NEURITIC MANIFESTATIONS IN DIABETES MELLITUS

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A man (case 9,009) of quiet and controlled temperament was brought in an ambulance to the hospital. He was moaning and writhing in pain, although his pupils were already contracted by morphine administered for an attack of suspected ureteral colic. A second patient (case 10,349), a former football player and coach, was admitted to the hospital because of such unaccountable depression, restlessness and severe burning sensations in his feet that he could not sleep. A third patient (case 10,405) was admitted because paralysis of the muscles of the foot had prevented his working for the preceding two months. A fourth patient (case 8,428), a man 30 years of age, was admitted to the hospital because of gangrene following a burn from an electric pad applied to a painful foot and lower part of the leg. All four suffered from diabetic neuritis. In 1864 Marchal de Calvi drew attention to the causal relationship between diabetes and disturbances of the nervous system, and in 1931 Wendt and Peck again emphasized diabetic neuritis. Sevringhaus (1931) reported diminished activity of the reflexes in 57.3 per cent of 75 diabetic patients studied for this condition, and Bolduan (1932) observed that 2 per cent of the population died of diabetes. Thus one sees that a large number of persons are afflicted with diabetic neuropathy.

HISTORY OF THE CONDITION

Early Observations.—In 1864, when Duménil was drawing attention to multiple neuritis and shortly after Bernard and his co-workers by their experiments had given such impetus to the consideration of lesions of the central nervous system as a cause of diabetes, Marchal de Calvi pointed out that diabetes may be the cause rather than the result of neurologic disturbances. Even prior to 1864, symptoms suggestive of diabetic neuropathy had been described.[1] As summed up by Auché (1890), the reports of the early writers,[2] from 1864 to 1884, dealt in a rather theoretical manner with the mechanism causing the nervous symptoms, which were described to a limited extent.

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1. Rollo (1797). Frank (1842). Bardsley (1807). Billiard (1852).

2. Christi-Buici (1873). Worms (1880). Mary (1881). Raymond and Oulmont (1881). Berger (1882). Drasche (1882). Rosenstein (1882). Charrin and Guignard (1882). Bouchard (1882). Bernard and Féré (1882). Demange (1883). Barth (1883). Dreyfous (1883). Dieulafoy (1884). Cornillon (1884).

Later Observations.—According to Charcot (1890), Bouchard presented in a lecture in 1881 his observation that the knee jerks are often absent in diabetic persons; he published this report in 1884. Marinian in the same year published a similar report, and, according to Woltman and Wilder (1929) and Wright (1931), Althaus also recognized this pseudotabes of diabetes in 1884. From then until 1910 the literature concerning diabetic neuropathy increased rapidly. Since 1910 sporadic descriptions have appeared, one of the most notable, other than those in such comprehensive books as Joslin's (1928) and von Noorden and Isaac's (1927), being that by Woltman and Wilder (1929). After Bouchard's paper appeared, reports of the signs, as well as of the symptoms, became more numerous. Pryce (1887) described a sluggish pupillary reaction and ataxia, the latter of which was also mentioned by Pavy (1887) and von Leyden (1888). Von Leyden, who in 1880 had stimulated interest in nonspecific multiple neuritis, in 1888 reported cases of diabetes with paralysis and separated diabetic neuritis into three groups: the hyperesthetic, the paralytic and the ataxic. Von Ziemssen (1885) attributed the neuralgia of diabetes to peripheral neuritis but gave no pathologic proof. Von Hösslin (1886) commented on the absence of paralysis in diabetic persons with neuralgia; but in 1890 typical cases of diabetes with paralysis were reported by Althaus, Auché, Buzzard and Charcot. The case reported by Althaus was one of mononeuritis of the circumflex nerve, with atrophy of the muscles. Trophic ulcers were present in a case reported by Pryce (1887) and in one recorded by Buzzard (1890); and Raven (1887) reported a case with associated atrophy of the optic disk. Auché (1890), in a good article, summed up the literature and stated that the nervous complications of diabetes may involve all nerve functions: motor, sensory, special sensory, intellectual and nutritional. He listed among the symptoms pain especially at night, deep pain, lancinating and lightning pain, paresthesia, hyperesthesia, anesthesia, tenderness of nerves, changes in the reflexes, paralysis and vasomotor and trophic difficulties. He did not think that there was involvement of the bladder and rectum. He believed that this form of neuritis was not rare in diabetes, and he compared it with alcoholic neuritis, which had been done by von Leyden (1888), Minor (1889), Charcot (1890) and Buzzard (1890). Thus one sees that by 1890 the clinical picture of diabetic neuritis was rather complete.

Since 1890, many phases of diabetic neuritis have been described. Williamson wrote several articles. Lépine (1909), Labbé (1922), von Noorden and Isaacs (1927) and Joslin (1928) devoted sections in their books to the subject. Woltman and Wilder (1929) wrote a comprehensive paper, especially on the pathologic process, and Root and Rogers (1930) reported 11 cases with associated paralysis.

OBSERVATIONS

Selection of Cases.—The cases described here were selected from those of patients treated at the Joslin Diabetic Clinic in 1930, 1931 and 1932. Cases were chosen in which the symptoms and signs suggestive of neurologic disturbance were not obviously due to conditions other than diabetes. At first only cases generally designated as instances of neuritis were taken; but later, as it became evident that the condition in these cases blended into other somewhat similar conditions, cases of other types of neuropathy were observed so that the significance and the relation of the conditions to neuritis proper might be studied.

Grouping of Types of Cases.—I have divided the series of cases into four groups, according to the nature of the manifestations: (1) hyperglycemic type, 34 cases; (2) circulatory type, 27 cases; (3) degenerative type, 45 cases, and (4) neuritic type, 120 cases. This classification was made not to establish a new nomenclature but purely for the purpose of this study. The term diabetic neuritis has gained significance, however vague, through long usage, and it conveys meaning to physicians in many countries. 1. The first group comprises cases in which neuritic symptoms (usually with no signs other than tenderness of the nerve or muscles affected) were associated with an abnormally high sugar content of the blood, disappeared within a few days after the initiation of adequate diabetic treatment and did not recur if the diabetic regimen was followed. 2. The second group includes those cases in which there was considerable circulatory deficiency in the legs and, in addition, pain, paresthesia or signs such as hyporeflexia and hypesthesia. 3. The third group is composed of cases in which rather mild neuritic symptoms and signs began insidiously and tended to progress slowly over a period of years. This group includes cases with such findings as sluggish pupillary reactions and hyporeflexia. Occasionally the neuropathy involved structures which by their nature drew attention to them, as in cases of involvement of the bladder. 4. The fourth group embraces the cases in which there were definite manifestations of neuritis, usually with relatively severe symptoms or signs, such as paralysis. The onset was relatively acute, and improvement usually took place within a few weeks or months.

1. HYPERGLYCEMIC TYPE

Thirty-four cases of the hyperglycemic type are reported on here. No attempt was made to include all those cases observed during the thirty-two months of this study. The cases were selected at random from those encountered. They seemed to show the various features of the condition and to be fairly representative of the group as a whole. The cases were segregated because there were neuritic symptoms (with

no signs of neuritis except tenderness), which disappeared simultaneously with the reduction of the glycosuria. In 2 of the 34 cases the diabetes was controlled with great difficulty, and it was a matter of months before it was well regulated and the symptoms were relieved. In these 2 cases there were other features that rendered them a little atypical. In 1 (case 5,932) the patient had pulmonary tuberculosis, and signs of neuritis developed about the time the pain disappeared. In the second case (case 6,659) pain and tenderness of various nerves and muscles developed immediately after the extraction of an abscessed tooth, with an exacerbation of symptoms after the extraction of a second abscessed tooth; and the patient did not become symptom-free until five months after the second episode. Incidentally, the neuritis became much worse when pills of ferrous carbonate were given, possibly owing to constipation. In both of these cases the patient was young and had severe diabetes. Even with treatment there were hyperglycemia and glycosuria; so it is not surprising that pain persisted so long.

Site, Symptoms and Signs.—The site of this type of neuritis[3] varied little. In 26 cases (76.5 per cent) it involved only the legs. In the other 8 cases, there was more or less generalized involvement, either of the arms and legs together or of the entire body. The outstanding symptom was pain, especially at night when the patient was in bed. Some patients had pain only at night, and in most instances relief followed pacing the floor. Cramps, again especially at night, were at times the outstanding symptom. Sometimes the pain was transitory and sharp, and at other times, merely a dull ache. Once it was described as "a tearing of the calf muscles." This nocturnal type of pain is often referred to circulatory deficiency, but that did not seem to be true in these cases. At least, there was no obvious circulatory deficiency, and many of the patients were young and had little if any arteriosclerosis. Sometimes only paresthesia was present. This was manifested by coldness, numbness or prickling. Hyperesthesia to touch has been noted, as has a sensation of weakness, although I did not observe muscular paresis in any case. Some patients became nervous, irritable or depressed, but only 1 patient (case 6,659) showed a definite psychic upset. Tenderness of the nerves and muscles was not infrequently noted, and in some instances there was hyperesthesia. In 1 case (case 10,416) there was hypesthesia of the left side of the body, with no other evidence of cerebral vascular accident. Paresthesia of the left side of the body had been present for the six months during which the patient had had diabetes, and yet it disappeared on the second day after diabetic treatment was started. A decrease of the tendon jerks was noted in 5 cases, in each of which there was a combination of two or more of

3. For convenience I shall refer to each type as neuritis.

the types described. In each of these cases symptoms were relieved at once by diabetic treatment.

Fever and Blood Picture.—A tabulation of the temperature was not made for this group, although routine readings of temperature were noted for each patient, no one of whom had a noticeable febrile reaction not accounted for by other conditions. A white blood cell count was made in 6 cases, and the values ranged from 6,450 to 10,350. In 5 cases a blood smear was made. In 1 of these cases there was an abnormality, presumably due to an acute pulmonary infection of which the patient died in a few days. In another case (case 10,945) there was 7 per cent eosinophilia without known cause. In the other 3 cases smears were normal.

Pathology.—Prompt recovery prevented a study of the pathologic process.

Etiology.—Discussion of the etiology of each type separately necessitated considerable repetition, but it seems worth while as an aid in determining the various factors at work.

Sex and Age: Of the 34 patients, 23 were women and 11 (32.4 per cent) men. The age at the onset of the neuritis varied from 18 to 70 years, with an average of 46.4 years. Nine patients (26.5 per cent) were less than 40 years old, and 7 (20.6 per cent) were below 30 years of age.

Severity and Duration of the Diabetes: The diabetes was not always severe, but at the time symptoms appeared it was always uncontrolled. In 10 cases (29.4 per cent) the diabetes was mild, and in only 3 (8.8 per cent) was it severe. Thus, one sees that even though a diabetic patient has considerable glycosuria and neuritic pain, by adhering to treatment he may be relieved of the pain within a few days and may prove to have mild diabetes, requiring little or no insulin. Several of the patients had symptoms of neuritis before the apparent onset of the diabetes. This is not surprising, since marked hyperglycemia and glycosuria are often unassociated with hunger, thirst and polyuria. Two of the patients had had diabetes for thirteen years before neuritis began. The average duration of the diabetes prior to the appearance of neuritis was three and three-tenths years.

Dehydration and Acidosis: The clinical appearance of the patient or a gain of several pounds in weight within the first few days of treatment was used as a measure for dehydration. By this standard it was noted that dehydration was present in 10 cases (29.4 per cent). Furthermore, as judged by the clinical appearance of the patient or the finding of acetone bodies in the urine, acidosis was present in only 9 cases (29.5 per cent). In 22 cases (64.1 per cent) there was neither dehydration nor acidosis. Such evidence suggests that neither of these

factors is essential for the production of the symptoms. Furthermore, it is well known that whereas in many cases diabetic coma is accompanied by severe pain, in others there is none, even though acidosis and dehydration are marked. Recently I closely questioned 9 diabetic patients with marked dehydration, 4 of whom had definite acidosis (in 2 the carbon dioxide-combining power of the plasma was below 20 volumes per cent), and none had the slightest symptom of neuritis.

Cholesteremia: I used the cholesterol content of the blood as an index of the disturbance of fat metabolism, especially in the patients without acidosis. Such an analysis was made on 13 of the patients, 6 (46.2 per cent) of whom had hypercholesteremia. Such a percentage is not high, for in all these patients the diabetes was uncontrolled. The lowest cholesterol value was 145 mg.; the highest, 305 mg. (230 mg. being the maximum of normal), and the average, 225 mg. Two factors tend to exclude hypercholesteremia as a cause of the symptoms. First, more than half the patients tested showed normal cholesterol values. Second, the level of cholesterol in the blood changes slowly under the treatment at the clinic, and these patients obtained relief within a few days after treatment was instituted.

Accessory or Nondiabetic Factors: Foci of infection were present in 25 per cent of the cases, but relief from the symptoms was not postponed until the infection was removed. Arteriosclerosis is so prevalent in diabetic persons that its high incidence is not significant. In 6 cases (17.77 per cent) there was no arteriosclerosis, and in 3 others there was only a slight degree of it. A previous dietary deficiency had not existed in the 5 cases in which there was specific questioning about this. Achlorhydria was present in only 2 of the 10 cases in which a test was made, and in these 2 there was no other evidence of pernicious anemia or combined system disease. Tuberculosis was present in only 1 case. The prompt relief of symptoms tends to exclude all these factors as causative agents. No other possible causes were discovered.

I cannot say that hyperglycemia alone causes the symptoms, for it is often present in diabetic persons who have no symptoms and whose immunity is unexplained. Nevertheless it was the only factor noted in all cases, and correction of it was followed immediately by a disappearance of the neuritic symptoms. Furthermore, it is recognized that in diabetic persons pain of a different nature from that described here is often worse when the value for blood sugar is high and less severe when the diabetes is controlled.

Prognosis.—The criteria for the selection of these cases necessitated a good prognosis. However, it is interesting to note that several patients who had had symptoms for more than a year obtained prompt relief when diabetic treatment was instituted. One patient (case 10,562) had had pains and cramps in the calves of the legs for the preceding seven

years, and yet twenty-four hours after the excretion of sugar in the urine decreased below 1 per cent all the symptoms stopped. In another patient (case 11,036) the right ankle jerk, which had been sluggish, became definitely more active within three days after the patient became aglycosuric. In all but 2 of the cases the diabetes was fairly easily controlled, and in only these 2 was relief from the pain delayed. In 31 of the 34 cases the symptoms disappeared within a week after the initiation of diabetic treatment. One patient (case 11,092) was not so fortunate, as his symptoms lasted sixteen days, but he had a carbuncle and considerable diabetic acidosis. The average duration of symptoms after treatment was begun was three and six-tenths days. The future course of these patients should prove interesting and instructive. Sufficient time has not elapsed for me to say what this hyperglycemic pain may signify. However, 4 patients have subsequently shown evidence of real neurologic disorder. One patient (case 9,913) nine years after the first attack of hyperglycemic symptoms had advanced circulatory deficiency of the legs, and there was absence of the tendon reflexes. Another (case 5,932), a boy of 18 years, although essentially symptom-free, had sluggishness of the knee jerks and right ankle jerk and absence of the left ankle jerk. Sensitivity to pinprick diminished on the anteromedial surface of the lower portion of the legs. Another patient (case 9,759) had neuritis with definite signs, although she had been aglycosuric and had been receiving insulin during the interim between the disappearance of the hyperglycemic symptoms and the onset of the neuritis. Incidentally, during the same period the pulsation in the dorsalis pedis arteries diminished practically to the point of absence. Another patient (case 9,765) experienced an almost identical course, including the circulatory change, in a period of ten months. The relatively slight increase in the duration of the diabetes in the 3 last mentioned cases is hardly sufficient to explain the changes.

Treatment.—The treatment was the regular regimen for diabetes. Relief is so prompt that other treatment is usually unnecessary. Heat, salicylates or hypnotics may be used if necessary. Massage was very effective in 1 case (case 6,659). The general condition of the patient and foci of infection should be given the attention required.

2. CIRCULATORY TYPE

To study this type, I have taken at random 27 cases. The frequency of the condition is illustrated by the large percentage of diabetic persons who have sufficient circulatory deficiency to warrant amputation of the legs. Labbé (1931) mentioned certain symptoms and signs observed in this condition.

One can quickly dispose of this type by stating that in all essential features it resembles the degenerative type. The onset, symptoms and

signs, course, site, etiology, age at onset, prognosis and treatment are the same in both groups, with few exceptions. The patients with circulatory deficiency occasionally have intermittent claudication, which was not present in the patients with the other type of neuritis. Parts of the body with no evident circulatory deficiency were affected in patients in this group, and those with degenerative nerve lesions in other parts of the body occasionally had sluggish circulation of the lower part of the legs. I believe that a separation of these two types is not indicated, that they should be grouped as one under the degenerative type. Provision for poor circulation of the feet can be made easily by prescription of Buerger's exercises and more careful attention to the feet to prevent and treat lesions which might receive surgical intervention. I shall therefore combine pertinent data on these 27 cases with those of the degenerative type.

3. DEGENERATIVE TYPE

Of the many cases of this type encountered I have used 45 for this study. Among these are cases illustrating the various features of this type of neuritis and also cases which disclose the difficulty of segregating some cases of this type from those of the hyperglycemic and neuritic types. These cases represent the type of neuropathy from which such a large percentage of diabetic persons suffer. They include the type of cases in which the routine examination discloses hyporeflexia or areflexia of the tendons or sluggish reactions of the pupils. Mild pain or paresthesia is usually acknowledged if one questions the patient, but the symptoms of neuritis are rarely a major complaint. The onset is insidious and the course prolonged. The supervention of other conditions may complicate the picture, so that a decision as to the type of neuropathy is reached with difficulty.

The earlier symptoms in case 8,166 suggested that the patient might have had real neuritis, but at the time of examination the mildness of the symptoms, the minor signs and the ten years' duration of the neuritis suggested rather a degenerative condition.

Site and Symptoms.—In 18 cases (40 per cent) there was involvement only of the legs; in 6 cases, of the arms and legs alone; in 10, of the pupils and legs, and in 2, of the pupils alone. In the remaining 9, there was generalized involvement. The predominant symptoms were pain, cramps and paresthesia. All symptoms were worse at night, usually markedly so, and were increased occasionally with fatigue. The pain was at times dull and at other times sharp, steady or momentary. Burning pains were complained of less among this group than among those with the circulatory type. One patient (case 10,100), in addition to neuritis of the leg, with a sense of vibration and a sensation as of "cold water poured down the bone," complained of neuralgia of the gums of two years' duration. The left pupil reacted sluggishly to light. Another

patient complained of a binding feeling around the calf, especially at night, so severe that he could not lie still. Fifty-seven and one-tenth per cent of the patients had pain of some type, and 55.3 per cent had paresthesias. The paresthesias included numbness, prickling, burning, coldness and, rarely, generalized itching. One troublesome and unexplained symptom, occurring in case 9,643, was numbness, as if the hands and feet were asleep. There were no other symptoms; and the only sign was absence of the knee jerks, although the ankle jerks were normal. There was no obvious circulatory deficiency or anemic condition. The gastric free hydrochloric acid showed 64 degrees of acidity. There was moderately advanced arteriosclerosis. In case 11,075 there was intractable numbness of the hands. There were also pain and tenderness of one arm and rectal incontinence, apparently dependent on a relaxed sphincter. In case 6,331 there were slight urinary incontinence and absence of the right ankle jerk. The cases in which there was loss of control of the sphincter will be discussed later.

Signs.—The neurologic observations included sluggishness or absence of the tendon jerks, weakness of the legs or of isolated groups of muscles with or without atrophy, weakness of the anal sphincter, tenderness of the nerves and muscles, hypesthesia, anesthesia, an abnormal pupillary reaction and, in 1 case, a positive Romberg sign. The hypesthesia was noteworthy. In 1 case in which there were no symptoms there was generalized hypesthesia, most marked on the lower portion of the left leg, and there were sluggishness of the left ankle jerk and absence of the right ankle jerk. One patient (case 10,528) did not show a noticeable decrease in sensitivity to pinprick, but she experienced almost no pain when the surgeon cut and probed the infected foot. The signs in 1 case were so striking, albeit rare, that I report it as follows:

CASE 10,451.—A 56 year old woman, with moderate arteriosclerosis and diabetes of fourteen years' duration, noted paralysis of the muscles elevating the foot. The ankle joint became swollen but not tender. Bits of bone were painlessly extruded from the toes. The lesions would heal but recur, or new ones would develop. The ankle joint became useless and instable. The process then involved the other ankle and foot. One ankle improved, the cutaneous lesions healed, and the foot drop became less noticeable. Two years after the onset I observed a rather typical, painless Charcot joint of the ankle, in addition to chronic osteomyelitis of the foot of an unusual type and without obvious etiology. There was partial left foot drop, with hypesthesia of the lower portion of the legs, most marked in the distribution of the external peroneal nerve. The knee jerks were normal, but there was absence of ankle jerks. The Wassermann test of the blood and spinal fluid gave negative results, but the colloidal gold curve resembled the type associated with dementia paralytica. Leprosy seemed an unlikely cause. The similarity of the disturbances produced by syphilis and diabetes and the absence of proof of the former in the history, the physical examination and the serologic study led me to consider this tentatively as a diabetic process of a neurologic trophic nature.

In 13 (28.9 per cent) of the 45 cases the knee jerks were normal; in 8 (17.8 per cent) there was absence of the patellar reflexes, and in 24 (53.3 per cent) there was absence of one or sluggishness of one or both reflexes. The ankle jerks were normal in only 7.3 per cent of 41 cases, and in these 3 cases there were other definite signs. Sensitivity to pinprick was normal in 55.6 per cent of 27 cases and decreased in the remaining 44.4 per cent. Sensation to touch, heat and cold corresponded to sensitivity to pinprick in the cases tested, but these tests were not employed frequently. In general, sensitivity, when abnormal, decreased progressively from the thighs down to the feet; but usually the distribution was patchy, so that one might strike sensitive points in areas otherwise insensitive. In case 5,112 there was sudden numbness of the dorsum of the left foot, with loss of sensation of pain and light touch. The pulsation in the dorsalis pedis artery was questionable. The following day the pulse was felt, and sensation was normal. I believe that sensitivity decreases with decreasing circulation and increasing arteriosclerosis, although there are a number of exceptions to this rule. Position sense of the great toe was tested in 25 cases and was decreased in only 3.

Pathology.—The pathologic process was not studied in these cases. Many of the cases reported in the literature seem to fall in this group of the degenerative type, and I shall mention here the pathologic process described in the literature. Changes were noted in the spinal cord by nine authors,[4] in the cord and nerves by eight,[5] in the peripheral nerves by eight[6] and in the posterior roots by three.[7] The early report and summary by Auché (1890) and the recent one by Woltman and Wilder (1929) are good. In the latter article are transcribed the histories of 42 cases reported in the literature, in 24 of which there was degeneration of the peripheral nerves, in 16 degeneration of the funiculi, in 8 changes in the anterior horn and in 4 intramedullary degeneration of the posterior roots. Auché described a case of parenchymatous neuritis with considerable myelin degeneration and changes in the axis-cylinder in isolated nerve fibers. The process seemed chronic and progressive, involving first one fiber and then another, the first affected often showing sufficient

4. Minor (1889). Lichtheim (Sandmeyer, 1892). Williamson (1898; 1904). Van Leyden and Goldscheider (1895). Nonne (1896). Souques and Marinesco (1897). Naunyn (1906). Schweiger (1907). Root and Rogers (1930).

5. Leichtentritt (1893). Van Leyden (1893). Bonardi (1897). Findlay (1902). Ossokine (1902). Bramwell (1907). Marinesco (1901). Woltman and Wilder (1929). In the last two reports chief stress was laid on lesions of the peripheral nerves.

6. Pryce (1887; 1893). Nonne (1889). Auché (1890). Eichhorst (1892). Fraser and Bruce (1895; 1896). Hensay (1897). Fleming (1897). Wittmaack (1907).

7. Williamson (1904; 1924). Hensay (1897). Schweiger (1907). According to Wright (1931).

regeneration so that the function of the nerve seemed never to be lost. Auché noted normal nerve tissue proximal to markedly diseased nerve tissue and concluded that the changes in the nerve were not secondary to changes in the spinal cord. Pryce (1893) was struck by the association of arterial disease with the degeneration in the nerves. Marinesco (1901) also commented on the thickening of the walls of the intraneural arteries. Woltman and Wilder (1929) noted slight changes in the cord and marked changes in the nerves. These changes consisted of patchy degeneration of the nerves, with myelin disintegration and at times infiltration by lymphocytes, polymorphonuclears and fat-laden cells. The lesions were more marked in the peripheral than in the proximal parts of the nerves, an observation described also by Auché. Woltman and Wilder noted sclerosis of the intraneural vessels and concluded that this arteriosclerosis was a most important etiologic agent. In 1 of their cases regenerated fibers were observed. Similar regeneration was reported by Nicolescu and Raileanu (1926; 1927) in their description of the pathologic changes in the brain in diabetes. Warren (1930) studied the pathologic process in many diabetic patients, a large number of his nerve specimens having been obtained from limbs amputated because of diabetic gangrene. The pathologic process in the nerves was not very conspicuous, but the small peripheral branches of the nerves were not studied. Sclerosis of the intraneural arterioles and occasionally myelin degeneration were observed.

Etiology.—Sex and Age: Two thirds of the patients were women, and this may be explained by the fact that the women were more nervous and probably drew attention to their neuropathy more often than did the men. The age at the onset of the neuritis varied from 40 to 77 years, with an average of 59.2 years. In the cases of the circulatory type the average age was 58.1 years, and the youngest patient was 40 years old.

Diabetic Factors: In this group the average duration of the diabetes before the onset of the neuritis was four and five-tenths years, but sometimes the neuritic symptoms preceded the apparent onset of the diabetes. In 6 cases the average duration of the neuritis prior to the diabetes was four and five-tenths years. The record for case 10,582 is interesting. The patient was admitted to the hospital with an occluded femoral artery and a neuritic condition of the diabetic type. However, throughout the first stay at the hospital tests of the urine and blood did not reveal evidence of diabetes, and my associates and I concluded that the neuritis, which we had thought rather characteristic of diabetes, was of a different etiology. Within a short time the patient returned with an inflammatory condition of the foot, and under this added strain the diabetic condition became evident, with a blood sugar content of 0.23 per cent. This patient had had neuritis for twelve years before the presence of diabetes was proved, although slight glycosuria had been noted previously. One may

contrast this with case 5,866 in which diabetes was present for twenty-four years before the neuritis was noted. In 18 cases (41.9 per cent) diabetes had been present for one year or less. Thus, there is no evidence to prove that long continued diabetes is necessary for the production of these nervous changes. The diabetes was mild in 31 cases (68.9 per cent) and severe in 3. Similarly, in 69.7 per cent of the cases the diabetes had previously been at least fairly well controlled, as judged by the tests of the urine cited by the patients. The values for cholesterol in the blood were not so good, as illustrated by the fact that in 7 of the 13 cases in which tests were made the values were above the maximum normal level, the average for the 13 cases being 236 mg. In the cases of the circulatory type the average value for cholesterol in the blood in 9 cases was 267 mg., which is 16.1 per cent above the maximum normal value.

Arteriosclerosis: By examination of the arteries I detected moderate or advanced arteriosclerosis in 41 of the 44 cases in which there was a record of this condition, and in 1 other a condition of the foot required surgical intervention, which in diabetic persons usually implies at least moderate vascular disease. Angina pectoris was present in 7 cases (15.6 per cent), a condition of the feet requiring surgical intervention in 19 (42.2 per cent) and apoplexy in 4 (in 1 of which it was questionable). The circulation in the legs seemed normal in only 20 per cent of the patients, and it was very deficient in 35 per cent. Of the entire group arteriosclerosis was present in every case, and in 95.5 per cent there was evidence of moderate or advanced vascular disease.

Dietary Deficiency: Fourteen patients questioned about their diets prior to the neuritis gave no history of a definite deficiency, although 1 patient (case 10,582) might not have eaten as much meat, fresh fruit and green vegetables as is usually considered normal. No deficiency of the nature of pernicious anemia was detected, although achlorhydria was present in 5 of 11 patients tested. Of the other 6 patients, only 1 had less than 25 degrees of free acidity, and the average for the 11 patients was 30.5 degrees. Among the patients with the circulatory type, only 1 of 7 tested had achlorhydria.

Alcohol, Foci of Infection and Syphilis: Of the 41 patients for whom there was a record of the consumption of alcohol, only 3 (7.3 per cent) had imbibed any. The incidence of foci of infection was also slight (11.6 per cent), but it is to be remembered that in many cases abscessed teeth may have been removed prior to my examination. Syphilis was present in none of the 45 cases.

To summarize the etiologic data, I may say that the only two factors, primary or contributary, which I have observed are the diabetes and the vascular disease. It seems that some obscure feature of the diabetes.

and not simply hyperglycemia, is at fault. The abnormality in the cholesterol content of the blood suggests a possible factor in the production of this neuropathy.

Prognosis.—The chronic and at times progressive nature of the condition precludes a good prognosis. The signs are likely to remain, if not to progress, in spite of the best treatment; and even the symptoms linger for months or years, although they may at times decrease considerably in severity. In some patients in whom the diabetes has been inadequately controlled relief from symptoms is moderate and rather prompt when they adhere to the diabetic treatment. Nine patients received relief in this manner, although in 4 the alleviation was slight. Two patients always paid by an increase in symptoms for any relapse in treatment. Amputation on account of markedly deficient circulation ended the symptoms in 1 case, but the absence of the knee jerk in the remaining leg testifies to the presence of the neuropathy. One patient received much benefit from Buerger's exercises. One patient (case 8,965) wrote that after two and one-half years she has had no more neuritis, and another (case 9,860) was relieved in one year; but in neither instance have I been able to examine the patient to see if the absence of the tendon jerks and other signs have been restored to a normal state. In case 1,217 the symptoms began when the patient was aglycosuric, according to her, and progressed during the three years prior to the time I saw her; yet rest and heat afforded relief. In 3 cases the neuritis has lasted ten years or more. One of these (case 8,166) is interesting. The manifestations of neuritis consisted of pain, paresthesia, weakness and areflexia in the legs. During the past several years the carbohydrate content of the diet has been gradually increased. In the past three years the neuritis has improved definitely. The symptoms and weakness disappeared, and the patellar reflexes have returned to the point where both can be obtained without reenforcement, and this in spite of hyperglycemia and a cholesterol value 41 per cent above the maximum normal. In case 10,135 there was also a lessening of signs. In a period of ten months during which the patient was treated with insulin, one knee jerk, which had been very sluggish, became practically normal and the paresthesia ceased. In case 9,643 there was absence of knee jerks, which later were partially regained. In case 6,331 there was absence of the ankle jerk on the right side but a normal ankle jerk on the left, the side on which there was hemiplegia. The average duration of the neuritis in the 45 cases has been three and five-tenths years. In the group of the circulatory type improvement in tendon jerks was noted in 3 cases (cases 1,696, 2,843 and 9,287). The average duration of the neuritis in this group was four and four-tenths years. Obviously this short duration is due at least partially to the fact that in general the patients have been observed over a period of only two and one-half years or less and

some were observed for the first time only a few months before this study was completed.

Treatment.—Persistent treatment of the diabetes should be demanded. One should not expect too much, because in 69.7 per cent of these cases the neuritis has appeared or persisted in spite of apparently well controlled diabetes. However, in a number of cases quite a little relief was obtained after the institution of diabetic treatment. Observation of roentgenograms of the legs of some diabetic patients makes one both discouraged and hopeful. The calcification of the arteries is often extreme and completely obliterates the lumen, but at the same time one sees evidence of smaller collateral arteries developing to care for the area formerly deprived of its blood supply. Buerger's exercises have given fairly good results in some cases and should be tried. In 19 of the cases of the circulatory type I know the effect of these exercises. Five patients obtained much relief, and 8, moderate relief, a total of 68.4 per cent. Only 3 patients failed to receive apparent benefit. Even these patients should continue the exercises, because in time sufficient collateral circulation may develop. Sedative measures, similar to those used for hyperglycemic symptoms, may be employed for the temporary relief of pain, but one must be more careful in prescribing drugs, because the condition persists for a long period. Furthermore, the vascular disease, with hypesthesia and susceptibility of the tissues to injury, makes it essential that extreme care be used in applying heat. In the hospital I have used an electric baker, regulated by a nurse who understands both the apparatus and the condition of the patient. Warm baths are sometimes recommended for the relief of pain, but it is well for a young person with sensitive skin to test the temperature of the water. Hot water bags, especially of the chemical type, are looked on with disfavor. Meticulous care and cleanliness are essential in trimming toe-nails, calluses or corns. In many cases this is better left to a skilled chiropodist who understands the diabetic and vascular conditions. One homely remedy, occasionally effective for patients with low blood pressure and impaired circulation in the legs, is a glass of water at bedtime. Sometimes it permits a night of uninterrupted sleep.

4. NEURITIC TYPE

In this group belong the cases ordinarily described as cases of diabetic neuritis or diabetic tabes. I have observations on 120 such cases to present. Some probably would not be classified as cases of neuritis by many physicians, but they have some features in common and they serve as examples for purposes of discussion. In many cases the same features were present as those exhibited in cases in the three preceding groups, but this is not surprising when one considers the two apparent causes (hyperglycemia and arteriosclerosis) operating in the former groups. Certain other manifestations in the group may represent merely an exten-

sion or exaggeration of the processes in the preceding groups, but the clinical picture and the course of the disease suggest that the condition in these cases is possibly different; and I have put them in a separate group for study, so that conclusions drawn may not be false owing to improper selection. In this group are cases of neuritis possibly resulting from causes other than diabetes and its related concomitants, but I believe that even in these the presence of the diabetes had an effect on the type or degree of neuritis produced. In general, the condition in cases of the neuritic type differed from that in cases of the degenerative type in that the neuritis was usually a cause of real difficulty, the onset was often acute and the neuritis tended to improve markedly within a reasonably short time. In some cases the patient improved rapidly and was free from both symptoms and signs. This contrasts sharply with the chronic course and absence of complete cure in the former group.

Incidence.—It is difficult to determine the incidence of diabetic neuritis because it is difficult to decide what constitutes neuritis. Furthermore, contact with the patient must be maintained from the onset of the diabetes until death, because the neuritis, unlike the diabetes, is at times transient. One author reported the incidence of pain, another the absence of knee jerks and another the frequency of abnormal knee jerks, and another made a more general statement as to the frequency or rarity of the condition.

Bouchard (1884) noted absence of the patellar reflexes in 28.5 per cent of diabetic patients, Auerbach (1887) in from 35 to 40 per cent, Maschka (1885) in 30.6 per cent, Eichhorst (1892) in 18.8 per cent, Grube (1893) in 7.6 per cent, Williamson (1924) in 49 per cent and Melander (1931) in 3.8 per cent. Auché (1890) believed that diabetic neuritis was not a rare complication in diabetes. Pitres (1902) reported 1 case of diabetes in which there was absence of the pupillary reflex and 20 of 32 showing weakness or absence of the patellar reflexes. Williamson (1905) reported decreased vibratory sensitivity in 15 of 45 diabetic patients. Kraus (1922) noted abnormal knee jerks in 40 per cent of 450 such patients. Stewart (1925) stated that the nervous system is involved in 50 per cent of diabetic persons. Von Noorden and Isaac (1927) stated that 31 per cent of diabetic patients have pain, but Woltman and Wilder (1929) noted pain in only 10 per cent and paresthesia not accounted for by arthritis, myositis or trauma in 10 per cent. Wendt and Peck (1931) mentioned persistent pain in 5 per cent of their cases. Murphy and Moxon (1931) reported neuritis in 0.6 per cent of their cases. Sevringhaus (1931) noted pain in 49 per cent and reduced reflexes in 57.3 per cent of his diabetic patients especially examined for these conditions.

This high incidence of neurologic derangement in 1931 seems to cast doubt on the assertion of Melander that the administration of insulin

has decreased the incidence of abnormality of the reflexes by enabling persons with diabetes to remain in better general condition, although he did use absence of the reflexes rather than mere abnormality of the reflexes as his guide. The incidence of diabetic neuritis in my cases was arrived at in two rather inadequate ways. Sluggishness or absence of one or more of the knee jerks or ankle jerks probably gives a fair idea of the presence of the degenerative changes of the nerves, but it includes such an abnormality due to any cause. It indicates the presence of the neuropathy only at the time of the examination and fails to include those cases in which such a neuropathy develops later. Among 461 unselected cases of diabetes, normal knee jerks and ankle jerks were noted in 252 (54.7 per cent), except that the left knee jerk in 1 case was hyperactive. In all other cases there was a decrease of one or more of the four tendon reflexes. In no case was there hyperactivity of the tendon jerks as a whole; in only 2 cases were there hyperactive knee jerks, and in both cases there was absence of the ankle jerks. The knee jerks improved in six months in 1 case, and in another the ankle jerks improved in seven months. There was absence of all the knee jerks and ankle jerks in only 22 cases (4.8 per cent). The second method of determining the incidence of neuritis has its faults also. This study extended over a period of two and one-half years. I noted real neuritis in 25 of 1,000 consecutive cases observed for the first time in the period of this study. Neuritis may appear later in many more of the 1,000 cases, but so far the incidence has been only 2.5 per cent.

Site.—I had 120 patients, 1 of whom had two apparently unrelated attacks of neuritis. The site of the neuritis in these 121 cases was as follows:

	Cases	Percentage
Legs	81	66.9
Arms	8	6.7
General involvement and other special sites	32	26.4

The neuropathy may involve almost any part of the body from the pupils to the feet. The optic, the oculomotor, the facial, the auditory and the recurrent laryngeal nerves have all been affected directly or indirectly, as evidenced by abnormal function of the structure innervated. I have mentioned 1 case in which the condition simulated ureteral colic. Disturbance in the bladder, as revealed by incontinence or by retention with paralysis of the wall of the bladder, has been observed. Cases of abdominal symptoms have been observed. The predominance of involvement of the legs is striking and is in accord with previous reports.

Clinical Picture.—The student of diabetes is apt to forget the ordinary significance of certain neurologic signs. He sees them so often in diabetic patients that he becomes accustomed to changes that would greatly perturb the student of other diseases, who knows these signs are often

of serious portent in nondiabetic persons. To describe the clinical picture of diabetic neuritis, it is necessary to report several cases at least briefly. Others will be described because it is a moot point whether or not the condition was neuritic, and I wish to present them for consideration and discussion. To mention all the symptoms and signs met with in this condition would confuse rather than clarify any ideas of the disease, for they are protean and may simulate many other diseases of the nervous system. It is well to remember that pain (especially at night), paresthesia, decreased activity of reflexes and paresis are the most frequently encountered features and that in the great majority of cases the legs are affected. Even considering the defectiveness of ordinary observation, memory and subsequent description, one is impressed by the vagueness of the condition. It seldom involves only the area innervated by one nerve, and often it does not involve all this small area. Feiling (1921) and Hyslop and Kraus (1923) implied that multiple neuritis and lead neuritis may also be diffuse and cause changes in the central as well as in the peripheral nervous system. The person with diabetes who can definitely outline the boundaries of the area affected by the neuritis is rarely seen. Even the time of onset is not always well marked, although some patients describe a definite, acute onset of symptoms. The very vagueness of the descriptions and the widespread area affected by symptoms or signs suggest a diffuse and patchy involvement of the nervous system, an insidious process rather than an isolated and sharply demarcated one. It is difficult to conceive of true neuritis, involving all the fibers of a nerve trunk, causing most of these neuropathies. It is not unusual to note an abnormal tendon reflex in one leg whereas the patient complained of neuritis of the other leg. Another patient may complain of discomfort in only one leg and yet on close questioning acknowledge symptoms in the other also. The indefinite nature of the condition may be explicable on the basis of two conditions, neuritic and degenerative, affecting the nervous system simultaneously. It is hardly fair to interpret all the changes as being due either to the more acute process or to the chronic degenerative one. It seems definite that at times there is acute neuritis superimposed on a chronic condition. The former responds well to treatment, yet slight symptoms or signs remain, and I am inclined to think that these are due to the chronic condition and are dependent on a different cause from that of the neuritis itself. For example, in case 9,468 there was acute neuritis with foot drop which disappeared within six months. Yet two years later the patient still showed change in the reflexes. I interpret the foot drop and the change in the reflexes as separate conditions. The patient certainly views the two conditions differently. He says that he had neuritis but that now he is cured, and I am inclined to agree, although I believe that now he has a diabetic neuropathy, though of a somewhat different nature.

Case 1,930.—A woman of 35 years began to have pain and paresthesia. The pain was very severe and shooting and was felt over the entire body. The paresthesia was described as numbness of the toes, as if there were cotton under them. Two months after the onset the patient consulted me and was given the usual diabetic treatment for patients who are not admitted to the hospital. Diabetes was so severe as to be controlled with great difficulty, but the patient stated that there had not been much glycosuria until the neuritis made the diabetic condition worse. Six months after the onset the neuritis was so severe that the patient was admitted to the hospital; but it was another three months before improvement became definite. A year after the patient was admitted to the hospital the neuritis was much better, although another year elapsed before the patient considered herself cured. Three and a half years after the onset of the neuritis, physical examination revealed a sluggish right knee jerk, absence of ankle jerks, soreness of the calves and hypesthesia of the lower part of the legs. At this time the patient was 39 years old, had moderate arteriosclerosis and had had diabetes for more than eleven years. The treatment in this case consisted of treatment of the diabetes, rest, application of heat, removal of abscessed teeth and the addition of liver extract and yeast to the diet.

Case 3,869.—A woman, 59 years old, with moderate arteriosclerosis and diabetes of three years' duration, had neuritis, which began suddenly with severe pain in the left hip, the posterior portion of the thigh and the lower part of the leg, even to the toes. This was associated with cramps in the calves and numbness in the legs. After six weeks, weakness of the legs developed and caused almost complete paralysis. The knee jerks were normal. Gradually, with the routine treatment for diabetes and neuritis, she improved considerably. At the second visit, seven years later, the patient was still troubled with some paresthesia, cramps and weakness of the legs, especially when there was glycosuria. Examination at this time revealed sluggish knee jerks (especially on the right), absence of the left ankle jerk, weakness of the left peroneal nerve and some weakness and atrophy of the left calf and thigh. The circulation was somewhat deficient in the feet, especially in the left foot. The cholesterol content of the blood was normal. In spite of some discomfort and disability the patient had worked well in the past six years. On the third visit, ten months after the second, examination did not reveal particular change, except that the left ankle jerk was elicited at times. The cholesterol content was 250 mg. The neuritic symptoms appeared occasionally, but the application of heat usually gave relief.

In this case there was an acute onset, and the neuritis responded fairly well to treatment at first, but the symptoms and signs persisted to some extent for more than seven years. It is difficult to believe that the patient suffered from neuropathic involvement from two sources, yet the acute onset and severity of the disability, with improvement at first, are in contrast to the relatively mild symptoms and the prolonged course of the condition in the subsequent period.

Case 4,319.—A man, 70 years old, with advanced arteriosclerosis and diabetes of eight years' duration, had a left foot drop, with paresthesia. Two months later he consulted me, but because he felt so well he did not follow the treatment prescribed, even though there was considerable glycosuria. The paresis improved, but severe pain developed in the leg six months after I saw him. The pain occurred only at night and never when the patient was walking. One year after the onset of the paresis the patient returned on account of severe pain and a moderate degree of nervousness and depression. There were sluggishness of the right knee jerk, absence of the left knee jerk and of both ankle jerks, weakness

of the entire left leg except the calf, tenderness of the muscles of the leg and hyperesthesia from the hip and groin to the lower part of the leg, at which level deficient circulation became evident. Seventeen days of treatment in the hospital afforded considerable relief.

CASE 5,390.—A man 35 years old, with slight arteriosclerosis and diabetes of five years' duration, was admitted to the hospital with marked glycosuria, which responded well to treatment with diet and insulin. There were no symptoms or signs of neuritis. Abscessed teeth were removed at this time. A few days after the patient became aglycosuric a constant aching developed in his legs, associated with hyperesthesia so severe that even bedcovers caused pain. Numbness and burning of the feet occurred. Seven weeks after the onset of symptoms the patient returned to the hospital on account of the neuritis. Examination revealed absence of the ankle jerks, which had been normal at the time of the first examination. Hyperesthesia was present over the entire body, except on the lateral side of the right thigh. The muscles and nerves from the hips to the feet were tender. In another month he was unable to walk, and he was then admitted to another hospital, from whence he wrote that he was burned while receiving heat treatment, indicating either a change from the previous hyperesthesia to hypo-esthesia or an abnormal susceptibility to heat. While at the other hospital a tonsil became infected. Subsequent to this the patient began to improve, and he was well within ten months of the onset of the neuritis.

CASE 10,925.—A 64 year old man with diabetes of seventeen years' duration had neuritis, with pain in the left leg, tingling in the feet and hyperesthesia. The hyperesthesia diminished gradually, but weakness developed. Seven months after the onset the right leg became involved. There were tenderness of the calves and thighs and weakness of the thigh and iliopsoas muscles, especially on the left side. Sensitivity to pinprick was diminished on the anterolateral portion of the thighs, varying in intensity elsewhere. There was absence of the tendon reflexes in the legs. There were moderate psychic instability and depression, obviously exaggerated by the death of his wife, which occurred during the course of the neuritis. Gradually, during the next five months the neuritis improved markedly, especially in the left leg, which became almost normal.

CASE 10,972.—A 65 year old woman sought treatment because of neuritis, and it was discovered that she had diabetes. The neuritis began as pain in the thigh and then extended to the foot, being present only at night. Weakness of the thigh was noted when the patient went up or down steps. Examination revealed tenderness only of the internal lower aspect of the right knee. There was absence of the right knee jerk, but the other three tendon jerks in the legs were normal. There were atrophy of the right quadriceps muscle and weakness of the quadriceps and iliopsoas muscle on the right. The neuritis improved within a month after the onset, but a relapse occurred, the pain and tenderness returned, and the weakness of the leg increased so that the patient could not raise the leg to a couch nor could she rise from a sitting position. Psychic depression became marked. In another month the patient was much better and walked 1½ miles (2.4 Km.) daily. Six months after the onset she considered herself well, and the depression had disappeared.

CASE 8,428.—A 30 year old man with diabetes of one and two-tenths years' duration began to have slight numbness of the lower portion of the right leg. After about two and one-half weeks this became more noticeable but was still rather negligible. Three days later, as the patient was walking home, slight pain began in the leg and increased in about thirty minutes to such severity that he

called a physician, who recommended the application of an electric pad. Under the soothing effect of the heat, the patient fell asleep, to awake five hours later to find his foot badly burned. Within three days the pain decreased markedly, but he consulted me because of the burn. Examination revealed a queer burn on the lateral surface of the right foot and on the tips of the toes. The skin was dry, hard and discolored, like dry gangrene. There was a slight formation of blisters in spots. The foot was dry and cold, and the pulse was not detectable below the femoral artery; but the other foot seemed just as cold and had a palpable dorsalis pedis pulse. There was slight arteriosclerosis. There was absence of the right ankle jerk, and there was cutaneous anesthesia roughly in the area supplied by the external popliteal nerve but also of the whole foot except a small part of the dorsum. There was absence of position sense of the right great toe. There was tenderness of the external popliteal nerve.

The patient was admitted to the hospital, where readings for temperature of the skin showed lower values for the left than for the right foot, although the latter was colder than normal. The right foot was dry and the left was moist; and by wetting the right foot with a damp cloth I noted that the resulting evaporation lowered the temperature of the skin to the level in the other foot. I concluded that the sympathetic fibers to the right foot were damaged and that possibly a reflex stimulation of similar fibers to the other foot had caused the excessive sweating and lowering of the temperature in spite of uninterrupted circulation through the arteries. Owing to the inactivity resulting from the surgical treatment, foot drop developed on the right side, even though the ankle jerk and position sense had been partially regained; but eleven days of passive and active exercise overcame the foot drop. Gradually sensation returned in the previously anesthetic area. One may regard the whole attack as being due to sudden occlusion of the artery; but why such a sudden onset without demarcation, why the decrease of pain and return of the ankle jerk and position sense within a few days? Why, if the femoral or popliteal artery was occluded, was only the peroneal nerve affected? It seems more likely that neuritis developed in a limb to which the artery had been occluded slowly (about fourteen months previously the dorsalis pedis pulse was present) and that this vascular change played the rôle in the development of the neuritis that arteriosclerosis usually plays in older patients.

Symptoms.—Pain was present in 83.3 per cent of the cases. The most prominent characteristic was intensification at night and relief when the patient walked. The pain was at times dull, at other times sharp, sometimes continuous and sometimes shooting and momentary. Occasionally the pain was cramplike, burning, crushing or grinding. Usually it was ill defined, but occasionally it was limited to the course of one nerve, such as the sciatic. Of the 20 cases in which there was no pain, there was muscular paresis in 16, paresthesia in 2, optic neuritis in 1 and absence of reflexes in 1, with return of one knee jerk almost to normal in one year. Although frequently causing pain and other symptoms on the anterolateral surface of the thigh, diabetic neuritis differs distinctly from meralgia peraesthetica (Huddleson, 1928) in that the pain of the former is usually worse when the patient is in bed and is often relieved when the patient paces the floor. Paresthesia occurred in 70 per cent of all the cases and was often worse at night. The

paresthesia assumed the form of numbness, tingling, prickling, burning, coldness and a sensation as if the patient were walking on wool. Dizziness was occasionally experienced. Certain special symptoms will be described more fully later.

Signs.—Tendon Jerks: The most frequent sign was hyporeflexia, or areflexia, which occurred in 75.4 per cent of the cases. Sometimes, as in cases 8,167 and 10,279, the change in reflexes was more marked in the leg less affected otherwise by the neuritis. In general, when a change in the reflexes occurred, it was present in the area otherwise affected by the neuritis; but sometimes there was no change, and in many cases the changes occurred in areas otherwise free from neuritis.

Paresis: Muscular paresis, varying from slight weakness to complete paralysis (case 11,044), occurred in 65.8 per cent of the 111 cases in which a record of this sign was made. In each of 30 cases various muscles of the leg were affected. In 31 cases the dorsiflexor muscles of the foot were involved (bilaterally in 1 case), and in 16 of these no other muscles were weak. The quadriceps femoris muscle was involved in 21 cases, in 7 of which there was no other weakness. The hamstring muscles were affected alone in 2 cases and in conjunction with other muscles in 6 cases and the iliopsoas muscle alone in 2 cases and with other muscles in 8. In 3 cases there was weakness of some group of muscles of the arm. In 1 case (case 9,230) there were weakness and atrophy of both arms and legs. The paresis is not detected with ease in all cases. A patient lying in bed may not notice foot drop, and repeated examinations of bedridden patients are advisable, in order that paresis may be discovered promptly and corrected before it has become severe. Some patients suffered falls; some had difficulty in stepping up into a street car or in climbing or descending steps, and some recognized the difficulty by the flapping of the foot when they walked. In case 9,360 syphilis was suspected because of the unsteady and steppage gait, which Charcot (1890) described. At times the paresis is sufficient to incapacitate the patient completely. Atrophy may or may not be present. Occasionally it is marked and at other times slight; sometimes it is well localized and at other times widespread and manifested merely by the smaller circumference of the affected leg. As in case 4,319, paresis may be the initial symptom of the neuritis, and pain may not supervene until several months later.

Atrophy of Muscles vs. Atrophy Caused by Injection of Insulin: In connection with atrophy of muscles one might consider briefly the atrophy caused by the injection of insulin sometimes observed in persons with diabetes. No connection between this form of atrophy and diabetic neuropathy has been observed. In 1 patient (case 9,832) who had been injecting insulin in the arms and legs for about six years, I noted numerous areas of atrophy, some at sites where the patient said she had not

injected insulin, although the atrophy was in the general vicinity of the injections. The areas of atrophy were said to have appeared regularly overnight in the limb in which the injection was made the preceding day, and the many areas appeared in the course of one month. Furthermore, the husband said that the areas of atrophy appeared only when the skin was prepared with alcohol, never when mercurochrome or iodine was used. Examination revealed obvious atrophy of the subcutaneous fat, and it did not follow the course of a cutaneous nerve. There were no tenderness or abnormal sensation at the site, no muscle weakness and no abnormality of the reflexes. If atrophy occurred through the medium of nerves, it must have involved only the tiny peripheral branches. The occurrence of all the changes in only one month of the six years during which insulin had been used suggests that possibly a particular supply of insulin was at fault.

Tenderness.—Tenderness other than hyperesthesia of the skin was noted in 61.2 per cent of the 98 cases in which the condition was recorded. One may contend that neuritis without tenderness does not occur. I do not insist that this is a form of neuritis involving all the fibers of one nerve trunk. I believe it more likely that it is a patchy involvement which is not limited to the peripheral nervous system. In 35.6 per cent of the cases of muscular paresis, which is good evidence of a real neurologic disturbance, no tenderness was present. In other cases, as in the 2 with involvement of the optic nerve, the affected nerve cannot be examined for tenderness or else it does not carry such sensory fibers. Even when tenderness exists, it usually is not limited to the nerve itself but often is just as marked in the muscles.

Sensation to Pinprick and Touch: For cutaneous sensitivity the patients were tested only by pinprick and by light touch of the hand. I used the test for sensitivity to heat and cold only occasionally and observed that it yielded results similar to those obtained with the test for pain. Cutaneous sensitivity was tested in 100 of these cases and was found to be abnormal in 51. Hypesthesia was noted in 56.9 per cent of the 51 cases, hyperesthesia in 29.4 per cent and a combination of the two in 13.7 per cent. The area affected is seldom sharply demarcated, and areas of normal sensitivity are interspersed between abnormal areas. In general hypesthesia involving the lower part of the legs is more marked in the lower portion and gradually changes to normal sensitivity at about the level of the knee. I have attributed this in many cases to impaired circulation at the lower level; but often diabetic persons with infections or trophic lesions of the feet and relatively good circulation have greater insensitivity than those with gangrene and poor circulation. This lends some support to the conception that these lesions are at least partially neurogenic, as was suggested by Buzzard (1890) and Lépine (1909). The case reported by Holt (1928) was of this type. However,

there are cases with associated gangrene in which no pain is experienced during surgical maneuvers (case 10,582), and rarely one sees a diabetic patient with circulation so poor that amputation is carried out, and yet surgical procedure causes severe pain (case 9,429). McKittrick and Root (1929) attributed the trophic ulcers of the feet to pressure, poor circulation and infection rather than to a neurologic cause; but blisters and ulcers on the feet occur at times without an obvious precipitating cause. Some patients (cases 5,361 and 5,390) have had hyperesthesia and also sufficient hypesthesia to burn themselves without noticing the pain. Two other patients (cases 2,411 and 8,428), suffering only from hypesthesia, burned themselves and felt absolutely no pain.

Position Sense and Ataxia: Considering the lesions in the posterior columns described by many authors, one would expect to find ataxia and loss of position sense frequently, but this has not been true in my experience. I tested for position sense in 82 cases and noted that there was decrease or absence in 13 (15.9 per cent). In 4 of these 13 there was a history of at least a slight consumption of alcohol, and in 1, of syphilis. One patient had pernicious anemia, 1 had secondary anemia and 1 had ocular lesions attributed by the ophthalmologist to syphilis, but there was no other evidence of syphilis according to the history, physical examination or serologic study. There remained 5 cases in which there was no evidence of alcoholism, syphilis or anemia in which there was loss or decrease of the position sense. Ataxia was very rare; in this series it was recorded only four times, for 1 patient with syphilis, for 1 with combined system disease and for 2 who said that they consumed small quantities of alcohol. In the following case the patient was definitely addicted to the use of alcohol as well as being diabetic.

Case 5,841.—A 55 year old man began to have severe shooting pains throughout the whole body, especially in the legs and especially at night. Burning sensations supervened. Finally, the patient noticed that he had to watch his feet when he walked. The examination revealed tenderness of the nerves, hyperesthesia of the legs with an indefinite upper level, slight weakness of the flexor muscles of the feet and slight general weakness, slight ataxia and sluggish tendon jerks. Galvanism made the symptoms worse. In eighteen months, with diabetic and general treatment, the patient was able to walk normally, and he seemed to be cured of the neuritis.

Fever.—An elevation of temperature was recorded in 25 per cent of the 112 cases in which readings of temperature were made. The elevation was usually slight, and the temperature was never high, ranging from 98.8 to 100.6 F. In some cases there were days of normal temperature interspersed between days with fever. Many patients other than the 28 mentioned here had fever due to some obvious cause, but in these 28 cases no cause was found, unless it was the diabetic neuropathy.

Leukocytosis and Differential Count.—Of the 50 patients for whom a white blood cell count was carried out, 13 (26 per cent) had more than 10,000 white blood cells, and 4 of these also had fever. Ten of the 13 patients had a normal blood smear, examination of the blood smear was not carried out for 2, and for 1 the cell count showed 85 per cent polymorphonuclears. Of the 4 patients with fever and leukocytosis, only 1 had an abnormal blood smear (85 per cent polymorphonuclears). In 47 cases a study of the blood smear was made. Three of the patients had pernicious anemia, and 32 others were normal. For the remaining 12 the cell count was as follows: 3 had 6 per cent eosinophilia, 3 had 3 per cent eosinophilia, and the other 6 had, respectively, 66 per cent lymphocytes, 56 per cent lymphocytes, 42 per cent lymphocytes, 85 per cent polymorphonuclears, 56 per cent polymorphonuclears and 49 per cent polymorphonuclears. I have no explanation for the slight eosinophilia. Foci of infection and obvious anaphylaxis were not present. One patient was taking liver extract, but the others were not. Of the 113 patients examined for fever or leukocytosis, 25.7 per cent had a temperature of at least 99 F. or a leukocyte count of more than 10,000 cells.

Spinal Fluid.—The spinal fluid was examined in 40 cases included in this study. In 3 of these the spinal fluid was normal. In 3 others an abnormality was not recorded, but no mention was made of the protein content. One patient was definitely syphilitic, and the values will not be considered except for the sugar content. The total protein content varied from 35 to 120 mg. per hundred cubic centimeters, being above 50 mg. in 22 cases and above 60 mg. in 15 cases. Globulin was noted in the fluid in 33 cases, there being more than a slightest possible trace in 18 cases. One specimen was bloody and contained 286 white cells. In 1 other specimen there were 9 white cells. In all other specimens the white cell content was well within the normal limit. The colloidal gold curve was normal in all cases in which it was recorded, except that in case 10,451, that of the patient with the Charcot joints, it was 3444310000 and in case 8,428 it was 0123210000. The spinal fluid and blood were obtained simultaneously in 22 cases. The sugar content of the spinal fluid varied from 80 to 150 mg. per hundred cubic centimeters, with an average of 99.5 mg., and its ratio to the sugar content of the blood varied from 34.8 to 85.7 per cent, with an average of 54.5 per cent. Rieger and Solomon (1916) reported the sugar content of the spinal fluid of 175 persons. They observed a range from 50 to 90 mg., with an average of 70 mg., except for the extremes noted in persons with diabetes and inflammatory conditions. Six diabetic persons yielded values ranging from 134 to 256 mg., but that was in the era before the use of insulin. Wahl (1931) reported simultaneous values of the blood and spinal fluid sugar for 5 patients. The ratio of

sugar in the spinal fluid to that in the blood was 75 per cent, being higher in the uncontrolled cases; and Steinitz' (1931) results were rather similar. My results show that the ratio for those patients with a sugar content of the blood of 200 mg. or more was less than the average for the whole group. The spinal fluid in the cases reported on by Major (1924), Angle (1928) and Root and Rogers (1930) contained more than the normal amount of protein. Furthermore, in Angle's case there were 30 cells per cubic millimeter. In the case of diabetic tabes reported by Bostock (1926) there were also many cells and other abnormal findings in the spinal fluid, but the patient may also have had syphilis. In the case reported by Wright (1931) there were an increased gobulin content and a colloidal gold curve of 1123210000.

Special Features.—Pupillary Changes: Pupillary changes (including Argyll Robertson pupils) not due to syphilis have been reported in various conditions,[8] including neuritis and arteriosclerosis. Moore (1931) reported cases in which no known cause was noted. That diabetes is a cause of Argyll Robertson pupils was denied by Williamson (1907), Smith (1926) and Grafe (1927) but affirmed by Parker (1928). Adie (1931) and Merritt and Moore (1933) insisted that the true Argyll Robertson pupil is found only in syphilitic persons, and that those attributed to other conditions do not fulfil the requirements of Argyll Robertson. Pryce (1887) and Major (1924) each reported the case of a diabetic person with sluggish pupils, and Pitres (1902) noted the absence of the pupillary reflex in 1 of 32 diabetic persons. Laudenheimer (1896) reported the case of a diabetic patient with unequal pupils, and Ingegnieros (1905) mentioned the case of a diabetic patient with poorly defined Argyll Robertson pupils. I have encountered changes in the pupillary reflex in many diabetic patients for which there was no explanation except the diabetes. Most of my 23 patients with pupillary changes had definite abnormalities, although 1 patient had only inequality and irregularity of the pupils and 2 others had unequal pupils which reacted normally according to one observer but not according to another. In the other 20 cases there were indisputably abnormal reactions to light and distance or to light alone. A true Argyll Robertson pupil (fixed to light, reacting to distance, dilating only partially with mydriatics and in some cases contracted) was noted in 5 cases, and in 8 others there was sluggish response to light, with a normal response to distance. In 7 cases the pupils were fixed or sluggish to both light and distance. Irregular pupils were observed in 7 cases and unequal pupils in 5. Syphilis was not present in these

8. Tinel and Goldflam (1912). Mériel (1926). Thomas (1931). Wilson and Robertson (1932). Nielsen and Verity (1930). Feiling and Viner (1922). Ashby (1927). Voegtlin and Lake (1919). Woltman (1921). Price (1923).

cases according to the history, physical examination and Wassermann reaction of the blood. In 5 cases spinal puncture was carried out, and the spinal fluid did not show evidence of syphilis. In all the cases, of course, diabetes was proved, and in all but 1 there were other neurologic changes usually attributed to diabetes. One case was of the circulatory type, 13 of the degenerative and 8 of the neuritic. One was in the group with changes in the bladder. The youngest patient was 37 years old, but he was an astonishingly heavy drinker of whisky. The other 22 patients were 49 years of age or more, and all 23 had arteriosclerosis, in only 2 of whom it was of slight degree. In résumé, in 20 of these 23 cases there were definite abnormalities of the reflexes, with no apparent cause other than diabetes, arteriosclerosis and, in 1 case, alcoholism, although in 6 other cases the patient admitted some consumption of alcohol in the past.

Involvement of the Optic Nerve: Involvement of the optic nerve or retrobulbar neuritis has been described in connection with various conditions,[9] including peripheral neuritis. It has been mentioned in association with diabetes,[10] but other authors [11] have questioned or ignored this relationship. I have examined 2 diabetic patients with neuritis of the optic nerve with no obvious cause unless it was diabetes. One patient (case 9,312) with diabetes and arteriosclerosis had diabetic neuritis of the legs, which was quickly relieved. She then had some abscessed teeth removed. Several weeks later neuritis of the optic nerve developed. A boy (case 3,880) of 13 years had neuritis of the optic nerve without any apparent cause except the diabetes. In both these cases recovery occurred with no treatment other than the usual diabetic regimen.

Paresis of the External Ocular Muscles: Paralysis of the ocular muscles in persons with diabetes, according to Collier (1930), was described first by Ogle (1866). Lyon (1891) and Dieulafoy (1905) noted the frequency of this association, as did Collier, although Parker (1925) believed otherwise. Such paralysis may not always be apoplectic, as Collier stated. At times it resembles paralysis of the muscles of the legs associated with diabetes. The onset is not always abrupt, and recovery is rapid and complete in some cases. Furthermore, the

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9. Mayou (1926). Davis (1923, 1926). Harris (1914). Archer-Hall (1920, 1922). Smith (1929). White (1916). Stark (1921). Crane (1927). Mason (1922). Mahoney (1932). Aub.

10. Tardieu (1862). Moore (1862). Raven (1887). Fraser and Bruce (1895, 1896). Moore (1921). Cohen (1923). Francis and Koenig (1926). Wagener (1929). Grafe (1927). Collier (1930). Dunphy (1930). Manes and Malbran (1931). O'Donoghue (1931).

11. Lépine (1909). Smith (1926). Parker (1925). Davis (1926). Paterson (1927).

condition of the eye is frequently associated with signs of diabetic neuropathy in other parts of the body, occurring in 3 of the 5 cases reported by Root (1922). Defective cranial nerves have been reported in other forms of neuritis,[12] and I have noted changes in the pupillary reflexes apparently due to diabetes. I report 1 case of diabetes with paralysis of the ocular muscles.

CASE 10,045.—A 64 year old man with diabetes of seven and eight-tenths years' duration had paralysis of the muscles of the eye which developed over a period of from one to three days. Examination revealed moderate arteriosclerosis and paralysis of both superior rectus muscles and of the left external rectus muscle.

The involvement of the various muscles of the eye is difficult to explain on the basis of hemorrhage or thrombosis, and the onset of the condition was not abrupt. Furthermore, the patient had had pains in the legs, and the biceps reflexes were sluggish, although all the other reflexes were normal.

I report these cases only that they may be given consideration and not with the intention of classifying cases of this type in a definite way. The course in some of them resembles so much that in cases of diabetic neuritis and the association of arteriosclerosis and such neuritis occurs so often that I wonder if perhaps at times the ocular paralysis may not be of a nature similar to that of the neuritis.

Involvement of the Auditory Nerve: Neuritis of the eighth cranial nerve has been described. Davis (1916) reported the condition in syphilitic patients; MacKenzie (1916) reported it in a case of unknown origin, and Young (1932) reported the case of a patient with a polyneuritis with progressive tinnitus and nerve deafness. Wittmaack (1907), Heiman (1907) and Merrill (1911) described involvement of the eighth nerve in persons with diabetes, Merrill attributing it in his case to the toxemia of diabetes. I observed 1 patient (case 10,262) in whom deafness developed during the course of diabetic neuritis and whose hearing improved as the neuritis improved.

Facial Paralysis: Whether or not facial paralysis is ever of the nature of diabetic neuritis is difficult to say. That it is at times of an apoplectic nature is certain, but in the cases of peripheral origin it is not easy to say that it is not of the type seen in nondiabetic patients. Grégoire (1883) and Bernhardt (1899) noted the frequency of facial paralysis in diabetic patients, the former (according to Auché [1890]) attributing it to bulbar lesions. As mentioned before, facial paralysis occurs regularly in one type of polyneuritis, and it is not impossible that the condition occurring in diabetic patients is of the nature of diabetic neuritis. I included 2 cases of diabetes with facial paralysis

12. Grimberg (1928). Taylor and McDonald (1932). Wilson and Robertson (1932). Déjérine (1914). Buzzard (1890). Aub.

in this series. In 1 (case 6,776) there was no other neuritic change. In the second (case 5,361) painful diabetic neuritis developed, involving both legs, which was still present the last time I saw the patient. In each case recovery of the facial movements was almost complete in about one year.

Paralysis of the Vocal Cord: I had 1 patient (case 9,429) who suffered from temporary paralysis of the superior laryngeal nerve associated with some tenderness of the thyroid region. New and Childrey (1930) reported paralysis of this nerve associated with arteriosclerosis of the central nervous system, and my patient had moderate arteriosclerosis and signs of degenerative neuropathy of the legs. The neuritis in this case may have been the result of thyroiditis of unknown origin and may have had no connection with the diabetes.

Abdominal Symptoms: The resemblance between tabes and diabetic neuritis has been commented on often, but usually with the reservation that Argyll Robertson pupils, Charcot joints, gastric crises and disturbances in the bladder do not result from diabetes. I have already described the pupillary changes and the presence of Charcot joints in 1 case, and now I shall discuss the other two conditions.

Case 4,127.—A 65 year old woman with diabetes of seven and nine-tenths years' duration was admitted to the hospital on account of nausea and abdominal pain. The symptoms, of four days' duration, were severe but occurred only at night and were relieved by walking. The examination revealed nothing abnormal except arteriosclerosis and diabetes. Roentgen examination disclosed no abnormality. A thorough search for diaphragmatic hernia gave negative results. After a week at the hospital, with symptomatic and diabetic treatment, the nausea stopped, and the pain diminished considerably. In this case the nocturnal occurrence of symptoms relieved by walking and recovery with the usual diabetic and symptomatic treatment suggested the possibility of diabetic neuritis.

Case 10,559.—A 63 year old woman was admitted to the hospital with uncontrolled diabetes and pain in the leg associated with sluggish knee jerks and absence of ankle jerks. Regulation of the diabetes relieved the pain at once. Four months later the patient was readmitted with more definite neuritis in the leg. This improved with treatment but recurred and persisted and became more widespread. Four months after the second visit she was admitted again. During the three months prior to admission, in addition to the obvious neuritis, the patient had had abdominal symptoms, beginning as a band of pain on the left side of the lower portion of the chest and the upper portion of the abdomen and after three weeks involving the right side also. The pain was always worse at night. After two months, the patient began to vomit, and this continued to the time she was admitted to the hospital. As a result of the pain, vomiting and small intake of food, the patient was very thin, weak and a "nervous wreck." Her neurosis was exceptionally severe, but it was interspersed with occasional days of dilapidated cheerfulness. Roentgen examination did not reveal pathologic changes except a gallstone. With symptomatic treatment the patient improved somewhat, but progress was so slow that operation for the gallstone was performed. The stone was reposing in an otherwise normal gallbladder, and no other abdominal abnor-

mality was disclosed. The vomiting, which had subsided just before the operation, recurred, and there was no amelioration of symptoms other than would be expected from the supportive treatment. The psychic disturbance was so great that the family acceded to the patient's request to take her home. During the next six months, with diabetic treatment, the nausea and vomiting stopped, and the neuritis in the legs improved.

This patient had definite diabetic neuritis and vague abdominal symptoms of insidious onset, similar to those of the usual neuritis. It is known that neuritis causes paresis of the skeletal muscles and that the psychic state of the patient varies in direct relationship to the neuritic symptoms. This patient had gastric atonia, and the gastric symptoms were better when she was less depressed. When depressed she would vomit almost as soon as the fluid intake by mouth amounted to from 16 to 24 ounces (472 to 708 cc.), but not when she was cheerful.

In 2 more of the cases of neuritis abdominal symptoms were present, the condition in 1 (case 11,113) suggesting carcinoma of the cecum or the ascending colon. The patient may have had carcinoma, but the roentgen and physical examinations gave negative results. Pain was worse at night, and it extended into the leg and was associated with muscular paresis. Pryce (1919) reported a case of neuritis of the leg in which subsequently the condition seemed to be due to a probable carcinoma that was not discovered on the first examination. Time may prove that the condition in my case was similar, but I have been unable to trace the patient, even though her son is a physician. In case 9,009 the condition was tentatively diagnosed as ureteral colic. Pain began in the posterior portion of the left flank and had gradually extended around to the groin and testicle at the time the patient was admitted to the hospital. The pain was excruciating, in spite of injections of morphine. Gradually, the pain extended into the left leg and within a few days had reached the foot, disappearing above as it spread below. The tenderness moved with the pain from the region of the kidney to the leg, and muscular paresis and hyperesthesia of the leg appeared. The knee jerk, at first only sluggish, disappeared completely, to return in three months as the neuritis improved. Roentgen and urologic examinations did not disclose evidence of genito-urinary disease, and the subsequent course of the condition showed that it was definitely neuritis.

Other abdominal symptoms, such as those reported by Fiske (1925) and those occurring in diabetic acidosis, are not considered here.

Disturbances in the Bladder: I am sure that disturbances in the bladder similar to those noted in syphilitic patients do occur in non-syphilitic persons with diabetes. Such changes are observed often in cases of tumor of the spinal cord and combined symptom disease; and such involvement has been reported with alcoholic neuritis by Boxwell (1914) and Campbell (1924), with lead poisoning by Campbell (1924) and Caulk and Greditzer (1916; 1917), with polyneuritis by Holmes (1917), Harris (1923) and Campbell (1924) and with diphtheritic neu-

ritis by Kennedy (1933). Thus, it is hardly surprising that one occasionally sees such a condition in diabetic patients. Le Bret (1852) was quoted by Marchal de Calvi (1864) as having reported the case of a diabetic person with slight disturbance in the bladder, but he did not disclose the nature of the disturbance. Bonardi (1897) reported the case of a diabetic patient, 72 years old, with loss of sphincter control. Von Noorden and Isaac (1927) referred to urinary urgency, especially at night, not apparently due to the polyuria shown by diabetic persons. McKittrick and Root (1929) reported neurogenic disturbances in the bladder in patients with diabetes. In the case of tabes diabetica reported by Angle (1928) symptoms in the bladder were relieved by the diabetic treatment, but there was also an enlarged prostate, and it seems probable that symptoms in the bladder were due to swelling of an already enlarged prostate, irritated by the uncontrolled diabetes.

I have examined 12 diabetic patients with urinary retention or incontinence or both, apparently due to diabetic neuropathy. None of the patients was syphilitic, nor did I find evidence of any nervous disease except diabetic neuropathy. The symptoms were not dependent directly on uncontrolled diabetes in the ordinary sense of the word or on a basically urologic factor. Seven of the patients had urinary retention, and the other 5 had incontinence suggestive of paresis of the sphincter. The first 7 cases are being reported in the ARCHIVES OF INTERNAL MEDICINE. In 7 cases the symptoms in the bladder began during the course of diabetic neuritis, and in 2 others there were signs indicative of the degenerative diabetic neuropathy. Arteriosclerosis was present in 11 cases and was not mentioned in the twelfth. The youngest patient was 42 years old.

CASE 5,494.—A 47 year old man noted involuntary urination at night at the onset of the diabetes. Five years later he noted paresthesia of the legs and, subsequently, pains in the legs. Two years later the bladder was observed to be distended (residual urine, 360 cc.). Examination revealed: moderate arteriosclerosis; normal pupils and cranial nerves; sluggish knee jerks and ankle jerks; weakness, atrophy and fibrillary twitchings of the muscles of the legs and less of the arms, and variable cutaneous sensitivity, with areas of both hypo-esthesia and hyperesthesia. The Wassermann reaction of the blood was negative, and the spinal fluid was normal, except for the slightest possible trace of globulin. A history of alcoholism was not obtained. Urologic examination revealed slight irregularity of the prostate, which was insufficient to cause obstruction. Trabeculation of the bladder was moderate.

The patient died seven months after examination of gas bacillus infection following an appendectomy.

CASE 9,759.—A 62 year old woman with diabetes of five and one-half years' duration and moderate arteriosclerosis was suffering from progressive diabetic neuritis of rather recent onset. During the evolution of the neuritis, she noted difficulty in retaining the urine. There was no burning or urgency but merely

difficulty in retaining the urine after a certain length of time. Examination did not disclose distention of the bladder or infection of the urinary tract. The knee jerks and ankle jerks, which had been normal a few months previously, became sluggish as the neuritis in the legs progressed. Considerable psychic depression also supervened, such as is often seen in cases of diabetic neuropathy. Although there was achlorhydria, there was no other evidence of combined system disease. There was no history of alcoholism or syphilis.

Although there is something horribly similar between syphilis of the nervous system and diabetic neuritis, there is also something pleasantly different. In the latter condition markedly incapacitating symptoms seldom occur, and this period of incapacity usually passes within a few months. Nor do the changes in diabetes usually progress or persist to the degree seen in syphilis. A diabetic person rarely experiences individually the many infirmities which one not infrequently sees in a tabetic patient.

Psychic Symptoms: The occurrence of psychoses with nonalcoholic neuritis and with plumbism was noted by Korsakow (1890), Harris (1923) and Aub. Cerebral symptoms, probably apoplectic, were described in diabetic patients by Marchal de Calvi (1864) and Desbonnets (1899); and Miles and Root (1922) and Dashiell (1930) studied the mental efficiency of diabetic persons. Depression, hypochondriasis, delirium, suicidal tendency, hallucination and ideas of persecution have been described.[13] Many times these symptoms were not produced by painful neuritis. Alcoholism was present in some cases but not in all. Masson (1923) listed diabetic toxin, arteriosclerosis, menopause and heredity as etiologic factors. The prognosis supposedly varies directly with the control of the diabetes. Diabetic pseudoparesis was mentioned by Laudenheimer (1896), Ingegnieros (1905, Bostock (1926) and Williams (1932). Diabetic treatment proved efficacious in the cases of the first three authors.

The psychic state usually encountered in patients with diabetic neuritis is evidenced by inordinate depression and emotional instability. Nervousness is often extreme, and the patient will neither rest nor be comforted. At times the symptoms are out of proportion to the apparent severity of the neuritis. Of 105 patients with neuritis, 52.4 per cent showed a sufficient degree of depression or nervousness to mark them as abnormal, and 14.3 per cent showed a marked degree of it. One patient (case 9,680) was totally irresponsible and was confined in a psychopathic hospital with a diagnosis of involutional psychosis. She also had neuritis of the external popliteal nerve. Another patient (case

13. Legrand du Saulle (1877, 1884). Lépine (1909). von Liebe (1889). Cohn (1892). Laudenheimer (1896, 1898). Madigan (1883). Mendel (1889). Bond (1896). Halberstadt and Arsimoles (1911). Sittig (1912). Singer and Clark (1917). Pike (1921). Reiter (1926).

6,659) became extremely irritable and completely unmanageable and suffered at home from brainstorms, so that his mother was forced to take him to a sanatorium for safe-keeping, but on the trip his psychic and neuritic symptoms improved so much during a stop at a "hot springs" resort that confinement in the institution became unnecessary. With continued physical therapy, especially massage, the patient recovered completely.

Not only do psychic symptoms occur in persons with neuritis, but neuritis is prone to affect nervous patients with diabetes. About 60 per cent of the first 100 neuritic patients examined had a nervous temperament. This may be due to the susceptibility to injury of a sensitive nervous system or to the more frequent detection of neuritis in complaining than in phlegmatic persons. Twice following emotional shocks one patient (case 9,340) had an exacerbation of symptoms. Such nervousness makes difficult an accurate estimation of cutaneous sensitivity and improvement in the neuritis.

Differentiation Between Poliomyelitis and Neuritis.—Included in this series are 2 cases which puzzled my associates and me because we could not decide whether the condition resulted from the effects of anterior poliomyelitis or from neuritis. To differentiate between these conditions is not always easy, as Dejerine (1914), Joughin (1915) and Harris (1923) pointed out. Involvement of the cells of the anterior horn of the spinal cord has been recorded in various forms of neuritis: in experimental beriberi by Eijkman (1897), in lead poisoning by Hyslop and Kraus (1923) and in diabetes by various authors.[14] In some cases of diabetic neuritis there is rather sudden paralysis of isolated muscles or groups of muscles without other signs of neuritis. The 2 cases included in this study may fall into that group or there may have been true poliomyelitis. I dare say that the condition in both cases would have been unquestionably accepted as neuritis if it had occurred in elderly patients. In the following case the condition was diagnosed as poliomyelitis by the orthopedic consultant and as probable neuritis by the neurologist.

Case 9,230.—A boy of 18 years, with diabetes of five weeks' duration, was unconscious when admitted to a hospital, where he was treated for diabetic coma. When he regained consciousness he complained of pains in various places and weakness of various muscles. Shortly afterward he was transferred to the New England Deaconess Hospital. I observed that all the muscles were weak and small. There was wrist drop, and the triceps muscles were very weak. The muscular paresis involved the legs but to a slightly less extent than the arms. There was absence of the triceps reflexes and of the right knee jerk. The left

14. Leichtentritt (1893). Nonne (1896). Bonardi (1897). Marinesco (1901). Findlay (1902). Bramwell (1907).

knee jerk was sluggish. All other tendon jerks were normal. There was considerable tenderness of both the muscles and the nerves, especially of the upper radial and the right femoral muscle and nerves. The left wrist was swollen, and the patient said that his feet had been swollen just after he recovered from coma. He also stated that his right thumb had been numb, possibly before the onset of coma as well as after. Improvement began in about five weeks and was practically complete in nine months. Fifteen months after the onset the patient had no symptoms and felt as strong as ever; but atrophy, especially of the muscles of the shoulder and the left triceps muscle, was still present, and the left radial tendon jerk and both triceps reflexes were slightly weak.

In 1 other case (case 10,405) the patient first noted paralysis after he recovered from diabetic coma. This patient had merely a left foot drop, which disappeared in six months with the usual treatment for diabetes and neuritis.

Pathology.—We have no pathologic data on these cases. Auché (1890) described myelin degeneration and other changes in the nerves of a young diabetic patient with neuritis, and Wittmaack (1907) described degeneration of the eighth cranial nerve of a diabetic girl 10 years old. It is possible that the pathologic changes in these cases with neuritis were similar to those described by other authors in the cases with associated degenerative neuropathy.

Etiology.—The etiology of the neurologic changes in diabetes has been variously attributed, at least partially, to the excess of sugar,[15] cachexia,[16] venous congestion of the abdominal organs (Rosenstein, 1882), incomplete combustion of the organic acids (Charrin and Guignard, 1882), vascular disease,[17] dehydration (Auché, 1890; Dieulafoy, 1884), an unknown toxin due to the diabetic condition,[18] acetonemia [19] and deficiency disease (Harris, 1922). Auché studied the effect of various solutions of sugar on nerves and concluded that sugar alone was not the cause of these changes, although in concentrated solution it caused injury. Eichhorst (1892) put nerves in solutions of dextrin, acetone, beta-oxybutyric acid and physiologic solution of sodium chloride and did not note distinguishing changes. Pitres and

15. Marchal de Calvi (1864). Christi-Buicli (1873). Worms (1880). Drasche (1882). Barth (1883). Dreyfous (1883). Florain (1885). von Hösslin (1886).

16. Althaus (1890). Raymond and Oulmont (1881). Bernard and Féré (1882). Pryce (1893). Woltman and Wilder (1929).

17. Bouchard (1882). Pryce (1893). Woltman and Wilder (1929). Root and Rogers (1930). Labbé (1931).

18. Fraser and Bruce (1896). Pryce (1887). Eichhorst (1889). Auché (1890). Merrill (1911). Pike (1921). Williamson (1907). Sergent and Kaufmann (1925). Root and Rogers (1930).

19. Auché (1890). von Liebe (1889). Cohn (1892). Laudenheimer (1898). Lépine (1909). Sittig (1912).

Auché (1901) were unable to produce neuritis by the injection of sugar, but Wright (1931) said that Grube reported marked neuritis after such an injection.

In my group of cases with neuritis were some in which neuritis evidently developed, at least partially, from factors not connected directly with the diabetes. I consider these factors as accessory or precipitating causes, because I believe that the diabetes first makes the patient abnormally susceptible to such factors.

Sex and Age: Sixty-nine patients (57.5 per cent) were female and 51 (42.5 per cent) were male. The age at the onset of the neuritis varied from 13 (in case 3,880, with optic neuritis) to 76 years (case 990), the average age being 54.7 years. Only 12.5 per cent of the patients were less than 40 years, and only 5.1 per cent were less than 30 years, whereas 40 per cent of all persons with diabetes have the disease before the age of 40 (Root, 1934). Two patients were less than 20 years old; 1 (case 3,880) had neuritis of the optic nerve and the other (case 9,230) may have had poliomyelitis and not neuritis. This low incidence in young persons may be associated not only with the low incidence of vascular disease but also with the incomplete development of the myelin sheaths, since Moore and his co-workers (1927) noted in their experiments that neuritis did not appear in young rats until the time when the myelin should be fully laid down. Careful study of all cases of neuritis in young persons with diabetes should be worth while. Marton (1929) observed that both diabetic and nondiabetic persons showed decreased nerve-muscle irritability in proportion as the age increased.

Duration, Severity and Control of the Diabetes: The duration of diabetes at the onset of the neuritis varied markedly. Four patients had neuritic symptoms before the apparent onset of the diabetes, and in 7 others there was a simultaneous onset of the two conditions. Buzzard (1890) reported a case in which thirst and polyuria supervened during the course of neuritis. In 1 of my cases the diabetes had existed for twenty-nine years before the neuritis was noted. The average duration of the diabetes prior to the onset of neuritis in the 120 cases was five and nine-tenths years, and in 28 cases diabetes had been present for only one year or less. In 42.2 per cent of the cases the diabetes was mild;[20] in 43.6 per cent, moderate, and in 15.9 per cent, severe. In 35.9 per cent of the cases glycosuria was not present (based on tests carried

20. The mild cases were those in which the usual daily dose of insulin was from 0 to 9 units, the moderate cases, those in which the usual daily dose of insulin was from 10 to 29 units and the severe cases, those in which the usual daily dose of insulin was 30 units or more. All the patients were on an adequate diet with the diabetes controlled.

out in the hospital or reported by patients) prior to the onset of the neuritis, and in 11.7 per cent more there was only slight glycosuria, a total of 47.6 per cent in which the diabetes was at least fairly well controlled. Furthermore, in 50 per cent of the cases in which I could judge the effect of regulation of the diabetes, there was no apparent effect on the neuritis; but it must be stated that controls were not used. A slight benefit resulted in 21.7 per cent. In some cases control of the diabetes did not cause apparent benefit, even over a period of months. It is difficult to believe that hyperglycemia alone causes this neuritis, although Marton (1929) noted decreased nerve-muscle irritability in proportion as the sugar content of the blood rose and the duration of the diabetes increased. The early experiments, with the exception of Grube's, bore out this statement. Kraus (1920) expressed the opinion that the severity of the diabetes was of importance but not the duration. Harris (1922) expressed the opinion that neither ketones nor sugar was the cause. Herschmann (1932) reported neuritis in cases of latent diabetes similar to that in my case 10,582. There must be some factor, as yet unknown, that gives rise to diabetic neuritis. The fact that one observes neuritis so often in diabetic patients is fairly good evidence that diabetes in some way causes neuritic changes.

Cholesteremia: The fact that the lipoid myelin sheaths of the nerves bear the brunt of the attack suggests that the disturbed fat metabolism of diabetic persons may be connected with the neuritis. Certainly frank acidosis was not an important factor in this group of cases. The cholesterol content of the blood was determined in 44 cases, but unfortunately one cannot always make an examination at or before the beginning of the neuritis. When carried out subsequently, it may give an erroneous idea because of the upset in the diabetes that is likely to be caused by severe neuritis or it may be a false value caused by the previous institution of diabetic treatment. The values in my cases ranged from 120 to 445 mg., with an average of 233.8 mg., the normal being not more than 230 mg. Values above 230 mg. were obtained for 52.3 per cent of the patients examined, but 1 of the patients had nephritis with edema. In studying the relationship between neuritis and fat metabolism I have collected diabetic nerves for analysis in the laboratory of Dr. William R. Bloor. The lipoid constituents show definite abnormalities, which are being reported in the ARCHIVES OF INTERNAL MEDICINE.

Dehydration: The upset in water balance, with resulting dehydration, occurring in untreated diabetic persons might be considered to exert some influence, but in 84.8 per cent of the cases there was no obvious dehydration. One patient (case 10,216) obtained no relief from the pains when saline solution was administered intravenously at the beginning of diabetic treatment. One frequently observes diabetic patients

with marked dehydration and no neuritic symptoms, and in 1 such patient neuritis developed after dehydration was entirely relieved.

Arteriosclerosis: Arteriosclerosis is associated with many neurologic conditions [21] and seems to play a causative rôle. It involves the peripheral [22] as well as the central nervous system. In diabetic persons the legs are markedly affected by arteriosclerosis but, as Morrison and Bogan (1929) pointed out, seldom when the patient is less than 40 years of age. If one assumes that arteriosclerosis is a factor in the production of diabetic neuropathy, the observations of Morrison and Bogan are compatible with mine, that neuritis and degenerative lesions usually affect the legs and occur rarely in diabetic persons less than 40 years old. As early as 1893 Pryce suggested extensive vascular disease as one of the causes of diabetic neuritis. Rimbaud (1909) entertained a similar idea, and Woltman and Wilder (1929) expressed the opinion that arteriosclerosis is the most important cause. Many times one notes in the literature the association of arteriosclerosis and this neuropathy. Marinesco (1901) noted thickening of the walls of the intraneural vessels. The 3 diabetic patients with paralysis whose cases were reported by Root (1922) all had arteriosclerosis.

Among the 120 cases in this group, arteriosclerosis was present in all except 9 (7.5 per cent), although it was only slight in 7 cases. Disease of the coronary vessels was present in 20 per cent, and in 30.8 per cent there was evidence of angina pectoris, apoplexy or a circulatory condition of the feet requiring surgical intervention. Of the 9 cases without arteriosclerosis, there was no pulsation in the dorsalis pedis artery in 2, and in 1 of these the oscillometer needle showed diminished excursion at the level of the left calf. One patient was a man of 39 years, who had had diabetes for two years. The fourth was a woman of 50 years with diabetes, and she may have had arteriosclerosis which was not disclosed by palpation of the radial artery. The fifth and sixth cases were the 2 discussed as possible cases of poliomyelitis. The seventh patient was the boy with neuritis of the optic nerve. The eighth was a man of 35 years with diabetes of twelve years' duration and some obvious but undiagnosed infection that may possibly have been similar to the infectious neuritis recently described by Taylor and McDonald (1932). Furthermore, there was evidence of some impairment of the circulation in the legs. The last patient (case 7,538) was a woman 21 years old who had had diabetes for five years. Neuritic pain was promptly relieved by diabetic treatment, but sluggish activity of the

21. Woltman (1921). Price (1929). Wright (1924). Critchley (1931). Bing (1932).

22. Schlessinger (1895). Franceschi (1903). Woltman (1921). Price (1923). Priestley (1931). Alpers and Wolman (1931).

reflexes persisted. The youth of 18 years (case 5,932) in the hyperglycemic group, in whom sluggish reflexes developed subsequently, was suffering from active pulmonary tuberculosis as well as from uncontrolled diabetes.

It is not sufficient to examine only one artery to determine the presence of sclerosis. At times the sclerosis is much more advanced in one site than in another. In case 10,100 there was only slight detectable sclerosis in the radial arteries, yet roentgenograms showed sclerosis of 4 plus degree in the legs. Similarly, in case 4,458 there was only slight sclerosis in the optic fundi, yet sclerosis of 4 plus degree was present in the legs. Even in the same artery, the sclerosis varies in degree at different places. A cursory examination is sometimes misleading; but, even considering this, I noted moderate or advanced arteriosclerosis in 86.7 per cent of the cases. Evidence of impaired circulation in the legs, as judged by the methods recommended by McKittrick and Root (1929), was present at least to a slight extent in 65.8 per cent of the cases in which a test was made.

Of the 120 cases there were 5 in which there was no evidence of vascular disease either by signs of arteriosclerosis or by defective circulation in the legs. The absence of detectable vascular disease in these 5 cases indicates either that arteriosclerosis is not the only cause of diabetic neuritis or that the condition in these cases was not diabetic neuritis. Other evidence against the theory that arteriosclerosis is the chief cause of diabetic neuritis is found in the relative rarity of neuritis in elderly nondiabetic patients with arteriosclerosis. In 10 cases in patients 70 years or more of age there were no neuritic symptoms and the knee jerks were normal. The ankle jerks were normal in 9 cases. In the tenth case the right ankle jerk was sluggish and the left absent. Sensation to pinprick was normal in the 2 cases tested. These findings are compromised by the fact that I have not made studies on a large group of cases, but certainly they are at variance with my findings in diabetic patients of similar age or with a similar degree of sclerosis. Even among diabetic patients sclerosis does not invariably produce manifestations of neuritis. Even when the sclerosis is so advanced that the feet and lower portion of the legs are dusky red, there may be no evidence of neuritis. In 5 such cases recently observed the only evidence of neuritis was sluggishness of the ankle jerks in 1 case. Deficient circulation probably plays its part in addition to the sclerosis. It seems to cause hypesthesia, which was well shown in case 4,319. The patient had hyperesthesia of the leg from the hip downward to the middle of the lower part of the leg, where there was a gradual transition to the hypesthesia existing below this level, and this hypesthesia coincided with the dusky area caused by impaired circulation. But that

hypesthesia is not due solely to the vascular disease is indicated by the experience of surgeons who have noted insensitivity to a much greater extent in patients with diabetic gangrene than in nondiabetic patients.

The fact that the symptoms appear rather suddenly and that the signs as well as the symptoms improve or even disappear is no proof that arteriosclerosis is not a cause. The optic neuritis in the case reported by Alpers and Wolman (1931) disappeared clinically, although the sclerosis of the vessels had advanced so far by the time of death that the optic nerves were cut almost in two by the compression. Furthermore, it is known that the signs of apoplexy disappear and that retinal hemorrhages are absorbed spontaneously (Genet, 1927). An abrupt onset of pain, such as occurred in case 9,078, may be explained by a hemorrhage involving the nervous system. The indefinite and widespread nature of the neuropathy and the patchy distribution of the pathologic changes described by Woltman and Wilder (1929) may be explained by such a widespread and patchy distribution of arteriosclerosis as one sees in diabetic patients. A condition of repeated multiple minute hemorrhages, such as those in a case reported by Raeder (1921), in conjunction with pressure from thickened arteries and the impairment of nutrition of the nerve tissue, may explain many of the phenomena seen in cases of diabetic neuropathy. René le Fort (1916) reported a case of neuritis, especially of the sympathetic system, in the leg caused by hemorrhage from a contusion. Ischemic neuritis has been described by Chavany (1931), and Priestley (1931) attributed to ischemia the degeneration he noted in cases of arteriosclerotic gangrene. It seems unlikely that ischemia or Volkmann's (1881) contracture plays any rôle in the production of diabetic neuritis.

One feature not easily explained is the nocturnal occurrence of the neuritic symptoms, which is true in cases of involvement of the leg, the arm and the abdomen. It occurs in young diabetic persons with symptoms of hyperglycemia and no evident vascular disease, as well as in older, arteriosclerotic patients. It occurs in phlegmatic as well as in nervous persons. If one attributes it to ischemia, how is one to reconcile it with Lewis' (1932) contention that the pain of ischemia arises from a working muscle, especially since diabetic patients obtain relief by pacing the floor? Furthermore, it must be attributed to arterial rather than to venous incompetency, for the latter condition is apt to be improved when the patient is prone; and yet many young diabetic patients without demonstrable arterial disease suffer from pain of this character. The explanation that at night all is quiet and one has the opportunity to humor one's ills hardly seems acceptable because of the difference in temperament in various patients with the symptom. Furthermore, walking around a room at night is not a well recognized

sedative. Nor does it seem reasonable that, were the pain based on an emotional state, so many patients would have such severe pain at night and not notice it during the day.

Anemia: Another aspect of ischemia is furnished by anemic persons. Van Bogaert (1927) reported a case of splenic anemia with peripheral neuritis. In the only case of severe secondary anemia in this series (case 11,253) there were also advanced arteriosclerosis and chronic infection of the leg. Pernicious anemia is a different matter. My cases had something in common with cases of pernicious anemia (Smithburn and Zerfas, 1931), but in the case of multiple neuritis with pernicious anemia reported by Robertson and Gowen (1930) spasticity and increased tendon reflexes were present, neither of which has been present in any of my cases of neuritis. Of course, combined system disease is associated with marked nervous changes: and I had 4 cases of pernicious anemia in this series. In each there was absence or sluggishness of tendon reflexes, and there were clinical features which suggested that diabetes played a part also in the production of the condition. The fact that of 46 of these cases tested achlorhydria was present in only 30.4 per cent and the average amount of free hydrochloric acid was 33.9 degrees is good evidence that the presence of pernicious anemia is not essential for the development of diabetic neuritis. As a matter of fact, the incidence of achlorhydria in unselected cases of diabetes is 39 per cent (Rabinowitch, Fowler and Watson, 1931).

Dietary Deficiency: Root and Rogers (1930) suggested that diabetic neuritis might be due to food deficiency, such as occurs in cases of beriberi. This idea has been indirectly or directly expressed by many authors for many years. Marchal de Calvi (1864) noted that a not too great restriction of the diabetic diet was more likely to give relief from sciatica than keeping the patient aglycosuric, and Althaus (1890) confirmed this. Bouchard (1884), Raven (1887), Woltman and Wilder (1929) and Schmidt (1930) noted return of the knee jerks in diabetic persons regaining proper nutrition and health. Angle (1928) reported improvement in a case of diabetic tabes in which the carbohydrate content of the diet was increased, and this occurred in my case 8,166. Nutritional polyneuritis, such as that reported by McCollum and Kennedy (1916), is well recognized as being due to a deficiency of vitamin B and is cured rapidly by the administration of vitamin B. There are some points of resemblance between it and diabetic neuritis. For example, its effect (Voegtlin and Lake, 1919) on the pupillary reactions, its tendency to affect chiefly the hindlegs of cats, its tendency to cause slight changes in the cord and more marked changes in the myelin sheaths of the nerves, especially that of the sciatic nerve, are similar to the changes wrought by diabetes. Then there is neuritis

attributed to nonspecific food deficiency (Gram, 1924; Shattuck, 1928; Wechsler, 1930). Wechsler suggested that this might be the cause of diabetic neuritis. It is known that occasionally diabetes is associated with some dietary deficiency disease (Wohl, 1926; Bitzer, 1931), and it is only reasonable to suppose that it occurs in other diabetic persons with a deficiency not severe enough to cause recognizable symptoms. Such a deficiency might be a cause of the neuritis. The course under treatment corresponds to that noted by Sugiura (1918) in birds with nutritional polyneuritis, although recovery is not usually so prompt in cases of diabetes, certainly not so prompt as that reported in cases of nutritional neuritis by Voegtlin and Lake (1919) and McCollum and Kennedy (1916). One of my patients obtained relief from neuritis in the leg within two weeks after she began taking yeast; but, while taking the yeast, there developed neuritis of the optic nerve of no known cause unless it was diabetes. Against the hypothesis of a nutritional cause is the fact that of 63 of the patients questioned about any previous abnormality in the diet only 1 admitted a definite deficiency. The patient ate very little meat, cheese and eggs, but, on the other hand, she drank a great deal of milk daily. Two other patients ate only a little meat, and 1 ate very few green vegetables. The diabetic diet is fairly rich in vitamin foods: meat, green vegetables, butter, cream, cheese and fruit. And patients on such a diet do have neuritis. Furthermore, many of the patients improve or recover without any change in diet. Still more evidence is derived from the fact that the addition of yeast, cod liver oil or liver in some form has not hastened recovery, as compared with recovery in patients not so treated. It is conceivable that the deficiency lies in the absorption or utilization rather than in the consumption. Against that are the facts that patients recover without any dietary change and that children, who have the severest and least well controlled diabetes, seldom have neuritis. An answer to the latter may lie in the supposition that the neuritis depends partly on arteriosclerosis, which is rarely severe in children. I might state that I do not call a diabetic patient a child simply because diabetes developed in his childhood. If the patient lives he will eventually become an adult and will become subject to the factors operating in adults.

Lipase: One highly hypothetic etiologic factor was suggested by the work of Brickner (1931), who found myelinolytic activity in the blood serum of patients with multiple sclerosis. Cherry and Crandall (1932) and Weil and Crandall (1932) investigated such lipolytic activity in the blood after pancreatic and after hepatic injury. The latter authors concluded that in experimental damage to the liver a neurotoxic agent is present in the blood serum. In 39 of 100 patients with diabetes Meyer (1931) noted definite laboratory evidence of hepatic dysfunction, which

occurred most frequently in the older patients in whom the diabetes had remained uncontrolled for a long time. Furthermore, he observed that the modern treatment for diabetes aids in improving hepatic function. These observations present an interesting possibility yet to be investigated.

Accessory Causes.—Insulin: Caravati (1933) reported a case of neuritis caused by insulin with numbness, tingling and pain in the legs occurring only with the use of insulin, to which the patient was sensitive. It at least gives one food for thought. I have observed patients in whom neuritis developed in the hospital immediately after the diabetes had become controlled. It was puzzling, and the insulin administered was a conceivable cause. It is well recognized that insulin causes local and general cutaneous anaphylaxis, and at times its administration is followed by hemorrhage.[23] Wohlwill (1928) observed cerebral pathologic changes which he attributed to hypoglycemia caused by insulin. Tzanck and Weismann-Netter (1929), Gordon (1932), Wilson and Hadden (1932) and Young (1932) described anaphylactic neuritis, and Campbell and Allison (1932) described cases of neuritis and urticaria. Insulin might act in such a way. The urticaria produced by insulin usually ceases within a few weeks, even when the same dosage of insulin is continued; and neuritis at times improves in a similar length of time. In 31.6 per cent of 98 cases in which I know whether or not insulin was being used at the time the neuritis began, insulin was being taken. In 2 of these cases (cases 9,230 and 10,405) neuritis was noted when the patient recovered from coma, the first time that insulin had been administered. In 6 other cases (cases 5,390, 8,962, 9,338, 9,452, 9,746 and 10,407) neuritis developed while insulin was being administered in the hospital. One of the patients was thin and confined to bed, and another was thin and had been crossing his legs. It seems likely that the foot drop and toe drop in these 2 cases resulted from pressure, as described by Woltman (1929; 1930). One patient (case 9,452) became aglycosuric in the hospital; foot drop developed at the end of his stay, and he recovered from it within two weeks. I hesitate to attribute any of these cases to insulin, and yet I can offer no better explanation.

Alcohol: Although 2 of the patients with ataxia said that they used alcohol to some extent, I did not find that alcohol was a factor of much importance in the series as a whole. I have a record of the admitted intake of alcohol in 97 cases; 79.4 per cent of the patients were total abstainers, and an additional 13.4 per cent said that they used it in only slight amounts.

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23. Gudemann (1926). Henderson (1927). Neale (1928). Lawrence and Hollins (1928).

Focal Infection: A focus of infection was present in 38.5 per cent of the 104 cases about which there is a record of the presence or absence of the usual foci, but in some of these the focus had been removed some time previous to the onset of the neuritis. There seemed to be a definite association between the neuritis and the focus of infection in 3 cases (cases 8,112, 9,312 and 10,773). In 1 of these, treatment of an infection of the sinuses was followed by a rapid disappearance of the neuritis. In another, amelioration followed the extraction of an abscessed tooth. In the third case the neuritis flared up once after tonsillectomy and once after extraction for an abscessed dental formation. Whether there was a specific streptococcus present, as in the case reported by Rosenow (1916), I cannot say. In case 4,319 the neuritis followed an attack of gallstones. Other sources of infection noted in this series were perinephritic abscess and pulmonary tuberculosis. The effect of the tuberculosis is problematic. Tinel and Goldflam (1912), Tarchetti (1918), Harris (1922) and Lévy-Valensi (1925) reported cases of neuritis in tuberculous patients; but Tarchetti noted that the condition in his 10 cases was due to aconite medication. It is worthy of note that in the cases of the hyperglycemic type the only 2 cases in which there was not prompt response to diabetic treatment the patient had tuberculosis and abscessed teeth, respectively. In the cases of the neuritic type 1 of the patients having only slight arteriosclerosis was tuberculous.

General Infection: Wilson (1923) reported 2 cases of neuritis which he attributed to influenza. One of my patients (case 8,167) had neuritis associated with fever and symptoms which simulated influenza. He was 29 years old, had had diabetes for four years and had only slight arteriosclerosis. Another patient (case 10,265), a man 35 years old, had had diabetes for twelve years, and arteriosclerosis was not detectable. His neuritis was of the sensory type, with exquisite pain and hyperesthesia. It was associated with fever and leukocytosis of considerable degree. The 2 cases may be instances of the infectious type of neuritis previously mentioned, although facial paralysis was not present in either case. Syphilis was present in 3 of the 120 cases and had been present in 1 other case, with apparent recovery: In 2 of the 3 cases there was prompt response to diabetic treatment, and in all 4 cases there were features that suggested that diabetic neuritis was present in addition to the syphilitic process. It seemed improbable in any case and impossible in some that the neuritis resulted from the arsphenamine commonly used in the treatment of syphilis, although it has been known for many years that arsenic is a potential cause of neuropathy (Minor, 1889; Sézary and Chabanier, 1925).

Toxic Causes: In no case did I note plumbism or any known toxic condition. Of course, it is not easy to remember to question each

patient about the use of depilatory cream or other products which are rarely toxic, and it is possible that I have overlooked cases such as those reported by Short (1931) and Mahoney (1932). Certainly I did not recognize cases of paralysis due to Jamaica ginger, such as that reported by Harris (1930) and many others.

Orthopedic and Mechanical Causes.—Various orthopedic or mechanical causes of neuritis have been reported,[24] and among my cases are some in which the condition was probably affected by such factors. Subdeltoid bursitis, sacro-iliac strain, pressure from crossing the legs or lying in bed and inactivity or excessive use of an extremity have contributed to the neuritis. Toe drop in thin patients has followed rest in bed or crossing the legs in a number of instances. Often the neuritis involved nerves other than the nerve affected by the orthopedic condition. Conditions resembling neuritis from a subdeltoid bursitis have had features suggesting that the process was in reality diabetic neuritis or at least was affected by the diabetes; and Sergent and Kaufmann (1925) stated that in all cases of circumflex neuritis diabetes should be suspected. Occasionally the mechanical cause seemed too slight to have produced neuritis unless the patient was susceptible to neuritis on account of preexisting diabetes.

Case 22,576.—A 45 year old man with diabetes of twelve years' duration complained of pain in the region of the shoulder joint and upper part of the arm and of difficulty in elevating the arm. The pain was much worse at night and disappeared when the patient paced the floor. There were moderate arteriosclerosis, tenderness along the course of the radial nerve and in the area of the subdeltoid muscle and normal reflexes. There was no paralysis or atrophy. The pain was similar to that experienced by patients with diabetic neuritis.

Case 10,407.—A 55 year old man with diabetes of ten months' duration, advanced arteriosclerosis and active pulmonary tuberculosis had worn rather tightly fitting round garters for a few days early in September. About a week later, while he was attending a lecture, he sat with his right leg crossed over the left. He noticed a beginning numbness in the toes of the right foot. He thereupon reversed the position, only to notice numbness in the left foot. Associated with this, as he ascertained a few minutes later when he returned to his room, was his inability to elevate the left great toe or to spread apart the toes, as he had done earlier that day. Within a few days, passive and active exercise of the affected muscles resulted in improvement.

Miscellaneous Factors.—Occupation, fatigue and mental strain seem to have little or no effect on the causation of the neuritis, although neuritis did occasionally occur in patients at a time when they were under the strain of excessive work or responsibility. Since most of the patients lived in New England and were exposed to only one climate,

24. Guillain (1901). Rimbaud (1909). Breneman (1912). Babinski (1915). Woltman (1929, 1930). Ober (1930).

I have no data on the effect of climate, except that in a few cases the neuritis was worse in inclement weather. In some cases the neuritis began in midsummer and in others in the winter.

In summing up the etiologic data I may say that diabetic persons suffer from neuropathy of three types: (1) hyperglycemic, (2) degenerative and (3) neuritic. The first seems to be due to hyperglycemia or some closely associated condition, without regard to the presence or absence of vascular disease. The degenerative lesions seem to depend on an unknown diabetic factor and vascular disease. Although these lesions seem definitely associated with vascular disease, one must not forget that the arteriosclerosis and the neuropathy may be due to the same cause. The one may be merely an accompanying condition and may have no etiologic significance with respect to the other. Sluggish circulation in the lower part of the legs apparently leads to two symptoms, intermittent claudication and cutaneous hypesthesia, but the other symptoms noted in these cases seemed more likely to be due to arteriosclerosis. How diabetes causes neuritis, as opposed to degenerative neuropathy, is unknown. Vascular disease is usually, but not always, present. In some cases without such vascular disease infection seems to play a contributory rôle; and in all such cases a thorough examination for the secondary or precipitating cause should be made. Diabetic persons are subject to forces, such as pressure and alcohol, which produce neuritis in nondiabetic persons, but I believe that even in these cases the diabetes renders the patient more susceptible to the nondiabetic agent and modifies to some extent the type or severity of neuritis produced. Therefore, I caution my patients to avoid carefully such agents as alcohol and crossing the legs, which have been reported as causes of neuritis.

Prognosis.—As might be inferred from the reports in the literature and as Williamson (1924) emphatically stated, diabetic neuritis of itself does not cause death. Certainly none of my patients died of neuritis, and the duration of life after the onset of neuritis in my cases is already two and nine-tenths years, even though the period of this study extended over a period of only two and one-half years. Since there are no standard criteria for the diagnosis of the neuritis and I have not specified exactly what I mean by neuritis, it is impossible to give an exact prognosis. If by neuritis one means a simple hyperglycemic pain along a nerve course, the prognosis is excellent; but if by neuritis one includes all the neurologic symptoms and signs not due to another obvious cause, the prognosis is different. Furthermore, symptoms may disappear and later reappear. Are they due to the same agent as the previous attack or to a separate process? Sometimes symptoms disappear and minor signs remain. Is the neuritis cured or not? Sometimes complete inca-

pacity lasts for a few months, and then improvement occurs fairly rapidly, so that the patient can carry out the usual activities without too much discomfort or inconvenience; yet some symptoms and signs persist practically unchanged for a period of years. Can one say that the neuritis was cured and that the changes persisting are due merely to chronic degenerative changes? The question is difficult to answer. I believe that in some cases there is only the degenerative process and in others there is a separate and distinct process resembling real neuritis but that even in the latter the degenerative changes are prone to occur and thus modify the picture produced by the neuritis itself. Since there are degrees of severity of each process and no constant picture characteristic of either, it is at times impossible to state just when each process began, when it ended and what changes it produced. This being so, the difficulty of stating the prognosis for the cases with neuritis becomes obvious. Furthermore, the prognosis depends at least partially on the etiologic factors present. If the neuritis has merely a diabetic background and a definite mechanical precipitating cause, such as pressure, recovery is apt to ensue fairly promptly (in a few weeks), although it may be delayed for some months.

Prognosis for Symptoms: I agree with Parker (1928) that in general the prognosis is good, and recovery from the severe symptoms and disabling condition is almost certain. Seldom do severe symptoms persist for more than a few months. In those cases with sensory disturbance and marked hyperglycemia, improvement sometimes begins within a few days after the diabetes is regulated. In 1 case, however, the pain which began abruptly practically disappeared within thirty-six hours without any treatment. Certainly treatment has not brought about rapid recovery in the majority of cases, nor does improvement begin immediately after the institution of diabetic treatment, as Root and Rogers (1930) stated. It is discouraging to both the physician and the patient to note the slow response to treatment in many cases, especially in those in which the patient has a nervous temperament and shows psychic depression. In about 50 per cent of the cases improvement begins within two weeks after treatment is initiated, but in some relapse occurs shortly after the patient leaves the hospital. As Stewart (1925) and Root and Rogers (1930) remarked, the longer the duration prior to treatment, the longer delayed will be the improvement; but there are many exceptions to this. Major (1924) reported a case of diabetic tabes in which cure resulted in seven weeks by diabetic treatment, but he did not state that the ankle jerks returned and the sluggish pupils became normal. On the average, my patients did not yield to treatment in such a short period. In 47 of the cases, in which I may say that the neuritis has disappeared, the average duration of the neuritis after the initiation of treatment was eight-tenths year. Some patients

responded to treatment so well that they became symptom-free within from a week to ten days, and others still suffered to some extent more than two years after treatment was begun.

Prognosis for Signs: That the signs as well as the symptoms of diabetic neuritis disappear is recognized. Pitres and Marchand (1917) said that the neuritis, even in a severe form, is cured in a few months without persistent infirmities, although Fletcher (1925) stated that improvement of motor and sensory changes is unlikely. Bouchard (1884), Raven (1887), Woltman and Wilder (1929) and Schmidt (1930) reported the return of knee jerks in diabetic patients. Kraus (1920) mentioned rare improvement in the reflexes. Nölting and his associates (1926) reported a case with improvement in the knee jerks and return of the ankle jerks as the neuritis improved. In Angle's (1928) case of diabetic tabes there was improvement and the leg reflexes returned when a diet with a moderate carbohydrate content was substituted for the previous diet low in carbohydrates, and this occurred under similar circumstances in my case 8,166 in spite of persistent hyperglycemia and hypercholesteremia. Holt (1928) reported improvement in cutaneous sensitivity of the feet in a diabetic patient previously suffering from trophic changes in the feet. Marinesco (1895) noted return of the left knee jerk in a diabetic patient suffering from hemiplegia. Auché (1890) described signs of regeneration in diabetic nerves, as did Woltman and Wilder (1929) in 1 case; and Nicolescu and Raileanu (1926; 1927) noted signs of regeneration in the brains of diabetic patients. Two of my patients (cases 6,331 and 11,106)) had a normal ankle jerk on the side of hemiplegia and absence of the ankle jerk on the opposite side, but I do not know the condition of the ankle jerks prior to apoplexy. In 12 other patients there was an improvement in sluggish tendon jerks or a return of reflexes, which previously were not present. In 2 of these (cases 8,428 and 10,133) there was marked improvement in the position sense of the great toe as the neuritis improved, and in the former there was also partial recovery from cutaneous anesthesia of a part of the lower portion of the leg and foot. One patient (case 2,843) also regained sensitivity to touch. The period of improvement varied considerably. In 1 case (case 8,166), seven years after the onset of the neuritis the knee jerks, previously absent, were obtained with difficulty, and two years later they were easily elicited. Usually recovery occurs in much less time, in the course of a year or less. In 2 cases (cases 7,538 and 11,036) mere regulation of the diabetes was accompanied by return of the knee jerk and improvement in a sluggish ankle jerk, respectively. In 1 case (case 4,118) in which the neuritis was characterized by absence of the left knee jerk in April, there was a sluggish response in November of the same year and an almost normal response in May of the following year.

This change in reflexes was not accompanied by a corresponding change in the nutrition or health of the patient. Similarly in the other cases studied, the activity of the reflexes was not related to the nutrition except as the latter was influenced by the neuritis. It seems reasonable to assume that if lost reflexes and sensation return the nerves are not destroyed but merely damaged and complete recovery is possible.

Prognosis of Special Features: Moore (1921) and Francis and Koenig (1926) agreed that diabetic retrobulbar neuritis responds well to treatment. My 2 patients with neuritis of the optic nerve both recovered without special treatment. Patients with paralysis of the oculomotor nerve also improve. Collier (1930) said that in most cases recovery is complete and rapid, especially in those in which insulin is administered. My patients with paralysis of the facial nerve, deafness and abdominal symptoms improved over a period of months. No improvement in pupillary reaction has been noted. In the cases of disturbance of the bladder with only slight incontinence and no retention there is a tendency to improvement as the associated neuritis improves. In the cases with marked retention the difficulty has persisted, even for some years. The psychic depression parallels the neuritis, arising usually in the course of the neuritis and disappearing with it. The condition in the cases of diabetes with an associated psychosis reported by Laudenheimer (1896), Ingegnieros (1905), Pike (1921), Bostock (1926) and Reiter (1926) also improved with treatment for diabetes.

Treatment.—Treat the diabetes first, last and all the time. Treatment must be aggressive and persistent until the disease is controlled. Not the sugar content of the blood alone, but all the chemical conditions and the physical status, must be set right. Fletcher (1925) and Nölting and his associates (1926) expressed the belief that a persistently normal value for blood sugar is essential to recovery. The diet should contain a large amount of vitamin foods, fruits, green vegetables and dairy products. Meat, eggs and cereals are included in moderate amounts. The allowance of carbohydrate is at least 120 Gm. and not more than 200 Gm., not counting the antiketogenic portion of protein and fat.

If the neuritis arises shortly after the initiation of insulin therapy and has no other obvious cause, one should substitute a brand of insulin to which the patient is not sensitive.

Barker (1930) advised diaphoresis, regulation of the bowels, control of infectious processes, hot applications, sedatives, massage and electrical treatment. I have noted that heat, usually applied by means of an electric baker or warm baths, is the best agent for the relief of pain. Since the pain is of greatest severity at night, the treatments are given in the afternoon and late evening. In severe cases warm baths can be given during the night. Sun-baths have been of help, and 1 patient was much relieved by covering himself with sand and baking in the sun at

a beach. Warm but light bedclothes are of help, and 1 woman (case 10,216) received relief only by wrapping the entire leg in a blanket each night. Massage is at times very effective. Four of my patients thought it beneficial, but another (case 9,446) said that it increased rather than decreased the symptoms. Buerger's exercises should be prescribed for pain in the legs, or paresthesia, and poor circulation, as occasionally the exercises give marked relief even from the first trial. Paresthesia of the feet is more likely to be relieved by such exercises than by any other measure. One patient with pernicious anemia obtained relief from numbness of the hands when she soaked them daily in an astringent solution. In a recent case (case 11,075) without anemia this method was of no benefit during the seventeen days during which the patient was observed. I shall be interested to know what occurs in the future. However, it hardly seems reasonable to use a method which may decrease the sensitivity of the skin and thereby lead to a chance injury. Root and Rogers (1930) stated that absolute rest in bed is essential in the early stages of pain, a statement with which I do not entirely agree. Patients who stayed in bed did not always obtain relief, and 1 woman remained in bed for several months without relief. Many patients have learned that some exercise gives relief, and 1 patient refused to stay in bed because to do so caused severe pain. I am inclined to give the patient something to do, to apportion the day into periods of rest and some exercise, however slight. On the other hand, some patients with circulatory deficiency of the legs are considerably relieved while in bed. Salicylates and hypnotics are administered when necessary; but, knowing the protracted nature of the condition in some cases, I believe that opiates should be administered sparingly if not omitted entirely.

Electrical treatment for neuritis has been advised for many years.[25] Davies (1914) obtained good results with galvanism, and Piontkowsky (1930) noted recently that galvanism stimulates recovery in the severed sciatic nerves of guinea-pigs. My one experience with the use of the galvanic current was not happy, as the patient (case 5,841) stated that it increased his symptoms.

In the patients with paresis the condition has improved with baking and passive and active exercise of the muscles involved. For bedridden patients pillows have been used to take the pressure off the affected nerves. I shortened the stay in bed as much as possible in those cases. In 1 case (case 10,553), in which there was sensory neuritis of the external popliteal nerve, four days' rest in bed did not lead to paresis, however.

Attention to the general condition of the patient and to all special conditions, such as anemia, foci of infection and constipation, is given.

25. Althaus (1890). Somerville (1914). Martin (1926).

I believe it important that frequent contact with the patient be maintained, both to insure the proper execution of orders given and to reassure and encourage him. Patients with depression need particular attention, and a little encouragement sometimes seems more effective than much treatment. Sioli (1932) commented on the need for proper psychic handling of diabetic patients. One patient admitted that willpower did more for him than anything else. Another patient improved in the hospital, had a relapse at home for which even morphine gave little relief and yet improved rapidly in the hospital a second time without morphine and without any change in the regimen previously followed at home.

Accessory food substances have been given to some patients. Yeast alone was given in 5 cases, in 3 of which recovery followed an average duration of the neuritis of nine-tenths year, as opposed to eight-tenths year for the series as a whole. Similarly, in the 7 cases in which liver or liver extract alone was given, recovery occurred in only 1 case, and the neuritis lasted one year. Cod liver oil alone was given in 5 cases, in 2 of which recovery took place in an average of five-tenths year. Cod liver oil and yeast together were given in 7 cases, in only 1 of which cure was accomplished and after a duration of nine-tenths year. Yeast and liver together were given in 4 cases, in 2 of which recovery occurred in an average of one and five-tenths years. All three substances were given in 4 cases, in 3 of which recovery has not yet occurred, but in the fourth the patient was relieved of the pain in six weeks by wrapping the affected leg in a blanket at night. The results of this dietary treatment are too inexact and meager to warrant drawing more than a tentative, general conclusion that it is not apparent that cod liver oil, yeast or liver is necessary for recovery or even hastens recovery. In many cases recovery occurred without any such treatment. The diabetic diets and the previous diets on which the patients had lived were apparently fully adequate for normal nutrition provided the patients could utilize them. On the other hand, the evidence is not conclusive that these substances are not helpful. One cannot judge by the symptoms how severe the changes are in the nerves (Woltman and Wilder, 1929); and it is possible that the patients given these substances would have been worse without them.

Prophylactic treatment for neuritis is hardly recognized. Aggressive treatment of the diabetes is the prime factor. So far as possible the patient should be brought back to a normal state. The bedridden patient should be protected from pressure on the nerves and from too great inactivity; and all patients with diabetes should be cautioned to refrain from crossing the legs. Patients with a fracture and others for whom inactivity and immobilization are necessary must be treated with great care and must be allowed some use of the diseased part as soon

as practicable. Pressure of any sort along the course of a nerve or artery is to be avoided. Patients with pernicious anemia should be carefully watched and treated to prevent involvement of the nervous system. Removal of foci of infection and attention to the general condition of the patient may be of help.

One prophylactic feature applies to complications rather than to the neuritis itself. I have commented on the hypesthesia and the apparent ease with which the skin of many patients with hyperesthesia is damaged. The use of hot water bags, especially of the chemical type, is interdicted or is permitted only with careful supervision by a responsible person. Heat must be applied with great care, and the trimming of nails, corns and calluses must be done by a competent person who knows the susceptibility of the diabetic person to injury. One cannot forget the young man who sacrificed a toe and months of activity for the sake of a short nap. It would have been far better had he borne his pain a little longer and not resorted to the electric pad, which wrought so much damage in such a little while.

SUMMARY AND CONCLUSIONS

Two hundred and twenty-six persons with diabetes with neuritic manifestations were studied. In this series I noted manifestations of three types: (*a*) hyperglycemic, (*b*) degenerative and (*c*) neuritic.

The 34 cases of the hyperglycemic type were characterized by neuritic symptoms with almost no sign. The diabetes was uncontrolled at the onset of the symptoms in each case. Hyperglycemia and glycosuria were the only detected diabetic factors present in every case. Except in 2 cases no accessory factors were noted. Regulation of the diabetes gave relief within a few days. A more serious neuropathy developed subsequently in 4 cases.

The frequency of this neuropathy is not indicated by its proportion of the 226 cases studied. It is a common condition affecting both young and old persons with diabetes. Thirty-four cases were chosen at random from many that were observed in the clinic.

Forty-five cases of diabetes with relatively mild chronic neuropathy were observed. To these were added 27 cases considered separately as of the circulatory type at first, because of markedly sluggish circulation in the legs. There were evidences, however, of chronic lesions elsewhere than in the legs, and in etiology, manifestations and prognosis the condition seemed to be of the same type as that in the original 45 cases. Hence, the groups were combined. The outstanding symptoms were pain, cramps and paresthesia, of greatest intensity at night. The signs included hyporeflexia and areflexia, muscular paresis, tenderness of nerves and muscles, hypesthesia, abnormal pupillary reactions and paresis of the muscles of the bladder. The legs were involved more

frequently than any other part of the body. Although usually progressive over a long period of time, the neuropathy occasionally improved considerably. The process occurred in patients 40 years old or more, and arteriosclerosis was present in every case. The diabetic factor at fault was not detected. Regulation of the diabetes, use of Buerger's exercises, application of heat and prevention of lesions of the legs requiring surgical intervention constituted the chief means of treatment. As judged by sluggishness or absence of tendon reflexes of the legs, this type of neuropathy involves over 40 per cent of all diabetic patients.

One hundred and twenty cases of diabetes with relatively acute and usually severe neuropathy were studied. These represented the cases of diabetic neuritis and diabetic tabes. Among 1,000 consecutive cases of diabetes observed during a period of less than two and one-half years, there were 25 cases of neuritis. The neuropathy involved the legs in over 65 per cent of the cases. Pain, paresthesia, hyporeflexia and areflexia, muscular paresis, tenderness of the nerves and muscles, hypesthesia and hyperesthesia were the most frequent manifestations. The symptoms were much more intense at night than in the day. Fever and leukocytosis occurred not infrequently. The spinal fluid contained excess protein.

Special features included Argyll Robertson pupils, neuritis of the optic nerve, acute abdominal symptoms, paresis of the muscles of the bladder and psychic disturbances.

The neuritis affected old, rather than young, patients. The diabetic factor responsible was not detected, but hyperglycemia did not appear to be essential for the production of the neuritis. Evidence of vascular disease, primarily arteriosclerosis, was present in 95.8 per cent of the 120 cases. Although presumably playing a causative rôle, the arteriosclerosis may be the result of the diabetic factor which produces the neuropathy. Pressure was apparently a precipitating cause in a number of cases. Focal infection, alcoholism and sensitivity to insulin may have led to the neuritis in a few cases. Deficient dietary intake seemed of no significance, as judged by the dietary histories and the results of feeding accessory food substances.

The prognosis is good, marked improvement occurring within a few weeks in many cases and within a few months in most cases. Improvement in the signs, as well as in the symptoms, was noted at times. However, urinary retention in cases with paralysis of the bladder persisted indefinitely. Paresis of skeletal muscle usually improved rapidly and disappeared entirely. Abnormal tendon reflexes and cutaneous sensitivity often improved.

Diligent and persistent treatment of the diabetes should be given in all cases. Correction of any suspected causative factors should be

attempted. Buerger's exercises are beneficial in cases with circulatory deficiency. The application of heat has been my best sedative, but burns must be avoided.

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