DIABETIC NEUROPATHY*

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THE neurologic complications of diabetes mellitus remain a matter of perennial interest. Although there is little really new to present at this time, a "present-status" report with particular attention to some of the contributions during the last 5 years may be useful. Some particular aspects of diabetic neuropathy—its relationship to other diabetic complications, the prominence in it of autonomic nerve disease, etc.—can well be re-emphasized. Finally, I should like to point out some of the unsolved, but solvable, problems that should be engaging our attention as investigators.

I can best illustrate the type of disease we are dealing with by quoting from a paper published in 1885 in the Lancet by F. W. Pavy.[1]

"I am perfectly satisfied that certain symptoms of disordered nerve action . . . are very apt to accompany diabetes. . . . A lady aged 48, whom I saw for the first time in 1871, and who had then been diabetic for ten years, presented no symptoms of nerve disorder till February, 1880. She then began to complain of pains in her limbs, and by April of that year she was decidedly ataxic. The usual account given by these patients of their condition is that they cannot feel properly in their legs, that their feet are numb, that their legs seem too heavy. . . . Darting or 'lightning' pains are often complained of. Or there may be hyperaesthesia, so that a mere pinching up of the skin gives rise to great pain; or, it might be, the patient is unable to bear the contact of the seam of a dress against the skin on account of the suffering it causes. Not unfrequently there is deep-seated pain, located, as the patient describes it, in the marrow of the bones, which are tender on being grasped; and I have noticed that these pains are generally worse at night. With this there is the usual loss or impairment of the patellar tendon reflex.

"Sometimes pains and manifestations of perverted sensibility are

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noticed without ataxia. It is not always the legs that are affected; the arms may suffer. . . . A gentleman I have seen has had nerve troubles in one arm. . . . His skin and flesh were tender and the bone was painful; there was, moreover, some wasting of the limb."

Dr. Pavy's description is a vivid account of what we recognize today as diabetic peripheral nerve disease.

To visualize the functional and anatomical types of nerve fibers involved in diabetic neuropathy the two common medical diseases with important neurologic complications, diabetes mellitus and pernicious anemia, serve as a useful contrast. In diabetic neuropathy pain and thermal paresthesias are prominent symptoms. Diabetes produces to a greater extent than any other disease a profound disturbance in the function of the autonomic nerves.[2-4] Pain and thermal sensibilities and autonomic functions are mediated by small caliber, poorly myelinated neurons. In pernicious anemia the large caliber heavily myelinated neurons conducting motion, position and vibratory sensibilities are affected early and selectively.[5] Pain is rarely a significant complaint. In pernicious anemia degeneration of the lateral and posterior columns of the spinal cord is notorious, leading to exaggeration of the tendon reflexes, clonus, spasticity, and abnormal plantar responses. This type of spinal cord involvement does not occur as a result of diabetes. Nor does the cerebral involvement occasionally seen as a neurologic manifestation of pernicious anemia with confusion, depression, or outright psychosis occur as a result of diabetes.[5]

The incidence of neuropathy in diabetics is probably about one in twenty.[2, 6, 7] Its relationship to the natural history of diabetes has been clarified in recent years by the study of the diabetic background of patients who develop this complication.[7-10] Joslin and Root[11] pointed out that, in nearly all instances, neurologic disease begins during periods of diabetic non-regulation. In a large group of patients studied later a few developed neurologic difficulties as the earliest symptom of the disease. In general, though, months or years of uncontrolled diabetes preceded the development of serious peripheral nerve disease. The bulk of patients had had no previous diabetic treatment at all or only poor treatment. The majority had lost considerable weight due to the uncontrolled disease. Over half of them, of interest in reference to the possible harmful effects of long continued hyperglycemia, had never had coma, acidosis, or ketonuria even at the height of diabetic non-

CHART I—SYMPTOMS OF DIABETIC NEUROPATHY

Paresthesias, shooting or burning pain, numbness, tingling, "cold" feelings.

Muscular weakness, aches, cramps, tenderness, foot drop, wrist drop, flaccid paralysis.

Symptoms fluctuate, are worst at night, following infections, lapses in treatment, and sometimes after start of treatment. Begin in lower extremities, ascend to trunk, involve arms distally.

Precipitating factors (in group of 125 patients):

U. R. I.	2	Toxic hyperthyroidism	2
Pneumonia	1	Diabetic acidosis	4
Influenza	4	Diabetic coma	6
Pyogenic infections	4	Operations	4

regulation. The nerve disease was found to occur at nearly any age, without there being evidence of immunity either early or late.[2]

The neuritic symptoms (Chart 1) were found to fluctuate in intensity, paralleling generally the course of the diabetes, becoming worse following infection, after lapses in therapy, and sometimes after the start of treatment. A number of incidents notorious for aggravating the diabetic status were observed to aggravate or precipitate the neurologic disease, especially in those with a poor background of control.

A high incidence of other diabetic complications was found in patients with neuropathy. In the scale of diabetic complications, peripheral nerve disease occurred as one of a middle group that we can call sub-acute (Chart 2). Susceptibility to infection was common and an unstable and often severe diabetes the rule. A third of our group had diabetic retinal disease and more than a quarter hepatomegaly.[2]

A few years ago we were very much puzzled as to the origin of some bizarre complaints in patients with diabetic nerve disease:—night sweats without evidence of infection or fever, intolerance to heat and cold, tachycardia with weakness and fainting spells, gastrointestinal disturbances of an unusual type,[12] and distressing genito-urinary symptoms. As our study progressed it became apparent that these patients had autonomic nerve disease to an extent that had not been previously recognized, and which in many clinical situations escapes recognition.

Orthostatic hypotension was one of the striking results of autonomic nerve disease observed in more than a dozen patients.[2] This rare type of physiologic abnormality is one in which the blood pressure

CHART 2—COMPLICATIONS OF DIABETES MELLITUS

Acute: Acidosis, coma.

Sub-acute (curable):

Susceptibility to infection,
Cutaneous
Urinary tract
Pulmonary, especially tuberculosis
Increasing severity and instability of the diabetes.
Neuropathy.
Retinopathy, early.
Hepatomegaly.

Chronic (not curable):

Retinopathy, advanced.
Diabetic cataracts.
Occlusive arterial disease.
Renal disease (intercapillary glomerulosclerosis).

cannot be maintained when the individual stands upright. It has been associated with various diseases involving the sympathetic nervous system.[13] Characteristic symptoms included weakness with exertion, dizzy spells, "black-outs" or syncope when standing. The symptoms were aggravated by fatigue, dehydration, severe diarrhea, etc. The blood pressure taken with patients lying in the supine position was ordinarily normal, the pulse rapid. When standing the systolic pressure fell 50 or more mm. of mercury, the pulse at the wrist became very rapid, weak and sometimes imperceptible. As the blood pressure fell below 50 mm. or so of mercury syncope occurred. Some were able to carry on normal activities with upright blood pressures of only 60-70 mg. Hg. All of the patients had a uniform background of poorly treated diabetes of many years duration, and neuritic disease of some severity.[2] Diabetic neurologic disease has become the commonest cause on our medical services of orthostatic hypotension.

Why the normal circulatory adjustments fail to compensate for the effects of gravity in these and other patients has been an intriguing physiologic problem. Several patients with this disorder have been studied recently by Dr. John Hickam.[14] A low index of cardiac output was found in patients lying in the supine position. An excessive fall occurred as they were tilted to 60°. In spite of intensive study the exact

CHART 3—CLINICAL FINDINGS IN 30 PATIENTS WITH DIABETIC NEUROPATHY AND GASTROINTESTINAL SYMPTOMS

Impotence, atonic bladder (either or both)	18 cases
Diabetic retinopathy	16 cases
Orthostatic hypotension (drop of 50 mm. Hg. or more in systolic blood pressure)	8 cases
Hepatomegaly	6 cases
Gastrointestinal symptoms:	
Cramps, pain, borborygmi	22 cases
Anorexia	20 cases
Severe constipation	15 cases
Vomiting	13 cases
Fecal incontinence	8 cases
Diarrhea	7 cases
Alternating diarrhea and constipation	4 cases
Nocturnal diarrhea	3 cases

mechanism that becomes defunct in these patients and that is responsible for the circulatory abnormality is still in doubt.

Another manifestation of autonomic nerve disease in patients with diabetic neuropathy was disturbance in the motor function of the gastrointestinal tract. In our 125 patients over 60 per cent developed unusual gastrointestinal symptoms with diabetic neuropathy; 53 of them became severely constipated, and in 22 it was virtually intractable; 27 patients had alternating, recurrent or continuous diarrhea, often nocturnal;[15] 4 had, in addition, anorexia with nausea and vomiting. X-ray studies were subsequently undertaken in 30 patients with particular emphasis on gastric motility, gastric emptying and motor performance of the small intestine.[12] The gastrointestinal symptoms and co-existing diabetic complications in this group are shown in Chart 3.

While roentgenologic evidence of disturbed gastrointestinal function was less conspicuous than the clinical symptomatology would lead one to suspect, some degree of gastric retention, slow transit of barium through the jejunum and ileum, and segmentation of the barium column were fairly constant features. The abnormalities were greater in those with severe neuropathy and in those with the more pronounced intestinal symptoms.

The clinical symptoms and roentgenologic abnormalities in the

patients with diabetic neuropathy resembled in many ways those that followed vagotomy. The parasympatheticomimetic drug Urecholine was found to correct the motor abnormalities at least partially, and was useful in symptomatic treatment particularly in those with anorexia and gastric retention.

About 1 in 4 of our patients with diabetic nerve disease developed genito-urinary and sphincter disturbances. Most of them had gastro-intestinal disturbances as well (Chart 3). The major complaints in the male were impotence, symptoms mimicking prostatism and, in both sexes, urinary and fecal incontinence. Cystometric studies of the bladder showed a high incidence of atonic neurogenic paralyses.[2] Detailed studies of the vesical dysfunction and methods of urologic management have recently been published by Lich and Grant,[16] and Emmett, Daut and Sprague.[17] The potential usefulness of the parasympatheticomimetic drugs has been studied only to a limited extent.[3]

A whole gamut of neurologic abnormalities may be illustrated by a 22 year old male, an alumnus of eleven years of diabetes so poorly controlled that his growth was stunted. His right knee and left ankle had become painlessly swollen and deformed two years earlier. He complained of anorexia, inability to eat, and intolerance to heat and cold. On examination his pupils were miotic. They enlarged very little when shaded, showed no reaction or a slight dilatation to light, but did constrict on accommodation. Pin prick and light touch were blunted over his fingers. The right knee and left ankle reflex could not be obtained. Thermal sensibilities were lost below the L 3-4 level.

There was no history suggestive of syphilis and serologic tests on five different occasions were negative. The spinal fluid was normal on two occasions. Roentgen examination of the intestinal tract showed considerable gastric retention at 6 hours, segmentation and delay in transit in the small intestine. These motor abnormalities were corrected by the administration of 10-20 mg. of Urecholine by mouth.

The photographs reproduced in Fig. 1 were taken after he had been painted with iodine, dusted with starch, and heated until his body temperature had been elevated 1.5° C. The black areas show the extent of his sweat gland innervation. There was virtually no sweat response to body heating over his face, extremities, or lower trunk. In hot weather the area of sweat gland innervation over his back was constantly drenched.

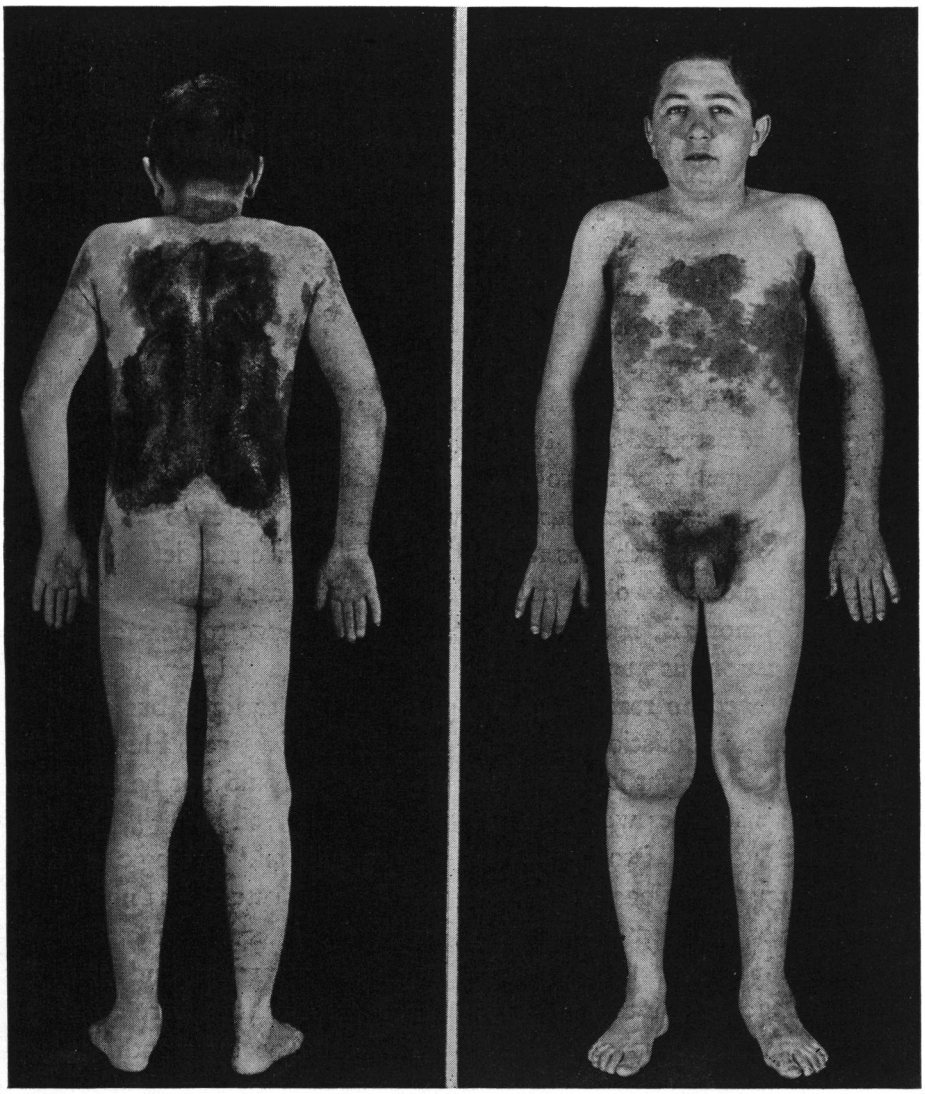

Fig. 1—Photographs showing area of sweat gland innervation, starch-iodine test, and neurotrophic disintegration of right knee and left ankle joints.

CHART 4—DIABETIC NEUROPATHY (NEURITIS)

1) *"Neuropathy":* Neuritic symptoms plus objective evidence of disease of peripheral nerves, persisting beyond any period of diabetic non-regulation.

Motor: Weak, tender, atrophic muscles.

Sensory: Areflexia, blunting of pain, thermal and touch sensibilities (motion, position, and vibration less affected).

Autonomic: Sweat secretion, pilomotor, vasomotor deficiencies; gastrointestinal and genitourinary disturbances.

2) *"Diabetic":* Related to natural history of diabetes:
Onset always during uncontrolled diabetes.
Made worse or better by factors influencing diabetes.
May become worse early in course of diabetic therapy.
Frequently associated with other diabetic complications.
Curable within limits only by diabetic therapy.

Over the dorsum of the left foot a scar was present where an infected ulcer persisted at one time for eight months. The right knee and left ankle were enlarged and deformed. X-ray examination of the knees showed bony proliferation, loose bodies and articular instability. Films of the left ankle showed similar bony changes typical of neurotrophic joint disintegration.[2, 8] He has now been followed for over three years. The right knee has become increasingly unstable and will probably require either fusion or amputation.

We have now come to the point where we can give a working definition of diabetic neuropathy (Chart 4). We have seen that it is a type of peripheral nerve disease, with sypmptoms and objective evidence of neurologic abnormality, in which there is a predilection for the involvement of small caliber neurons. Neuritic symptoms commonly occur in diabetics during periods of acidosis or ketonuria and subside promptly with diabetic regulation. The diagnosis of diabetic neuropathy should not be made unless evidence of disturbed nerve function persists well beyond any temporary period of non-regulation. As to the adjective "diabetic" we imply a definite relationship to the natural history of diabetes as already outlined. The diabetic etiology is confirmed by therapeutic experience. Successful treatment requires meticulous diabetic regulation over a period of weeks or months. No other type of therapy, physiotherapy, vitamin B injections, liver extract, vitamin B_{12}, etc., in my experience, has been of any definite value.[7, 10, 15, 18] In

patients with neurologic complications of recent onset, the prognosis is ordinarily good.[4, 6, 9] When the neurologic disease is of years' duration or complicated by such lesions as perforating ulcers or neurotrophic joint destruction,[19] the prognosis is, of course, poor.

Considering for a moment some unsolved problems, we are often asked what is the "pathology" of the nerve lesions in diabetes. While we are not lacking in confidence as to the validity of our functional studies and interpretations, we must admit that the morphologic aspects of the disease have received only fragmentary study. The technical problems involved in studying degenerative changes in poorly myelinated neurons are obvious. We would be looking for fibrils that were not there and that could presumably disappear leaving very little trace. Little is known about autonomic nerve pathology. Further pathologic investigations would be of great interest in instances of well-studied nerve disease.

Some have considered the neurologic complications of diabetes a result of vascular disease. Convincing pathologic studies, again, have not been made. Arteriography, study of blood flow by plethesmographic methods, etc. should bring out useful information.

It is frequently said that the "cause" of diabetic neuropathy, at least in metabolic or chemical terms, has not been discovered. The same can be said of all the complications associated with it clinically that result from chronic insulin deficiency. In addition to under-utilization of carbohydrate, excessive mobilization of fats and breakdown of proteins occur. Hypoalbuminemia seems to be characteristic and may reflect an inability of the body to manufacture the proteins necessary for tissue maintenance and repair.[18, 20, 21] As knowledge regarding the chemical effects of acute insulin deficiency progresses, the alterations that characterize the decompensated metabolism of diabetics with degenerative complications may be clarified.

The relationship of neurologic lesions in the extremities to the development of incapacitating foot infections is another important problem that has received too little attention. Perhaps a third or more of all foot infections in diabetics occur in those with neurologic disease. Neurologic factors are important not only in the development of perforating ulcers,[22] but in indolent infections, gangrene, traumatic blisters, etc. Effective therapy obviously requires an understanding of basic etiologic factors.

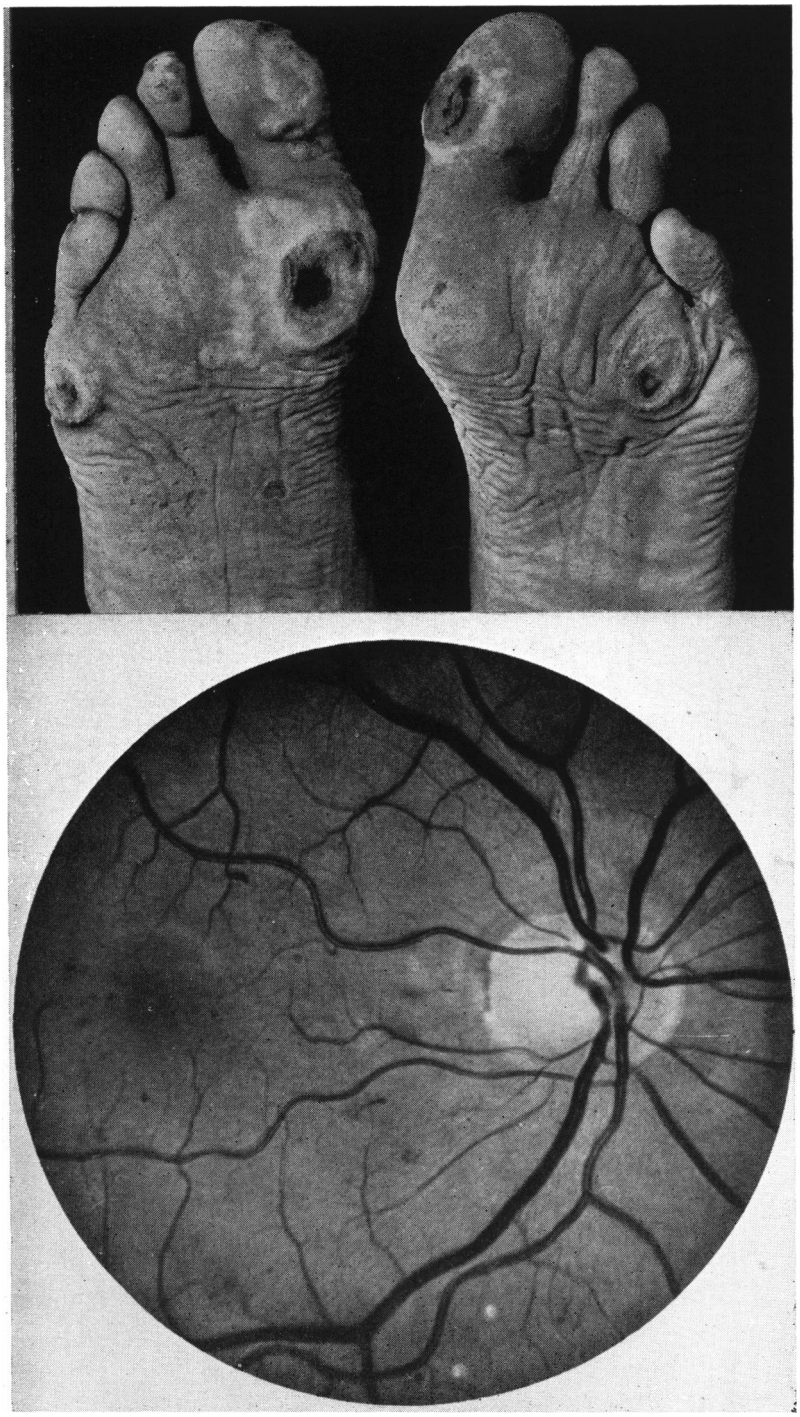

Fig. 2—Photographs (above) of chronic, ulcerated foot infections in a patient with diabetic peripheral nerve disease, and (below) punctate and superficial hemorrhages in retina, O. D.

The feet photographed in Fig 2 illustrate the problem. They belong to a 46 year old ship yard worker, who was admitted to our hospital in 1945, after having been disabled for eight months by chronic foot infections. He had developed diabetes eight years earlier and had symptoms of neurologic disease for one year. A toe had been amputated because of slow healing after trauma. After four months of neuritic symptoms he developed blisters about his toes that became infected. Healing was slow in spite of his being hospitalized for four weeks, and then resting 16 weeks at home. On examination he was thin and underweight. There were punctate hemorrhages in the optic fundi (Fig. 2). The skin over his lower extremities was thin, dry and shiny. There was no evidence of occlusive arterial disease. Neurologic examination showed unequal pupils, muscle weakness and atrophy in the legs, absent knee and ankle reflexes, and blunting of the cutaneous senses below the middle of the lower legs. Heavy glycosuria and ketonuria were present on admission to the hospital.

In the hospital he was kept in bed, the diabetes regulated, and the ulcers cleaned up. Healing was complete in a few weeks' time. He was able to resume work. In 1947 his diabetic regulation became lax again, neuritic symptoms reappeared, and further ulcers developed.

The relative importance of somatic and autonomic nerve disease, or other factors possibly responsible for the development of this type of foot infection is still uncertain. With careful diabetic regulation, prolonged bed rest if necessary, antibiotic therapy, local debridement and conservative surgery more infections are being healed and more feet saved for diabetic patients.[22]

One of the major objectives in the day by day management of diabetes is to prevent immediate and remote complications. We do not yet know what margin of safety we can assume for diabetic patients. Many of us have the conviction, though, that with the energetic use of presently available therapeutic methods we can prevent the bulk of the complications we have discussed from occurring.

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Discussions of Doctor Rundles' Paper

Foster Kennedy

War on disease is, indeed, not unlike war itself. For each to succeed one must have first, a plan of strategy, and second, sound tactics whereby the plan of strategy may be fulfilled. If the strategic conception be unsure or unsound, no matter how good the tactics, the result can hardly be fortunate. Strategy has to do with geography, topography, the disposition and placing of forces and the points at which best on such terms pressure on the enemy can be made. Tactics, that is to say, logistics, the transportation of troops from place to place (not necessarily the

right place for the carrying out of the grand design) may be developed so well, even though strategy be shaky, that success might come early, so that a war may seem about to be won by tactics, when suddenly it is found that tactics are not enough. I think it is something like this in the great war on diabetes. Our tactics have been extremely good. The introduction of insulin has saved millions of lives or at least prolonged millions of lives by the assumption that the origin of the disease lay in the islands of the pancreas. In the same way we have assumed that the neuropathies accompanying diabetes have been in the nature of a polyneuritis. On the contrary, I believe they are much more like what thirty years ago I called "neuronitis," that is to say, a degeneration not of the peripheral nerve only, but of the entire neurone. The charts shown tonight have demonstrated the existence of sphincter abnormality, sexual impotence and marked autonomic unbalance. These things do not occur as a result of mere peripheral nerve inadequacy. They are clearly the result of inadequacy in spinal roots, spinal cord and, I would suggest, of the autonomic system itself. It is by no means clear why peripheral nerves and radicals degenerate in the presence of diabetes. It has been said that they are the result of an ischemic neuritis due to a sclerosis of the blood vessels of the nerves. This has not been proven and is more a line of words than proven assertion in pathology. Certainly no such formula can account for the retinitis so often accompanying diabetes and I am sure that neuropathy often occurs in persons with very high blood sugar, in whom there is no spilling of sugar into the urine.

It would seem that one must look further back for causes of these conditions. One is reminded of the spinal cord changes called subacute sclerosis of the spinal cord occurring in the presence or *before* the presence of pernicious anemia. At first sight the anemia is a plausible reason for the occurrence of spinal sclerosis but more thought shows that both the anemia and the spinal sclerosis are due to the failure of gall bladder and liver function and the absence of hydrochloric acid in the stomach. So I put before this company the notion that diabetes and its neuropathies may not just be the result of disease in outlying functions such as the pancreas but may be due to a disorder in the balance of forces governed centrally in the nervous system. This is true of the stable maintenance of temperature; it is true of the stable maintenance of water balance. These are governed through the hypothalamus. If we

must look there for the causes of diabetes insipidus we had best raise our sights and look upwards perhaps to find the causes there of diabetes mellitus also.

MILTON B. HANDELSMAN

At the suggestion of the chairman, I shall introduce some physiological and biochemical considerations in this discussion of Dr. Rundles most thorough description of diabetic neuropathy. But first, we must reiterate the remarks of the first discussor, that we have a clearer definition of what diabetic neuropathy consists; we have a radiculo-myeloneuritis. It has been known since 1864 that diabetics complain of pains, weakness and numbness of various extremities but clinical descriptions have often been vague. Diabetes occurs in an age group where pains and aches commonly exist and diagnostic skill is needed to eliminate causes of complaints other than diabetes. These include many conditions that are commonly lumped together as "orthopedic causes," and include cervico-brachial syndrome, post-coronary left arm neuritis, bursitis, menopausal osteomalacia, low back syndrome with sciatica and humble flat-foot. We find in 1931 that Severinghaus recorded pain in 49 per cent of his diabetics while Wilder and Woltman found it in only 10 per cent of 2000 diabetics in the Mayo Clinic. Such and other varying statistical data demonstrate the need for rigid criteria in studies concerning the nature of diabetic neuropathy. We have mentioned some medical conditions that must first be ruled out; Dr. Rundles goes further in giving positive neurological findings that must be searched out when the diagnosis is to be made.

Those interested in diabetes are always interested in the question: how does diabetes cause or aggravate the sequelae. Again, we must say that the gap between physiological knowledge and clinical findings has not been overcome. It is a well established fact that neurones and nerve fibers depend on both glycolysis and oxygen utilization. This is somewhat different than in muscle physiology where function can go on for awhile in the absence of oxygen. The effect of anoxia on the nervous system is well known.

There is another significant difference, namely, that nerve survival and action are intimately associated with an electrical potential which

closely correlates with activity. As one nerve physiologist states: the electrical potential of a nerve is like the ticking of a clock—namely, the measurable outward phenomenon of an intricate system. The nerve potential has been carefully studied by neurophysiologists and has been shown to be due to changes in polarization along the neuronal surfaces. The cause of these progressive changes in polarization along the nerve has had many explanations. One, by Nachmanson has been most thoroughly studied; it attributes to the synthesis and breakdown of acetylcholine along the surface of the nerve the cause and biochemical groundwork. This worker has shown that the release and breakdown of acetylcholine is associated with alterations in the nerve membranes which break down the membrane resistance so that electrical impulses travel along the nerve. He has shown in electric organs that the voltage produced is proportional to the cholinesterase activity.

The connecting link of this system to glycolytic activity is through ATP and creatine phosphate which supply the energy to resynthesize acetylcholine. As in muscle, the utilization of carbohydrates supplies the energy to resynthesize the ATP, etc. Carbohydrate metabolism winds up the clock, so to speak. Although Nachmanson's work emphasizes acetylcholine as the *final* step in nerve activity, there is in the background an intensely complicated *biochemical* system involving glycolysis and all the related ancillary factors: the vitamin B components acting as coenzymes and metallic ions, sodium, potassium, calcium, magnesium, etc., which are also involved with the enzymatic reactions. Gerard, in fact, states, "I do not see how we can reasonably select one system from all this welter and just assign to it an essential role in conducting the nerve impulse." This neurophysiologist emphasizes ion action in the nerve and believes that the cause of the flow of electrons (viz nerve potential) is due to local changes in ion concentration at the molecular surface of the nerve cell.

Turning from the laboratory aspects to the clinical, we find that in diabetic neuropathy similar factors have been blamed, namely: improper carbohydrate metabolism, a vitamin lack, or changes in ionic balance. Dr. Rundles has described the fully developed syndrome. It is in the cases with earlier nerve involvement that we should look for clues concerning the etiology of diabetic nerve changes. For this, the classical classification of diabetic nerve involvement which has been studied clinically by many authors can serve.

1. Treusch in Wilder's Clinic has defined a group which he called "diabetes with pain." This applies to severe pain and paresthesias seen in diabetics who are completely decompensated, particularly in those with impending acidosis or in youngsters with acute onset of diabetes before treatment. There are usually few neurological signs and the condition is rapidly reversible with treatment. The Mayo Clinic workers attribute this condition to the derangement of mineral and water metabolism occurring during a decompensated diabetic state and point out that improvement comes rapidly after the establishment of normal salt and fluid balance. This emphasizes the "ion aspects" of nerve pathological physiology. Jordon reporting from the Joslin group calls this type "hyperglycaemic neuritis" and believes that the hyperglycaemia is the cause.

2. We have "neuritis following insulin therapy." This problem was first brought to general attention by Sydenstricker and his co-workers who showed that avitaminosis, notably pellagra, can be precipitated by insulin therapy. Similarly, diabetic neuritic pain can often be found in patients after insulin therapy has been started. In Dr. Rundles' monograph, one of his cases with severe neuropathy showed the first manifestations with insulin therapy. Sydenstricker believed that better utilization of carbohydrates stimulated by insulin therapy also led to the utilization of thiamin and other vitamins as *coenzymes*, thus creating a vitamin deficiency to the general organism. This seems to emphasize the role of vitamin deficiency as an etiologic agent.

A *third* grouping may be entitled "objective signs of nerve involvement in diabetics." Naunyn in 1898 considered the absence of the prepatellar reflex in diabetics as separate from the general problem of neuropathy and reviewed the vast literature that had been collected at that time. These observations made in the pre-insulin era are extremely interesting. The prepatellar reflexes could not be elicited in 20 to 30 per cent of all diabetics. Although they were more frequently absent in severe diabetics, a large percentage of severe cases retained it even during episodes of acidosis. Many patients with absent knee reflexes were followed for years without ever developing subjective or other objective symptoms of neuritis. With treatment, the reflexes returned in many patients. Recent observations are confirmatory of some of these facts. Severinghaus (1931) found reduced reflexes in 57 per cent and Jordon (1936) found that 45 per cent had diminished or absent patellar re-

flexes. More recently, interest has shifted from this reflex to a more sensitive measurement, namely, the determination of the vibratory sense. Collins and his coworkers (1946) found that "impairment in vibratory sense occurs in almost 90 per cent of diabetics and is present as frequently and almost as severely in diabetics without symptoms of neuritis as it does in those with symptoms." Barach (1947) also found that the vibratory threshold levels for diabetics were lower than for non-diabetics. Collins has found that the administration of large amounts of vitamin B has effected marked improvement in their patients; Barach finds that improvement of diabetic control and general nutrition are the chief influences in bringing about an improvement in the vibratory sensation.

There is a *fourth*, the last, grouping to be discussed, namely, "ischaemic neuritis." It is platitudinous to state that a great number of diabetics have peripheral vascular disease. Wilder has shown that the pathological picture found in the nerves of diabetics with severe resting or nocturnal pain and with the peripheral vascular disease is the same as that found in patients with other vascular disease such as thromboangiitis obliterans. Pure vascular neuritis probably exists in some diabetics and should be recognized, however, in view of the widespread disease often found in diabetics in the *smaller* blood vessels such as in the eye or the kidney glomerulus, as well as those larger elastic leg and coronary arteries, the role of ischaemia in diabetics needs further exploration.

Dr. Rundles has given us a picture of diabetic neuropathy with widespread ramifications. The clinician can no longer be satisfied by calling every pain in a diabetic patient a neuritis; we must look for all the ramifications. Are the 4 groups mentioned above early stages of diabetic neuropathy? Are they etiological factors in a reversible stage? What are the respective roles of ions, vitamins and blood sugar in producing diabetic neuropathy? Dr. Rundles has established definitely that deranged carbohydrate metabolism is at fault. How? Closing a discussion concerning a "degenerative" complication of diabetes by asking questions is a very orthodox procedure in the present state of knowledge.

[DISCUSSIONS CONTINUED ON NEXT PAGE]

FREDERICK W. WILLIAMS

I wish at the outset to compliment Dr. Rundles on his very excellent study and presentation of this extremely important complication of diabetes, one which has been to a great extent overlooked and neglected in recent years in the treatment of the disease. Briefly, I wish to emphasize again what Dr. Rundles has stressed: that neuritis in diabetics has diffuse or disseminate manifestations—it may be not only a simple peripheral neuritis of the extremities, but also gastrointestinal, genito-urinary, and cardiovascular neuritis. These last three are the ones which have, for the most part, been overlooked. We should constantly bear them in mind. We will find many if we look for them.

The neuritis of the extremities is the one which has been of greatest interest to me, personally. I wish to call attention to a few features which I regard, clinically important.

First, let us consider the onset. We all have seen and are well aware of the peripheral neuritis which is associated, as Dr. Rundles has pointed out, with long-standing, neglected diabetes. This is a stubborn condition to treat, and the important treatment is good, adequate diet with insulin for assurance of nourishment. We all use supplemental vitamin B therapy, but only rarely is the response rapid and dramatic. Rather, these patients slowly regain strength in their legs and the reflexes often are permanently gone. Then, there are the cases which develop rather rapidly. These, in my experience, are usually the ones which have a rather acutely developed and intense diabetes, with all of the cardinal symptoms, together with the neuropathy.

In my opinion the development of the neuropathy seems in some way related to the speed or acuteness of the disturbance in metabolism. This appears to be borne out by another type of case, in which the neuritic syndrome develops very soon after the patient has been in acidosis and dehydration, and has been rigorously treated and again restored to what we call "control." It would seem that the speed of these metabolic alterations has some bearing on the neuropathy. The explanation has been offered that this is due to changes in water balance and concomitant disturbance in ratio of the water soluble vitamins, especially B. This is only part, or one step in the process, since these cases are slow in response to vitamin therapy, even when it is pushed in doseage.

Finally, I wish to call attention to one other feature of neuropathy

in diabetics, which I have considered of vital significance, but which has not been adequately explored. This is the neuropathy of the extremities and the trophic changes resulting. Dr. Rundles touched on this in his observation of osteoporosis. We have carefully studied the lesions of the extremities in diabetics for a long time. We have gone to great length to classify these lesions on a basis of vascular impairment together with the presence or absence of infection. We have, for some time, been observing the extremities, trying to estimate the degree of neurotrophic changes that are present. We are all well aware of the vulnerability of the tissue, even in non-diabetics, in a case of transverse myelitis. Gangrenous pressure sores are common. The same neurotrophic factor may be contributing, in some measure, to the production of gangrene in lesions of the diabetic extremity. The problem is further complicated by the fact that the nerve pathology may be metabolic, or it may be avitaminosis, or it may be due to nerve ischemia on a sclerotic basis. These are the problems that still challenge us. Let us hope that further studies such as Dr. Rundles' will bring us ultimately to the solution and a sound therapy.