually determined by arterial disease (Woltman and Wilder, 1929) or even by a specific diabetic angiopathy (Sullivan, 1958; Fagerberg, 1959), and those who advance cogent arguments against such theories (Rundles, 1945; Martin, 1953*a*; Bischoff, 1959). There is therefore no agreement as to whether the important factor is metabolic or ischæmic, nor do we know the anatomical level of the early lesions, and for this reason anatomical terms are better withheld from diagnostic labels.

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