DIABETIC PERIPHERAL NEUROPATHY

PART I. A review of the literature.

PART II. An experimental study of abnormal vasomotor responses in diabetic peripheral neuropathy.

A Thesis

Presented to

The University of Manitoba

In Partial Fulfillment

of the Requirements for the Degree of

Master of Science

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by

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June, 1954.

ABSTRACT

PART I -

There is submitted a review of the English literature on diabetic peripheral neuropathy, up to May, 1954. It is shown that lesions of the nervous system are of frequent occurrence amongst the diabetic population. Most commonly there is evidence of impairment of function of the peripheral nerves, but in addition lesions may involve the brain stem, the spinal cord, and various parts of the autonomic nervous system. There is now a considerable body of evidence that these changes may occur independently of arteriosclerosis, or malnutrition, and that in many cases they are a direct result of the abnormal metabolism of diabetes itself. Failure to separate primary and secondary neuropathies in diabetes has resulted in considerable confusion in the literature. Knowledge of pathology, metabolic defects, and histochemistry of diabetic peripheral neuropathy is fragmentary.

PART II -

There is submitted a study of the clinical findings and the vasomotor responses in ten patients with diabetic peripheral neuropathy. Abnormal vasomotor reflexes in response to thermal testing were found in all. The neuropathic digits were shown to be abnormally sensitive to local cold and to circulating adrenaline. The responses were similar to those occurring in post-ganglionic sympathectomy or peripheral nerve section, and it is concluded that denervation sensitivity occurs in diabetic neuropathy as a result of participation of the autonomic fibres of the peripheral nerve in the degenerative process.

ACKNOWLEDGMENTS

The author wishes to express his appreciation to the staff of the Winnipeg General Hospital for their help and cooperation and to Dr. J. Doupe for his suggestions and criticisms.

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PART I. A REVIEW OF THE LITERATURE

CHAPTER I.

Introduction and Historical Review

It has been recognized for almost a century that neurological lesions occur in association with diabetes mellitus, and to these has been applied the term "diabetic neuropathy". In 1864, at the time of the researches of Claude Bernard on diabetogenic lesions of the central nervous system, Marchal de Calvi* suggested that the sciatic pains and peripheral areas of anaesthesia might be the result rather than the cause of the diabetes. Bouchard* in 1884 observed the frequent absence of the knee jerks in diabetes and in 1885 Althaus** described in detail the clinical symptoms of diabetic neuropathy noting in some cases the similarity to tabes dorsalis. In the same year, Rosenstein** performed the first pathological examination on a spinal cord from a case of diabetes with absent patellar reflexes. Pavy (62) contributed case reports to the English literature, noting the hyperaesthesia and the nocturnal intensification of the pains. The first definite association of the syndrome with disease of the peripheral nerves was made by Pryce (67) who reported cases with autopsy findings in the spinal cord and nerve trunks and observed that "--the glossy skin of Sir James Paget, which has been shown to depend upon injury or disease of the peripheral nerves, is sometimes seen in diabetes--". In the same year the

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*Quoted by Rundles (80)
**Quoted by Woltman & Wilder (105)

reversible nature of the changes was observed by Raven (68) who reported a case in which the knee jerks returned upon recovery from diabetic acidosis. Von Leyden* made the first attempt at classification, into neuralgic, paralytic, and ataxic forms. In 1890 isolated nerve palsies were first reported, by Buzzard (11) and Althaus (2). Althaus suggested treatment of neuropathies by exercises and faradic stimulation, and warned against too rigid dietary restriction. The first experimental work, injecting sugar solutions into peripheral nerves, was done by Auche (1890).**

By 1890 diabetic neuropathy had been accurately described and classified, with careful post-mortem examinations, its relationship to diabetic imbalance had been recognized, and rational means of treatment had been outlined. Little, in fact, has been added to the writings of the early authors. Today there is no agreement as to the signs and symptoms, classification, etiology, pathology, or even the relationship to diabetes. From 1890 to 1925 apart from Williamson's careful papers (99-103) little was written about diabetic neuropathy. With the beginning of the insulin era, new factors were introduced and confusion grew.

In modern times, attention had centred on the etiology of the nervous lesions. Unfortunately, there has been a significant neglect in definition, classification, and pathological anatomy.

Although separation of cases with circulatory or degenerative lesions from those with reversible "neuritis" was suggested as early as 1930 by Root and Rogers (72) many writers still fail to make this distinction, and it is difficult to tell whether they are discussing one, or the other, or both. The demonstration of the polyneuritis of thiamin deficiency naturally raised the question of the relation of the dietary factors in diabetes to the nerve lesions, and led attention away from the diabetes itself. It is only in recent years that the opinion has grown that "diabetic neuropathy is not only truly 'diabetic' in etiology, but results from the abnormal metabolism of chronically unregulated diabetes (80)."

CHAPTER II

Classification

"Diabetic neuropathy is best classified, from the prognostic point of view, into two types:-

1. Cases associated with arteriosclerosis, and

2. Cases without demonstrable evidence of vascular disease.

The latter type indicates a good prognosis, whereas the prognosis is distinctly poor in the former. Poor control of diabetes in either type plays a role in the precipitation or aggravation of neuropathy" (19). This seems to be the most reasonable view in the present state of knowledge. The distinction between ischaemic and non-ischaemic types of neuropathy was first clearly set down by Jordan (35). Unfortunately many subsequent authors have not made this differentiation, in which case their considerations of incidence and etiology convey little meaning. Admitting that some cases cannot be clearly placed in one category or the other, further progress must lie in separating away the arteriosclerotic group from those cases in which the nervous lesions are due to diabetes itself. The view of Rundles (80) - "So much practical difficulty is encountered clinically in differentiating between the symptoms and signs of neuritic disease on the one hand and those of peripheral vascular disease on the other, that there is little to be gained from statistical analysis of collected diagnostic uncertainties" - is a step backward.

A satisfactory classification of diabetic neuropathy would be:

1. Associated with acute diabetic imbalance) - Metabolic.
2. Associated with chronic diabetic imbalance)
3. Associated with ischaemic due to arteriosclerosis- Ischaemic.

The various names which have been applied by different authors are shown in Table I.

Table I.

Author	I	II	III
Root and Rogers (72)	Abnormal nutrition	Diabetic neuritis with paralysis	Deficient blood supply
Jordan (35)	Hyper-glycaemic	Diabetic neuritis	Degenerative and circulatory
Treusch* (92)	Diabetes with pain	Diabetic polyneuritis	Ischaemic neuropathy
Karnash (42)		Primary diabetic neuropathies	Diabetic-vascular disorders
Hirson, Feinmann and Wade (30)	Hyper-glycaemic neuropathies	Active neuropathies	Asymptomatic neuropathies.

The Terminology Used by Various Authors in Describing the Types of Diabetic Neuropathy.

* Treusch described another group: "Diabetic visceral neuritis" - with burning paraesthesia of the feet, objective vasomotor changes and no objective neurologic signs. There is little support for this view.

CHAPTER III

Incidence

The overall incidence of diabetic neuropathy is very difficult to determine because of the selective nature of many of the series, and the lack of agreement as to criteria for diagnosis. The older writings based the frequency upon absence of the knee jerks occurring in diabetic patients. This has the advantage of allowing comparison on the basis of a single objective sign. The available figures are tabulated in Table IIa. It would appear that the overall incidence of abnormal reflexes in the diabetic population has remained around 50% despite the advantages of modern care. The absence of the reflex is much less common in series after 1922, reflecting the rarity of the more severe neuropathy due to chronic imbalance. Table IIb. lists the incidence given in the other available series by whatever criteria were selected. The extraordinary variation serves only to indicate lack of any agreement about what constitutes diabetic neuropathy.

Sex Incidence: Table III lists the sex incidence of diabetic neuropathy in various series. Some preponderance of cases in females is suggested.

Table IIa.

Incidence of abnormal reflexes amongst diabetics in various series.

Author	No. of Cases	% with absent reflexes	% with diminished reflexes
Bouchard*	?	36.9	
Auerbach*	?	35-40	
Maschka*	?	30.6	
Eickhorst*	?	20.9	
Grube*	131	7.6	
Williamson (100)	100	50**	
Kraus (42)	450		40
Sevringhaus (84)	500		46
Jordan (35)	461	4.8	49.1
Broch and Klovstad (10)	426	18.7	
Bonkalo (7)	150	24.6	44.6
Aarseth (1)	306		30.4
Hirson, Feinmann and Wade (30)	100	19	40

* Quoted by Williamson (100)

** Williamson, comparing his findings with those of Grube, pointed out that his cases were all indigent persons, usually suffering from advanced disease with wasting, and that often observations were carried right up until death by coma. 81% were under 50 years of age. In 26 cases in which he continued observations to terminal stages, jerks were absent in 19 and very feeble in 4.

Table IIb.

Total Incidence of Diabetic Neuropathy in Various Series.

Author	No. of Cases	Incidence
Woltman & Wilder (105)	2000	6%
Wendt & Peck (97)	1073	5%
Murphy & Moxon (57)	827	0.6%
Fein, Ralli & Jolliffe (20)	422	2.1%
Kauvar (41)	65	18 %
Rundles (80)	3000	4.2%
Brock & Klovstad (10)	426	20.6%
Bonkalo (7)	150	49.3%
Hirson, Feinmann & Wade (30)	100	57 %
Martin (51)	4105	5 %

Table III.

The Sex Incidence of Diabetic Neuropathy in Various Series.

Author	Total Cases	Male %	Female %
Jordan (35)	226	38	62
Rundles (80)	125	55	45
Rudy, Epstein (79)	100	34	66
Broch & Klovstad (10)	88	53	47
Bonkalo (7)	74	47	53
Epstein (19)	50	32	68
Aarseth (1)	93	37	63
Hirson, Feinmann & Wade (30)	57	23	77
Martin (51)	150	47	53

Age Incidence: Table IV shows the effect of chronological age in the few series in which the figures are suitable for this analysis. Table IV(a) gives the age distribution among groups of neuritic patients. Comparison of Williamson's figures with those after 1922 indicates decreasing frequency in young diabetics, with increasing frequency among the arteriosclerotic age group. Table IV(b) and (c) showing the percent incidence of neuritis amongst diabetics of different age groups, illustrate the same trend. There is also indicated a tendency for a peak incidence between 20 and 30 and again over the age of 50.

Incidence According to Duration of Diabetes. Few figures are available for comparison. In diabetes of from one year to over 10 years duration Broch and Klovstad (10) show a steady increase in frequency for 9.8 to 32.2%. Bonkalo (7) found the average duration of diabetes in patients with neuropathy to be 11.4 years, in patients without neuropathy to be 6.0 years. Herson, Feinmann and Wade (30) on the other hand, report an incidence of neuropathy of 58.7% in diabetes under 5 years, and 54.0% in diabetes over 5 years. All series show a great variation in the duration of the diabetes. No definite conclusion will be reached until ischaemic and metabolic cases are separated. It is generally considered that

Table IV(a)

Author	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70+	Total
Williamson (100)	0	13	17	8	5	9	3	0	55
Sevringhaus (84)	6	28	24	24	34	43	48	23	230
Rudy & Epstein (79)		1	4	2	16	33	41	3	100
Rundles (80)		8	11	14	26	44	19	3	125
Bonkalo (7)	0	2	11	12	9	17	18	5	74
Martin (51)		2	6	14	24	36	56	12	150

Table IV(b)

Author	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70+
Williamson (100)	0	81	74	44	26	69	27	0
Sevringhaus (84)	33	45	60	47	46	39	45	61
Bonkalo (7)	0	25	48	46	43	49	62	75

Table IV(c)

Author	Under 30	Under 50	Over 50
Williamson (100)	76	56	50
Sevringhaus (84)	48	47	44
Broch & Klovstad (10)	13	15	24
Bonkalo (7)	41	43	56

Table IV(a) - Age Distribution in Various Series of Neuropathic Patients.

Table IV(b) and (c) - Percent Incidence of Neuropathy Among Diabetics Within Different Age Groups.

the incidence of neuropathy is more closely related to the duration of diabetic imbalance than of the diabetes itself (80) (51).

Incidence According to the Severity of the Diabetes.

There is general agreement that the severity of the diabetes is not a factor in the incidence of neuropathy. This is not confirmed in the only figures available which relate the incidence to the number of units of insulin necessary for control (10). In the group receiving no insulin, 14% had neuropathy, in the group requiring over 80 units of insulin, 29% had neuropathy. They thought their series too small to permit a conclusion.

CHAPTER IV.

Signs and Symptoms

(a) Neuropathy Associated with Acute Diabetic Imbalance

Persons with hyperglycaemia may have pain and tenderness along some of the major nerve trunks in their limbs which disappears coincident with lowering the blood sugar. The cause is unknown*, and this type of "neuropathy" may be conveniently excluded from the general discussion.

(b) Neuropathy Associated with Ischaemia due to Arteriosclerosis

It is this lesion which nowadays constitutes the great bulk of cases of nervous system lesions associated with diabetes. The manifestations are mild but are extraordinarily frequent if searched for - the incidence is probably around 40-50% amongst "elderly" diabetics. The signs and symptoms are probably not different from those found with much less frequency amongst arteriosclerotic persons without diabetes. (41) The common symptoms are mild pain or cramps, and paraesthesiae, often not complained about, but acknowledged on direct questioning. Characteristically the discomfort is worse at night, in fact pains in the legs

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*A recent theory attributes this syndrome to the early involvement of non-myelinated pain fibres (50).

relieved by walking the floor may be the first sign of early diabetes (37). The usual signs are diminution of the tendon reflexes and the vibratory sense. Other modalities of sensation may be involved later; the loss is generally not extensive. Signs and symptoms are confined to the legs in the great majority of instances.

(c) Neuropathy Associated with Chronic Diabetic Imbalance.

"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" (35). The symptoms often appear rapidly or even abruptly, and may show remissions and exacerbations depending on the diabetic status. The chief features are pain (especially at night), paraesthesia, peripheral loss of sensation (often extensive), decreased activity of the reflexes and paresis. These do not seem to differ in any essential way from peripheral neuropathy due to other causes, although the predilection of diabetes for the sensory components of nerves has sometimes been stressed. Some cases exhibit only motor signs, sometimes involving a single group of muscles (2) (71) (72).

Hirson (29) has recently reported examples of localized atrophy more suggestive of a myopathy than a neuropathy. In severe cases the occurrence of ataxia, absent reflexes, shooting pains, sphincter disturbances, and pupillary changes has given rise to the term "diabetic pseudotabes". Its use should be discontinued if for no other reason than that it infers a knowledge of the pathological anatomy which we do not possess. Pyramidal signs do not occur (80). Genito-urinary and gastro-intestinal disturbances are frequent, and are described in subsequent sections. Amongst the other signs and symptoms of peripheral nerve degeneration there occur autonomic disturbances causing loss of sweating and vasomotor changes; the latter are described in detail in Part II. A frequent but often unrecognized symptom of the loss of autonomic vascular control is "postural hypotension", 8 cases of which with discussion, were presented by Rundles (80).

CHAPTER V.

Special Sites of Involvement

I. Cranial Nerves*

Pupillary changes: Jordan (35) reported 23 cases with abnormal pupils, 5 with typical "Argyll-Robertson" pupils. Rundles (80) stated that "one-quarter" of his cases had abnormal pupillary action, 3 of the Argyll-Robertson Type. They were said to return to normal coincident with other neurologic improvement.

Optic Nerve: Jordan (35) reported 2 cases with retro-bulbar neuritis with no other evident cause which recovered with diabetic management. Waite and Beetham (94) failed to find retro-bulbar neuritis in a series of 2000 consecutive diabetes, but Sykowski (91) recently reported 3 cases and affirmed the diagnosis.

Paresis of External Ocular Nerves: Dieulafoy** in 1905 collected 58 cases of paresis of the external ocular nerves. The incidence was abducent nerve 35 cases, oculomotor nerve 12 cases, trochlear nerve 5 cases, all three nerves 6 cases. Groenouw** found a

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* No attempt has been made to list all the references to cranial nerve palsies in diabetes. There are numerous scattered case reports.

** Quoted by Collier (14).

5.3% incidence of ocular palsies in 647 cases of diabetes, Waite and Beetham (94) 16 out of 2002 cases, Aarseth (1) 5 out of 312 cases. A recent case report is by Hareckson and Miller (17).

Facial Paralysis: Facial palsy is evidently very rare, and it is of course difficult to dissociate other causes. Jordan (35) reports 2 cases, Larsen and Auchincloss (44) 2 cases associated with other cranial nerve palsies.

II. Neuropathic Joints: There have appeared in recent years a number of reports (4, 6, 21, 28, 37, 47, 49, 52, 56, 60, 61, 86, 90, 107) of neuropathic bone lesions in diabetic neuropathy similar to the classical "Charcot joint" of tabes dorsalis. Bailey and Root (4) found 17 cases in 20,000 consecutive cases of diabetes. There was no relation to age, duration of diabetes, or duration, type, or extent of the neuropathy. Martin (49) presented a series of 12 cases, mostly asymptomatic, some with x-ray changes only. He stressed that the lesion is likely much more frequent than previously thought, later reporting an incidence of 6% in neuropathic patients (51). Martin (52) has also stressed the perforating ulcers, and other soft-tissue neuropathic lesions. The association of "mal perforans" with diabetic neuropathy had been observed as early as 1887 by Pryce (67).

In typical cases there occurs a painless disintegration of the joint. Cases have all been in the tarsal joints except for those of Shore (86) (left knee), Spear (90) (left knee), Foster and Bassett (21) (left ankle), Jordan (37) (lumbar body) and Zucker and Marder (107) (left ankle and 3 lumbar bodies). X-ray shows fragmentation and destruction of the tarsal and metatarsal bones with disappearance of the joint spaces. Pathologic studies (4) (21) (107) showed complete loss of bone structure, spicules of bone undergoing various stages of resorption, with the remaining periosteum attempting to form new bone. The etiology is as poorly understood as that of the "Charcot joint" of tabes dorsalis; it is thought to be connected with the sensory loss. Tabetic joints rarely occur in the feet.

III. Gastro-Intestinal Tract: In 1926, Bowen and Aaron (10) "encountered 10 diabetics with --- diarrhoea", first drew attention to gastro-intestinal symptoms associated with diabetes. In a selected series of 69 patients, they found achlorhydria in 29%. Root (73)(74) found achlorhydria in 30-40% of diabetic patients, collected 79 cases with combined diabetes and pernicious anaemia, and queried a relationship*. Neuropathy was not specifically mentioned in these series**. Bargen, Bollman and Kepler (5) showed that diarrhoea in diabetics was not due to chronic pancreatic insufficiency.

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* A point still not settled. (Weinberg (96)).

** Rabinowich (68) recently found achlorhydria in 41 of 100 diabetics. The incidence of neuritis in those with achlorhydria was said to be 17%, in those without, 3.4%.

It was not until 1940 that the first suggestion of a possible neurogenic origin was made by Marble*. White (98) noted the frequency of diarrhoea with neuritis in young diabetics. In 1945, Rundles (80) stated "Among an average group of diabetics receiving modern treatment, gastro-intestinal disturbances are probably no more frequent than among a similar group of non-diabetics. Striking abnormalities, however, in the form of severe constipation, chronic diarrhoea, anorexia and nausea often accompany the development of diabetic neuropathy." Of Rundles' 125 cases, 76 (61.8%) had gastro-intestinal symptoms whose onset coincided with the neuropathy. Chronic diarrhoea occurred in 27 cases. One particular manifestation is the liability to nocturnal diarrhoea, 40 cases of which were collected by Sherridan and Bailey (85)**.

X-ray studies demonstrating the so-called "deficiency pattern" were carried out by Hodges, Rundles and Hanelin (31) in a survey of 30 patients with diabetic neuritis and gastro-intestinal symptoms. The "deficiency pattern" had previously been demonstrated in a number of small bowel disorders including ideopathic steatorrhoea and vitamin B deficiency (45), (48).

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* Joslin, E.P. et al. The Treatment of Diabetes Mellitus. Philadelphia, Lea and Febiger, 7th ed. 1940, p. 467.

** For a recent case report see Muri (58).

Golden (25) in a jejunal biopsy of a person with a "deficiency pattern" in non-tropical sprue, noticed degeneration of the myenteric and submucosal plexuses, a finding previously produced experimentally in animals on deficiency diets. Largely on the basis of these observations the opinion has grown that "diabetic diarrhoea" is due to a degeneration of the submucosal nerve plexuses of the small bowel associated with diabetic neuropathy.

The roentgenologic findings, as quoted from Hodges, Rundles and Hanelin (31) "covered a wide range of abnormality falling under the heading of 'disordered motor function'- - - Some degree of gastric retention, prolonged barium transit through the intestinal tract and segmentation of the barium column were fairly constant features. The calibre of the gut lumen showed considerable variation, and localized segments of dilated gut were encountered. The mucosal pattern was well preserved in most cases. However, localized coarsening, irregularity and partial obliteration of folds were not infrequently observed.- - -"

The diarrhoea is said to be favourably influenced by liver injections (39) and by vitain B_{12} (28).

IV. Genito-Urinary Tract: As with gastro-intestinal lesions, it has only recently been recognized that genito urinary disturbances frequently accompany diabetic neuropathy. The earlier literature contains only occasional reports of unexplained bladder paralysis in diabetes without recognition of the cause. The first recognition of urological lesions due to diabetic neuropathy was by Jordan and Crabtree (34) who in 1935 reported 7 cases of "bladder paralysis", 6 of whom had neuritic symptoms. The following year, Gill (24) reported 2 diabetics with atoxic grossly distended infected bladders who at post-mortem had degeneration of the cord and posterior roots. Such cases were almost universally fatal prior to the advent of antibiotics, but Rudy and Muellner (78) suggested a more hopeful prognosis. Coincident with proper diabetic management seven of their 11 cases improved, 2 with complete clinical and cystometric recovery. The incidence of vesical complaints in neuropathy is approximately 25% (79,80).

Impotence in male patients is even commoner: 27.5% (80), 54% (51). Lich and Grant (46) in an unselected group of 87 male diabetics found 37 cases of morphological vesical abnormalities (42.5%). None of their patients had any distinct bladder complaints. All but 6 had some abnormality

of the tendon reflexes in the legs. Apart from careful management of the diabetes, urinary antisepsis and bladder training, the definitive management for retention in diabetic neuropathy is trans-urethral resection of the vesical neck whether or not this be morphologically abnormal. The rationale of this procedure is elaborated by Emmett (18). The vesical disturbance is identical to that of tabes dorsalis; the site of the neurological lesion in diabetic neuropathy however, is not known.

CHAPTER VI.

Pathology

"Knowledge of the pathology of this common condition is fragmentary" (39). "--- the pathologic aspect of the problem has yet to be settled, since clinical observation has shown diabetic neuropathy to be independent of arteriosclerosis. Often occurring in young, inadequately treated diabetics, it may last for months, only to disappear completely with adequate therapy. Thus far we have not had opportunity for histologic study of such a case. The pathology appears to be practically unknown" (95). The scattered pathologic descriptions which appear in the literature are summarized below.

1) Williamson (99)

a) Male, age 52, diabetic 11 months, "arteries markedly by atheromatous", paresis and wasting of shoulder girdles, numbness and tingling in hands, absent ankle jerks. Died of tuberculosis.

At post-mortem there were degenerated fibres in the posterior columns, remainder of the cord and the peripheral nerves appeared normal. Arteries were not mentioned.

b) Female age 21, diabetic 18 months. Absent knee jerks, leg pains. Died of tuberculosis.

At post-mortem there was degeneration of fibres in the posterior columns, the peripheral nerves appeared normal.

2) Williamson (101)

Male age 25, diabetic 9 months, absent knee jerks, tuberculosis.

At post-mortem "degenerated fibres, stained black, were seen in Goll's columns in the cervical, dorsal and lumbar regions, but they were most numerous in the cervical region ---. Degenerated fibres were also seen in the intramedullary course of the posterior nerve roots - - - best seen in the lumbar and cervical regions. The posterior roots, external to the cord generally presented no degenerated fibres. In a few sections, however, degenerated fibres were seen in the posterior roots for a very short distance, just outside the pia mater, but this degeneration ended very abruptly close to the cord." Peripheral nerves were not examined in this case.

It was Williamson's opinion that the pathology of diabetic neuropathy was a system degeneration of the intramedullary part of the posterior root and its extension into the dorsal columns. Although he did not mention the blood vessels, arteriosclerotic lesions seem unlikely in the latter two cases.

3) Bramwell (9)-(Autopsy report on the case of Pryce (67))

Male, age 56, diabetic 18 months. Alcoholic. Absent knee jerks, sensory loss, pain in the legs. At post-mortem there was generalized atherosclerosis, with thickening of the arteries of the cord and the peripheral nerves. The dorsal columns were normal except for some degeneration around the blood vessels. The peripheral nerves were degenerated.

The alcoholism and vascular disease make this case of doubtful value.

4) Woltman and Wilder (105)*

Woltman and Wilder in 1929 presented a series of pathologic studies on 10 cases of diabetic neuropathy; 3 cases were autopsy material, 7 specimens were from amputation. The 3 spinal cords which were examined were said to show only "senile" changes. The peripheral nerves in each case showed a patchy degeneration of the nerve fibres, and thickening and hyaline degeneration of the intraneural blood vessels. They concluded "the results of this study lend support to the opinion that the factor of greatest significance in the lesions of the nerves found in diabetes mellitus is atherosclerosis".

* Woltman and Wilder summarized the 42 pathologic descriptions in the literature to that time. Most were in foreign journals, and are not available for first-hand study. All were "pre-Wasserman".

Because this work has been the only modern definitive attempt to study the pathology of diabetic neuropathy it has unfortunately become a standard reference on the subject and is widely quoted. The material was extremely selective. All the cases were over 50, all had clinical evidence of moderate to marked atheroma. The seven amputations were done because of gangrene. There was no control material, and as the authors themselves stated "there is not an accurate correlation between the degree of degeneration of the nerves and the symptoms."

5) Gill (24)

Male, age 49. Diabetic 10 years, poorly managed. Ataxic, positive Romberg sign, absent tendon reflexes, marked loss of all sensations from knees down. Moderate sclerosis of vessels.

Post-mortem showed "- - - unmistakeable evidence of degeneration of the cord and posterior roots of a non-inflammatory nature.- - - Some sections also showed rarefaction and atrophy of the nerve cells in the anterior horns. The characteristic lesion appeared to be a wild diffuse gliosis of the dorsal columns with vacualization, rarefaction and loss of substance. -- There were numerous corpora amylacea present. The blood vessels of the spinal cord showed no evidence of arteriosclerosis."

It would seem likely that this case represents a primary degeneration of the posterior columns and dorsal roots due to diabetes.

6) Griggs and Olsen (27)

Male, age 46, unregulated diabetes 5 years. Rapid onset of marked ataxia, loss of position and vibration sense from clavicles down, but no marked impairment of any other sensation. Progressive atrophy of pectoralis and interosseous muscles.

At post-mortem changes were most marked in the cervical and mid-thoracic regions. The cervical region showed "almost complete destruction of the posterior fasciculi" with slight involvement of the lateral fasciculi. The dorsal roots "appeared to be normal".----"In the posterior fasciculi the necrotic area was occupied by myriads of compound granular corpuscles which were filled with fat." There were numerous corpora amylacea. "The walls of the small arteries in - - - the posterior fasciculi showed a moderate degree of thickening and hyaline change."

Although vascular changes were present, the clinical picture and the pathologic findings suggest a primary degeneration of the cord.

7) Zucker and Marder (107)

Female age 47, diabetic 14 years, unregulated. Rapid onset of areflexia, sensory loss to level of dorsal spines, ataxic bladder.

At post- mortem there was patchy asymmetrical degeneration of fibres in the gracile tract, with similar less marked changes in the cuneate tracts. "Anterior born cells were degenerated as evidenced by vacuole formation, increase in pigment, and some chromatolysis." ---"In the lumbar posterior roots there was marked thickening of the media of the medium sized arteries and some degeneration of the myelin sheaths." ---"Arterioles throughout the spinal cord were slightly thickened". The tibial nerve showed extension degeneration of the myelin sheaths and nerve bundles, marked thickening of the artery walls.

8) Frazer and Lennox (22)

Male, age 66, diabetic 12 years, unregulated. Hyporeflexia, wasting and anaesthesia below the knees, ataxia for 4 years.

At post-mortem spinal cord and posterior root ganglia were normal. Sciatic nerves showed no demyelinization, but marked sclerosis of the small arterioles. Posterior

tibial nerves showed a severe degree of demyelinization. The vascular lesions were considered sufficient to account for the changes.

In the other scattered reports of histologic examination of the peripheral nerves in diabetic neuropathy (20), Sancetta et al (80), Lister and Maudsley (45) arterial degeneration was present in each case.

In summary, the cases of Williamson, Gill, Griggs and Olsen, Zucker and Marder seem to substantiate the theory that there is a "diabetic myelopathy" involving principally the dorsal columns and likely the posterior nerve roots.* Cases with similar clinical findings, on the other hand, did not show these changes(Bramwell, Frazer and Lennox). Whether or not other portions of the cord may be involved is questionable. In this regard, Garland and Taverner (23) have recently published 5 cases with purely lower motor neurone lesions proven by electromyography which rapidly improved on diabetic care. Griggs and Olsen (27) classified involvement of the spinal into 3 types: (1) Degeneration of the motor cells of the brain stem and spinal cord; (2) degeneration of the intramedullary portion of the dorsal root fibres with secondary system degeneration; (3) funicular necrosis of the posterior columns. On the basis of present knowledge, this

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* The frequent elevation of the cerebro-spinal fluid protein in diabetic neuropathy is supporting evidence for spinal cord or posterior root involvement. (Jordan(35) 37 of 40 cases; Joslin and Root (38), 61 of 73 cases; Rundles (80), 21 of 31 cases; Joslin (39), 113 of 157 cases.)

classification would appear to be satisfactory, but there is as yet insufficient evidence to support it.

There are no reports in the literature of post-mortem examinations of the peripheral nerves from cases of diabetic neuropathy in which arteriosclerosis could be excluded. Martin (50) has recently carried out a series of nerve biopsies showing "conspicuous degenerative changes in all the sections." Unfortunately he fails to mention specifically the condition of the vasa-nervorum, and furthermore, this method is subject to the criticism that it does not exclude arterio-sclerotic changes at a point proximal to the biopsy.

CHAPTER VII.

Etiology

The approach to the etiology of diabetic neuropathy has been confused because of a number of factors: the failure to distinguish between cases with and without arteriosclerosis; the lack of satisfactory histologic studies; the similarity to other neuropathies, particularly that of vitamin B deficiency; the revolutionary change in the clinical aspects of diabetes which occurred with the introduction of insulin, disappearance of the young diabetic with chronic hyperglycaemia and ketosis, and evolution of a large population of aging diabetics with progressive arterial disease. It is only in very recent years that there has been a return to the idea that there is a disease of the nervous system which is a primary result of diabetes, and not due to inadequate diet or circulatory complications.

The early concept of diabetic neuropathy was that of a reversible or "functional" neurological defect due in some way to the diabetic state. In 1887, Raven (69) observed a case of diabetic acidosis due to bronchitis whose knee jerks

returned when he recovered and became sugar free. Althaus (2) observed recovery from paralysis of the circumflex nerve on proper dietary control. Williamson (100) considered that the high incidence of absent patellar reflexes in his series was due to their being indigent persons with advanced disease. He referred to cases which had "normal" peripheral nerves at autopsy, and postulated some "functional change".

When a renewal of interest in the etiology occurred after 1925, attention was directed to factors other than the diabetes itself, chiefly arteriosclerosis and vitamin deficiency. It has been well established that arteriosclerosis of the vasa-nervorum may cause a peripheral neuropathy, the pathology of which was documented by Woltman and Wilder (105). However, there still remains to be accounted for the acute and reversible cases occurring in the absence of arteriosclerosis. Furthermore, similar clinical and pathologic changes are to be found in arteriosclerotic persons without diabetes (Priestley, (66); Critchley, (15); Kauvar, (41)). Experimental occlusion studies have reproduced both the clinical (Wortis, Stein and Jolliffe (106)) and the pathological (Roberts, (70)) features of the nerve lesions in peripheral arteriosclerosis. The frequency of loss of vibratory sensation in diabetes was noticed

as early as 1905 by Williamson (102). In 1928 Pearson (63) showed that diminishing vibration sense in the periphery occurred "normally" with advancing age, a finding which he attributed to the inefficient blood supply of the posterior portions of the spinal cord. Several studies have recently been carried out on vibratory perception. The most recent and elaborate of these, by Mirsky, Futterman and Broh-Kahn (55) has shown a linear relationship between age and rising vibratory perception threshholds in both diabetics and non-diabetics. The mean vibratory perception threshhold of patients with diabetes was similar to that of non-diabetic subjects approximately 20 years older. They conclude that "the association of diabetes mellitus with increased impairment of vibratory perception may be accounted for by the fact that this metabolic derangement is associated with an acceleration in the development of arteriosclerosis." The fact that the diminution in vibratory perception bore no relation to the duration of the diabetes is in accord with the theory that the syndrome of diabetes mellitus consists of two distinct components, one resulting in insulin insufficiency and one resulting in accelerated vascular damage (Dolger, (16); Mirsky, (54)).

At the time when the various vitamin deficiency states were being intensively investigated, it was natural that a comparison should be drawn between the neuropathy of diabetes and that of vitamin B deficiency. Wohl (104) in 1926 was the first to suggest avitaminosis, reporting a diabetic of 6 years standing controlled by a very restricted diet who exhibited signs of xerophthalmia and beri beri. Angle (3) and Minot (53) reported cases with improvement following a diet rich in vitamins. (undoubtedly in those early days there were examples of avitaminosis brought on by rigid dietary control). With the crystallization of thiamin, and the demonstration of its specific effect in the polyneuritis of beri beri, malnutrition, alcoholism, there was much speculative writing about the "anti-neuritic vitamin". Vorhaus (93) considered all types of neuritis to be manifestations of thiamin deficiency. Fein, Ralli and Jolliffe (20) in a widely quoted paper presented 9 mild elderly diabetics living on borderline diets with minimal neurologic signs which improved on daily oral thiamin.

In more recent years the avitaminotic theory has been largely discarded, although recently revived by Collens et al (12)(13), Sancetta et al (82). Rowlands and Wilkinson (77)

found normal levels of vitamin B_1 in the blood in polyneuritis except when it was due to alcoholism or malnutrition. Sinclair (88) obtained similar results, and observed that the work on vitamin B_1 had been "uncritical and uncontrolled". Pollack, Ellenberg and Dolger (65) developed a tolerance test for vitamin B_1, and found it to be normal in a large group of diabetics. Needles (59) was unable to show any improvement in 7 cases of diabetic neuropathy treated over many months with oral thiamin, and found the thiamin tolerance tests to be normal. Lawry and Hegsted (43) found the thiamin requirements in alloxan diabetic rats to be less than in a control group. Root and Mascarenhaus (75) analysed the diet in 2 cases of severe neuropathy, and found it to be adequate in thiamin. They point out that the similarity between thiamin deficiency and diabetic neuropathy had been exaggerated; the mental dulling and cardiac dilation are absent from the latter. Although the essential defect in thiamin deficiency is known to be the inability to metabolize pyruvate (Peters, (64)) the pyruvate tolerance test in diabetes is normal (Joiner, (32); Martin (51)).

More recently, reports have again appeared regarding beneficial effects in diabetic neuropathy from large doses of vitamin B complex (Collens et al (12)), vitamin B_{12} (Sancetta et al (82)), and an extract of pregnant mammalian liver (Collens et al (13). These same materials in other hands have been ineffective (Shuman and Gilkin (87)). Evaluation of such conflicting reports is difficult, except to say that any change in diabetic control during the study would make the results invalid. Schneider (83) reported favourable effects on the subjective manifestations in 12 of 22 cases of diabetic neuropathy treated with 2, 3- dimercaptopropanol (British anti-lewisite; BAL), which contains easily available sulfhydryl groups active in many enzyme systems. This work, of theoretical interest, evidently awaits confirmation.

Out of the realization that arteriosclerosis and vitamin deficiencies do not satisfactorily account for all the aspects of diabetic neuropathy, has grown the conviction that true examples of this syndrome result in some way from the abnormal metabolism of diabetes itself. First clearly stated by Rundles (80) in discussing an impressive series of cases of advanced neuropathy, it is pertinent to quote him at some length. - "It has long been known that there is no correlation between the severity of the diabetes or any one

acute complication of diabetes such as coma, acidosis, or ketonuria and the incidence of diabetic neuropathy.--- There is a striking correlation, however, between diabetic neglect of a degree permitting the patient to survive in a debilitated state of health, without succumbing to the acute complications of diabetes, and the ultimate development of neuritic complications. A review of the relevant information available justifies the opinion that neither occlusive vascular disease nor a primary or conditioned vitamin B deficiency plays a definite etiologic role. From our clinical study the conclusion is inescapable that diabetic neuropathy is not only truly 'diabetic' in etiology, but results from the abnormal metabolism of chronically unregulated diabetes." These conclusions have recently been reaffirmed by Martin (51).

The explanation for degeneration of nervous tissue due to unbalanced diabetes is entirely speculative. It may be that excessive oxidation of fat leads to peripheral demyelinization. The peripheral nerves contain less phospholipid (Jordan et al (33, 36), the blood more phospholipid (Sirek et al (89)), in neuropathic than in normal subjects. A more likely possibility is the interference with the utilization of carbohydrate which is the principal

foodstuff in the metabolism of nervous tissue. An analogy is apparent with the "biochemical lesion" of thiamin deficiency, wherein there is a failure of pyruvic acid oxidation (Peters, (64)). While the biochemical defect in diabetes is dissimilar (Joiner et al (32); Martin (51)), the same end result on the function and structure of nerve tissue might be expected.

CHAPTER VIII.

Summary and Conclusions

It has been known for almost one hundred years that lesions of the nervous system occur in association with diabetes mellitus. Most commonly there is evidence of impairment of function of the peripheral nerves resulting in the syndrome of so-called "peripheral neuritis". In addition, however, lesions may involve the brain stem, the spinal cord, and various parts of the autonomic nervous system, causing more or less well defined clinical pictures including pupillary disturbances, ataxias, paralysis, vesical and gastro-intestinal disturbances, and abnormalities of vasomotor control. In addition to damage to the nervous system occurring as a result of impoverished blood supply due to arteriosclerosis, it seems apparent that there exists a specific degeneration in some way due to the disordered metabolism of diabetes itself. As a result of the failure and to a certain extent the impossibility of separating these two factors, figures relating to the incidence and background of the neurological lesions bear little meaning. Those lesions resulting

from arteriosclerosis will presumably bear the incidence and relationships of arteriosclerosis as it occurs in diabetes, and will be related to age, sex and duration of diabetes. Recent series (80, 51) suggest however, that the specific neurological lesions of diabetes are not related to these factors but to the duration of a period of diabetic imbalance. Knowledge of the pathology of diabetic neuropathy is fragmentary. There exist only scattered case reports and the majority of these are unsatisfactory due to the presence of arteriosclerosis and lack of controls. All the peripheral nerves which have been examined have shown arteriosclerosis, and whether or not degeneration of the nerves occurs in its absence has not been established. From the available material it would appear that in the spinal cord lesions are found in the dorsal columns, the intra-medullary portions of the dorsal nerve roots and in the anterior horns. Further progress in the study of diabetic neuropathy would appear to depend upon a selection of cases who do not have arteriosclerosis, upon careful examination of controlled pathological material, and upon continued investigation of the metabolism of the nervous system as it relates to diabetes.

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Part II. ABNORMAL VASOMOTOR RESPONSES IN DIABETIC PERIPHERAL NEUROPATHY.

CHAPTER I.

Introduction

In the course of carrying out skin temperature tests on diabetic subjects for the assessment of their peripheral circulation, it was observed that those with peripheral neuropathy exhibited abnormal vasomotor responses which were not related to reduction of the arterial flow by arteriosclerosis obliterans. In these cases there was found to be a disturbance of the reflex vasomotor changes normally obtained in response to body heating and cooling. Abnormal vasomotor reflexes in various types of neuropathy have been described by Wilkins and Kolb (15), Shumacher (14) and others. Rundles (13) and Martin (11) have drawn attention to the frequency of vasomotor disturbances in diabetic neuropathy. These changes have been ascribed to degeneration of the autonomic components of the peripheral nerves. The present work was undertaken to investigate the nature of the vascular reactions in patients with diabetic neuropathy.

CHAPTER II.

Subjects and Methods

The subjects were the 10 cases of diabetic peripheral neuropathy shown in Table I. The controls were 5 persons with diabetes but without neuropathy, and 12 healthy young normals. For the purpose of this study, peripheral neuropathy was diagnosed if there was a disturbance of the appreciation of light touch and pinprick in the feet; other symptoms and signs were of course frequently present. Cases were unselected except that they had to have a sensory loss which was definite and consistent, and no appreciable obstruction to the peripheral circulation by arteriosclerosis. For purposes of comparison the degree of sensory loss was graded as follows: 1. if the loss was confined to the distal two-thirds of the foot or hand, 2. if it extended to the ankle or wrist, and 3. if it extended on to the leg or forearm.

Vasomotor responses were demonstrated by the continuous recording of skin temperatures, measured by means of copper constantan thermocouples held in contact with the pads of the exposed digits by narrow strips of adhesive tape over the dorsum

of the second phalanx. The recording device was a "Speedomax Type G" Series Recorder, Leeds and Northrop Company, which permitted the automatic simultaneous recording of the temperature of any six digits, plus the rectal and room temperature, every 30 seconds. All recordings were carried out in a room whose temperature was kept constant at 18 to 20 degrees Centigrade.

The subjects reclined in the constant temperature room clad only in a hospital gown. Vasomotor reflexes were demonstrated by the reflex thermal test of Gibbon and Landis (7) which was performed on all the subjects and the controls. In this test reflex vasodilatation is induced by covering the body with warm blankets, leaving only the distal parts of the extremities exposed, and immersing the left arm in water at 45 degrees centigrade. Reflex vasoconstriction is induced by removing the blankets, and immersing the arm in a cold bath at 18 degrees Centigrade. The direct effect of cold on the peripheral vessels themselves was studied by immersing the left hand with the thermocouples attached in a cold bath for one-half to one hour, and then removing the sympathetic tone to the limb either by applying body heating, or by performing a novocaine block of the ulnar nerve at the elbow. If the temperature of the digits rose above that of the water bath, it was surmised that vaso-

dilatation had occurred. This test was performed on 6 normal persons, and on 5 neuropathic subjects. The reaction of the peripheral vasculature to adrenaline was demonstrated in all subjects and controls. After a definite plateau of maximal digital temperatures had been produced by body heating, 3 minims (0.2 cc.) of 0.1% adrenaline solution was injected subcutaneously. Liberation of endogenous adrenaline was stimulated in one subject by the intravenous injection of crystalline insulin to induce hypoglycaemic shock.

CHAPTER III.

Results

The 10 cases of diabetic peripheral neuropathy which were studied are enumerated in Table I. All of the subjects had some disturbance of their reflex vasomotor responses as shown by the reflex thermal test. There was a general relationship between the extent of the sensory loss, and the degree of vasomotor abnormality. All except one subject who had complete loss of vasomotor responses had an extensive sensory defect. Neither the sensory nor the vasomotor changes bore any relationship to the duration or the severity of the diabetes.

The normal response to the reflex thermal test is shown in Figure I A. Bringing the subject from a warm environment into the constant temperature room generally caused some initial vasoconstriction. Body warming brought a rapid and sustained vasodilatation after a short latent period, body cooling a sharp vasoconstriction. This type of curve was demonstrated in all the diabetic and non-diabetic controls.

Figure I B,C, and D show varying degrees of abnormal response. Subject 2 (Fig. I B) had minimal sensory loss in the feet, none in the hands. The fingers reacted normally, but the toes showed sluggish and incomplete responses. Subject 5 (Fig. I C) again with a sensory loss only in the feet, failed to show any vasodilatation in the toes despite body heating for almost 2 hours. The fact that this was purely a functional defect was demonstrated by the rapid and complete vasodilatation, which followed the intramuscular injection of 75 mg. of priscoline (4). Subject 10 (Fig. I D) had severe chronically neglected diabetes, and when first seen had a total sensory loss which extended almost to the elbows and knees. Prolonged body cooling to a temperature of 95.4 F with violent shivering failed to cause any cooling of the hands or feet which remained warm and flushed. It must be assumed that the sympathetic innervation to these digits had been completely destroyed.

In normal individuals the application of local cold to a digit did not cause vascular spasm except by acting reflexly through the central nervous system. If the sympathetic tone was released, the skin temperature increased, no matter what the temperature of its environment. This was demonstrated in 6 normal

persons by placing the hand in a cold water bath (18 C), allowing 30 to 45 minutes for thorough chilling to occur, and then releasing the sympathetic tone by body warming (Fig. II A), or by performing an ulnar block (Fig. II B). In each case the temperature of the digit at once rose above that of the water bath, and on removal from the bath a warm flush occurred. In one case bath temperatures from 8 C to 28 C were tried with the same result.

The vasculature ofpatients with neuropathic denervation on the other hand could be caused to remain in a state of sustained spasm by the action of local cold. Once their digits were cooled, they remained so despite body warming or interuption of their nerve supply. The foot of Subject 7 (Fig. II B) was chilled at 18 C for one-half hour. Subsequent body heating for over an hour failed to relieve the vasospasm, the toes remaining cold and blanched. But immersion of the foot itself in a warm bath for 30 minutes produced a full and sustained vasodilatation. Subject 10, who had complete loss of reflex vasoconstriction (Fig. 1 B), showed a sustained vasospasm in the hands and feet following their direct chilling by immerson in cold water (Fig. II C).

Again the vasospasm could be released by a brief period of warming. In the same subject, an ulnar block was performed following chilling of the hand (Fig. II E). Unlike the normal subject, there was no vasodilatation.

The peripheral vascular reaction to the subcutaneous injection of 3 minims of 0.1% adrenaline solution was tested in all subjects and controls. In both the diabetic and the normal controls adrenaline invariably produced no effect (Fig. III A). In all the digits with a sensory loss and vasomotor disturbance, it produced a prolonged vasoconstriction (Fig. III B, III C, and III D- Subjects 1, 6 and 10 respectively), lasting from one to three hours.

An experiment combining local heating with the injection of adrenaline suggested that the effect of adrenaline is probably relatively transient, and that the vasoconstriction which occurs is initiated by adrenaline, but maintained by the cooling which follows the reduction in blood flow. Immersion of the limb (Subject 10) before, and for 20 minutes following adrenaline injection did not inhibit the vasoconstrictor response (Fig. IV A).

But warming of the foot 40 minutes after the injection terminated the vasoconstriction. (Fig. IV B)

To find out whether endogenous adrenaline would induce vasoconstriction, hypoglycaemic shock was produced in Subject 9 who had complete loss of vasomotor reflexes in the feet, almost complete in the hands. A well marked vasoconstriction occurred.

CHAPTER IV.

Discussion of Results

Evidence has been obtained that in cases of diabetic peripheral neuropathy there is impairment of the vasoconstrictor and vasodilator reflexes, and a sensitization to the vasoconstrictor effect of cold and of circulating adrenaline. These abnormal responses are similar to those following sympathectomy (1) and peripheral nerve section (3, 8, 12), and are characteristic of denervated blood vessels (2). It is apparent that in diabetic neuropathy the blood vessels of the extremities become denervated as a result of participation of the sympathetic fibres in the degenerative process of the peripheral nerves.

Fatheree and Allen (5) in connection with a study of Raynaud's phenomenon had occasion to perform ulnar blocks while chilling the hands of normal subjects, using bath temperatures of from 0 C to 27 C. The present study confirms their observation that the block always produced a vasodilatation. These results indicate that local cold will not maintain vasospasm in normal blood vessels when they are acutely deprived of a previously intact nerve supply. This is not made clear in

the extensive work of Lewis and Grant on the vascular reactions to direct cold (9, 10). Vasospasm due to cold following degenerative nerve section is well known (1, 3, 8, 12). The presence of cold sensitivity in diabetic neuropathy however has not been fully appreciated, although Rundles (13) noted that the "cold feet" of diabetic patients were more often caused by neuropathy than by arteriosclerosis.

Adrenaline sensitivity was a constant finding in the patients with neuropathy; in fact its demonstration provides a useful test for the presence of early nerve degeneration. That endogenous adrenaline secreted under physiologic circumstances will induce vasoconstriction in the denervated extremity has been previously shown (3,6). The single observation made here of the occurrence of vasoconstriction in a neuropathic limb during hypoglycaemia suggests that the same may be true in the peripheral nerve lesions of diabetes.

Both adrenaline and cold are likely frequently to exert their effect during the everyday life of the patient. Amongst the present group "cold feet" was a common complaint. One patient volunteered the information that after exposure to winter weather she had to immerse her feet in a bath of warm water; otherwise they would remain painfully cold for many hours.

Ulceration of the extremities associated with diabetic neuropathy frequently occurs in the absence of arteriosclerosis. It seems reasonable to suppose that ischaemia induced by abnormal vascular sensitivity may be one of the factors in the etiology of these lesions.

CHAPTER V.

Summary and Conclusions

Abnormal vasomotor reflexes in response to thermal testing were found in ten cases of diabetic peripheral neuropathy. The neuropathic digits were shown to be abnormally sensitive to local cold and to circulating adrenaline. The responses were similar to those occurring in post-ganglionic sympathectomy or peripheral nerve section, and it is concluded that denervation sensitivity occurs in diabetic neuropathy as a result of participation of the autonomic fibres of the peripheral nerve in the degenrative process.

Subject	Age	Sex	Duration of Diabetes	Severity of Diabetes	Sensory Loss in Feet	Loss of Vasomotor Response in Feet	Sensory Loss in Hands	Loss of Vasomotor Response in Hands
1. A.T.	68	M	16 yrs.	Mild	1	Partial	1	Normal
2. H.H.	70	M	2 yrs.	Mild	1	Partial	1	Partial
3. E.W.	66	F	6 yrs.	Mild	1	Partial	0	Normal
4. L.C.	69	F	14 yrs.	Moderate	1	Partial	0	Partial
5. P.S.	75	M	25 yrs.	Mild	1	Complete	0	Normal
6. O.C.	52	F	3 yrs.	Moderate	2	Complete	1	Partial
7. T.I.	72	M	13 yrs.	Mild	2	Complete	0	Partial
8. J.Z.	66	F	½ yr(?)	Mild	3	Complete	1	Complete
9. P.B.	68	F	20 yrs.	Moderate	3	Complete	3	Partial
10. E.S.	24	M	4 yrs.	Severe	3	Complete	2	Complete

Table I. A comparison of the vasomotor changes with the clinical findings.

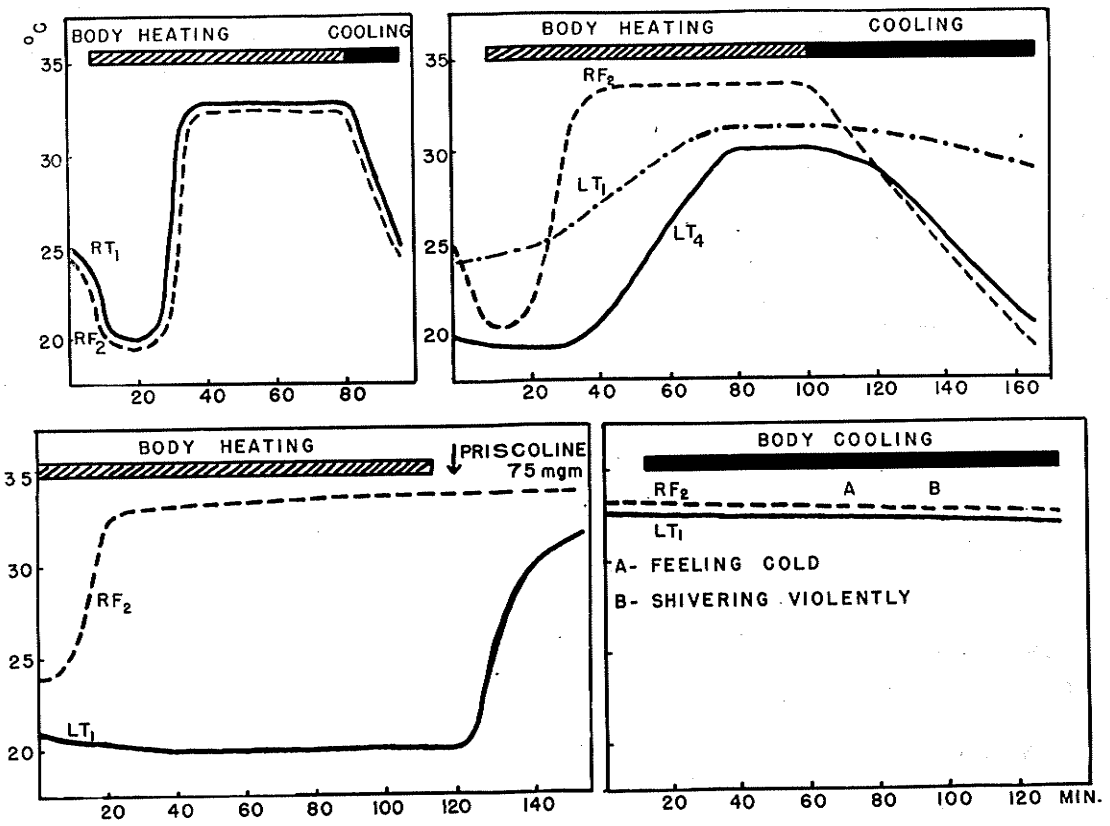

FIGURE I. Temperature charts of a normal person (A), and of Subjects 2 (B), 5 (C), and 10 (D), showing their response to reflex thermal testing. The abscissae represent time in minutes, the ordinates skin temperatures in degrees Centigrade. Body heating is shown at the top of the chart by the broken bar, body cooling by the solid bar. The particular digit tested is indicated by the initials (i.e. LF the left great toe, RF the right forefinger, etc.). In general, the solid line represents a toe, the broken line a finger, unless otherwise stated. In all the observations, the room temperature was 18 to 20 C. See text for discussion of results.

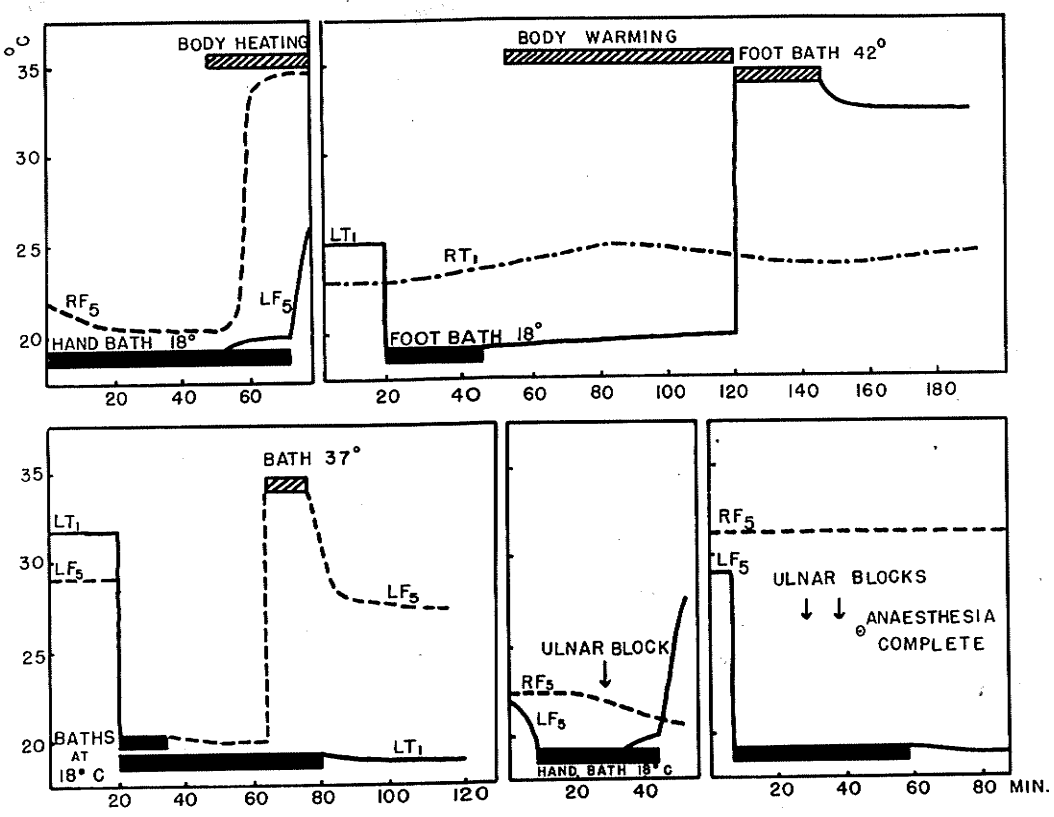

FIGURE II. Temperature charts illustrating the effects of local chilling on a normal person (A, D) and on Subjects 7 (B), 10 (C,E). See text for discussion of results.

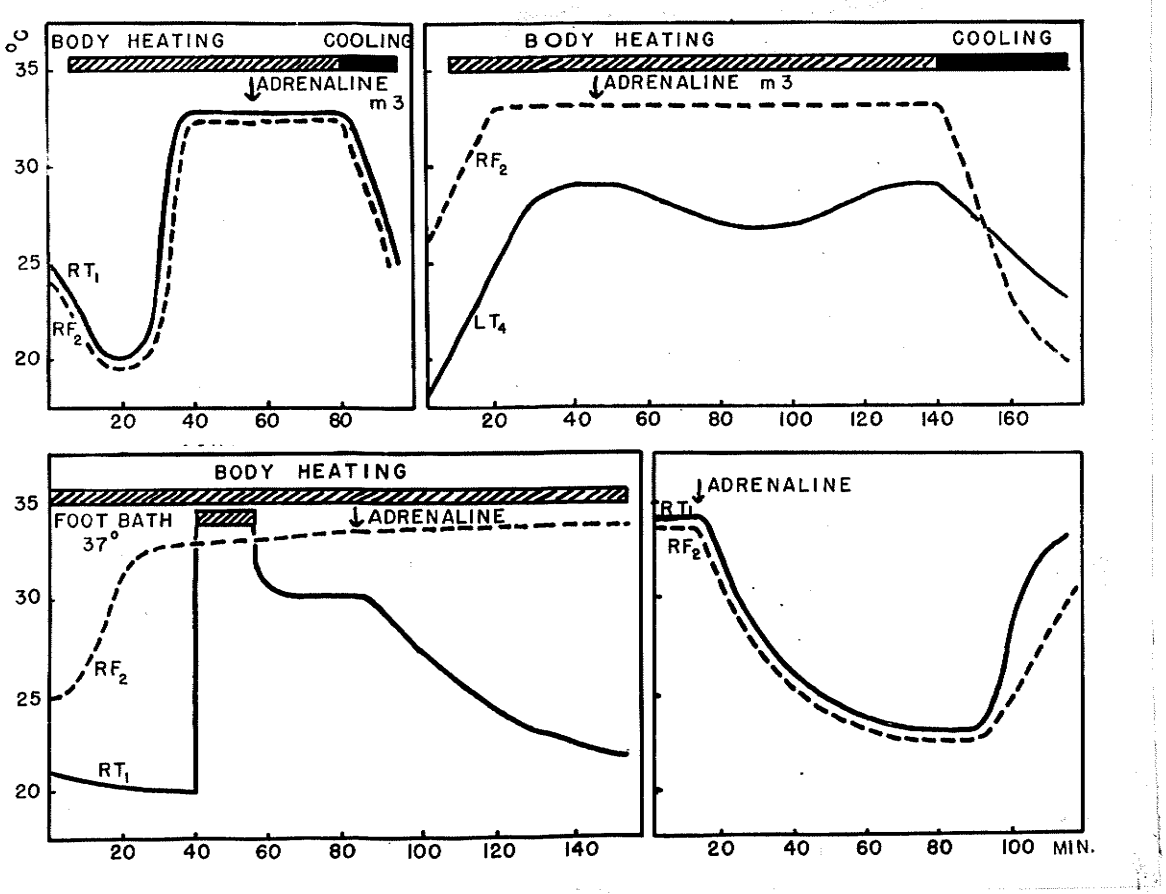

FIGURE III. Temperature charts showing the effect of the subcutaneous injection of 3 minims of 0.1% adrenaline solution on a normal person (A) and on Subjects 2 (B), 5 (C), and 10 (D). See text for discussion of results.

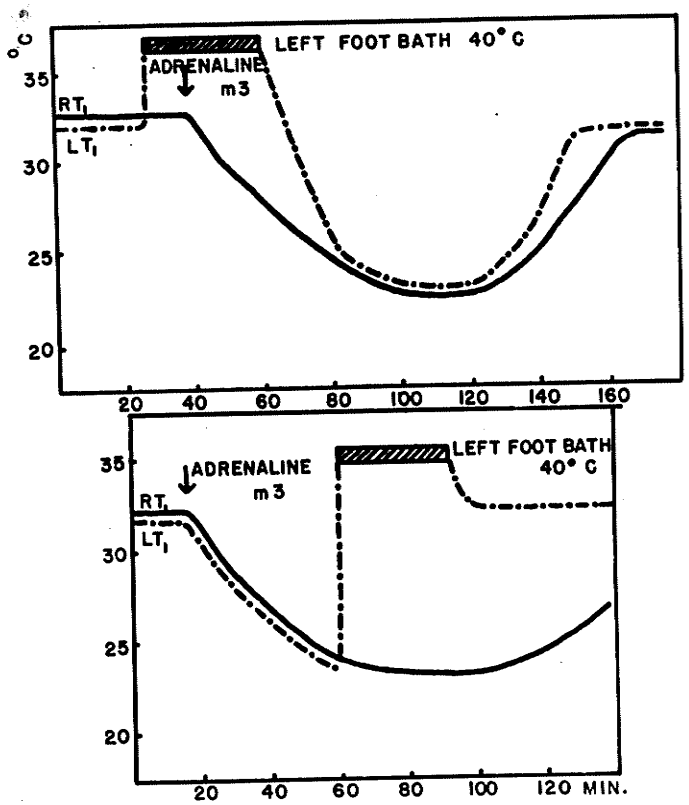

FIGURE IV. Temperature chart showing the effects of local warming on the vasoconstrictor action of adrenaline (Subject 10). See text for discussion of results.

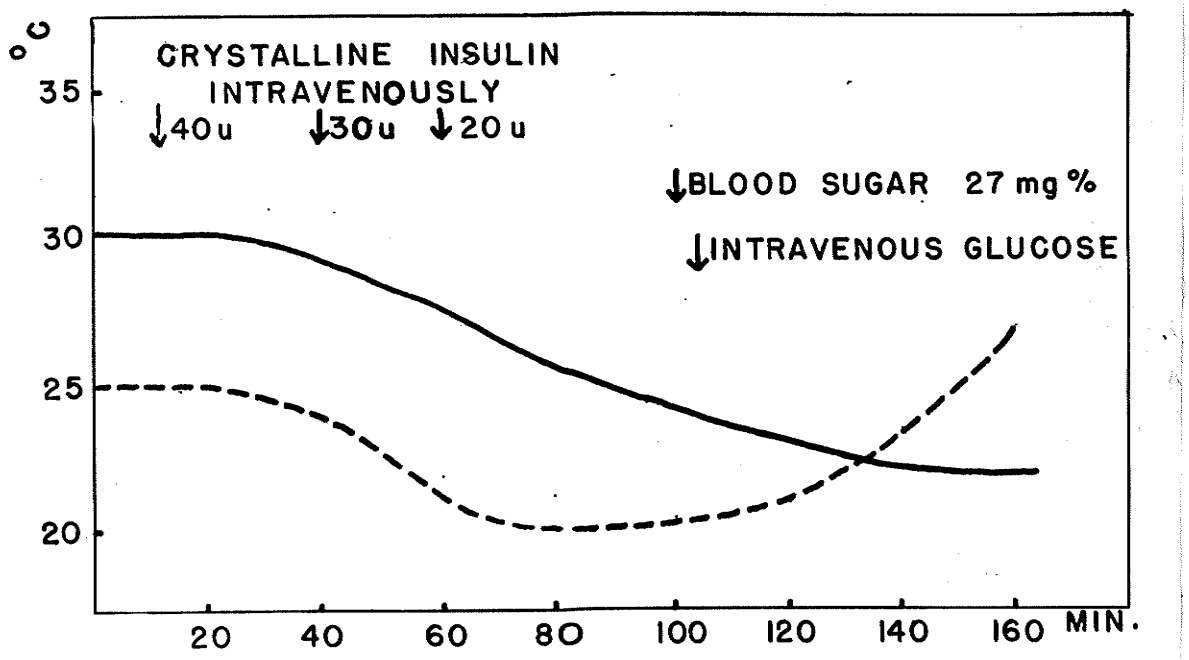

FIGURE V. Temperature chart showing the vasoconstriction which occurred in a completely denervated toe (solid line) as a result of the induction of hypoglycaemia. (Subject 9).

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APPENDIX

Case Histories

1. Mr. A. T. Winnipeg General Hospital O.P.D. No. 36414.

A 67 year old white male attending the out-patients clinic for management of diabetes known since 1937. The diatetes had always been well controlled, requiring 30 units of insulin daily. There were no symptoms in the extremities. Examination and skin temperature tests were carried out on April 17, 1953. The blood pressure was 120-80 sitting, 115-80 lying. The pupils reacted normally, the fundi were normal. The posterior tibial pulses were not palpable. The left dorsalis pedis pulse was clearly palpable, the right faintly. There was definite dependent rubor in the right toes on dependency, with a faint colour change on the left. The nutrition of the skin and nails appeared normal. All tendon reflexes were present. Sensation to touch and pin-prick was slightly blunted over the distal two-thirds of the feet and the distal two phalanges of the fingers. Position sense in the toes was slightly diminished; vibration sense was intact. The patient was considered to have early arterio-sclerosis obliterans and mild peripheral neuropathy.

2. Mr. H. H., Winnipeg General Hospital, No. A. 45317.

A 70 year old Japanese male who was admitted in April, 1953 for management of his diabetes. He had first been seen in the out-patients department in June 1951, complaining of numbness in the fingers and toes and blurred vision since 1949. He appeared a thin elderly man in good general health. The fundi showed numerous haemorrhages and exudates, and a fasting blood sugar was found to be 240 mgm.%. Both the Kahn and Wasserman reactions were doubtfully positive; these were thought to be due to the diabetes, although burned out syphilis was a possibility. He was put on a 2100 caloric diet, and 20 units of insulin daily. During the ensuing two years he gradually required more insulin and was never well balanced. Examination and skin temperature tests were carried out on April 14 and 17, 1953. His blood pressure was 150-80 sitting, 140-80 lying. The pupils reacted normally. The fundi were as previously described. Both dorsalis pedis pulsations were palpable, the left only very faintly. The posterior tibial pulses were not palpable. There were no definite changes in the nutrition of the skin and nails, and there were no colour changes on dependency. All the tendon reflexes were active except for the ankle jerks,

which were absent. Sensation to touch and pin-prick was diminished below the ankle, and position sense in the toes was slightly diminished. The patient was considered to have early arteriosclerosis obliterans, and mild peripheral neuropathy. He subsequently (Oct. 21, 1953) developed an arterial thrombosis of the left leg, necessitating amputation. The pathological report on the surgical specimen read "the vessels show marked arteriosclerotic changes with calcification. The changes are equally marked in the main vessesl of the nerve". Death occurred on the fifth post-operative day due to uraemia and a coronary occlusion. (Surgical No. 6876/53. Autopsy No. 9746).

3. Mrs. E. W. Winnipeg General Hospital, O.P.D. No. 42689.

A 67 year old white female who had had mild diabetes since 1947. It could be readily controlled on diet alone under hospital conditions, but at home she was careless of her diet and generally had glycosuria. In 1952 10 units of insulin daily was started. She had been very obese for many years. For about a year she had noticed that her feet became cold easily and that when cold it was difficult to get them warm. There had been no numbness, and no definite paraesthesiae. Examination and skin temperature

tests were carried out on April 16, 1953. Her blood pressure was 170-110 sitting, 160-100 lying. The pupils reacted normally. The fundi showed only slight tortuosity and spasticity of the arteries. Both dorsalis pedis pulses were strongly palpable, the posterior tibial pulses could not be palpated due to obesity. The nutrition of the skin and nails appeared normal, and there were no tendon reflexes anywhere. Sensation to touch and pin-prick was diminished over the distal two-thirds of the feet. Vibration sense was diminished at the ankles and below. Position sense in the toes was impaired. In conclusion there was no clinical evidence of obliterating arteriosclerosis; there was mild peripheral neuropathy.

4. Miss L. C. Winnipeg General Hospital, No. A.63036

A 69 year old white female with known diabetes for 14 years, which for at least the previous 3 or 4 years had been poorly balanced. In February 1950 following removal of an infected kidney she noticed that her feet were "numb". She also observed that her feet became cold more easily than previously. She began wearing felt boots when she went outside whereas "I never even used to have to wear rubbers". When her feet did become cold, it was particularly difficult to get them warm again.

On coming indoors she always applied a hot water bottle, or even immersed her feet in a tub of warm water. She was admitted to the hospital in April, 1953, following an attack of biliary colic. Examination and skin temperature tests were carried out on April 9 and 10, 1953. Her blood pressure was 170-85 lying, 135-75 standing. The pupils reacted normally, the fundi were not examined. The feet were warm, the dorsalis pedis and posterior tibial pulses were palpable. The nutrition of the skin and nails appeared normal except over an area corresponding roughly to the sensory loss where the skin was dry and finely scaly. There were no colour changes. There were no tendon reflexes anywhere. Sensation to pin-prick was diminished over the toes and for about 2" up the foot. Touch sensation was lost over the tips of the toes, and diminished over the same area as the impaired pain sense. Vibration sense was diminished below the knee, position sense in the toes was slightly impaired. The patient was considered to have mild peripheral neuropathy without clinical evidence of obliterative arteriosclerosis.

5. Mr. P.S. Winnipeg General Hospital. No. A62792

A 75 year old white male who was admitted to the hospital March 18, 1953 because of symptoms of mild congestive heart failure. He had had diabetes since 1928, managed on diet alone.

For the previous six weeks he had noticed a gnawing pain in his legs. Examination and skin temperature tests were carried out on March 20, 1953. The blood pressure was 175-85. The pupils reacted normally, the fundi showed slight arteriosclerotic changes. The ankle pulses were are readily palpable. The skin and nails were normal. The knee reflexes were active, the ankle reflexes absent. There was slight diminution in pin-prick sensation over the distal half of the feet. Vibration sense was present except over the distal phalanx of the toes. Position sense was intact. The patient was considered to have a mild peripheral neuropathy; despite his age and the duration of the diabetes there was no clinical evidence of arteriosclerosis obliterans.

6. Miss O. C. Winnipeg General Hospital No. A 36150, O.P.D. No.70478.

A 52 year old white female who gave a history of sudden onset of thirst, polyuria, loss of weight in February, 1950. The diabetes was "labile" and difficult to manage. Control was never satisfactory. The insulin dosage at the time of testing was 30 units daily although it subsequently rose to over 100 units. In addition to the diabetes she had a severe hypertension with early cardiac enlargement. She observed that her feet always felt numb and cold, that she was unable to keep them warmer even in summer. Examination and skin temperature tests were carried out on April 4, 1953. Her blood pressure was 240-150 sitting, 240-140 lying. The pupils reacted normally, the fundi showed hypertensive changes only. The right posterior tibial pulse was present, the left posterior tibila and both dorsalis pedis pulses were absent. The skin of the feet and the lower halves of both legs appeared shiny and atrophic and there was evidence of a healed ulcer over the left skin. There were no colour changes on dependency. The feet and lower legs felt cool. The tendon reflexes were generally diminished, and the ankle jerks were absent. Sensation to

touch and pin-prick were diminished in patchy areas over most of the foot, and over the distal phalanx of the fingers. Vibration since was diminished at the ankles and below, and absent over the toes. Position sense appeared to be intact. In conclusion there was evidence of a peripheral neuropathy of moderate severity, and also ischaemia of the lower limbs due to arteriosclerosis.

7. Mr. T.Y. Winnipeg General Hospital. O.P.D. No. 75762.

A 72 year old white male who had been a known diabetic for 13 years. The diabetes had not been cared for. His weight over this period had fallen from 250 lbs. to 165 lbs. When first seen at the hospital clinic in April 1952 the fasting blood sugar was 304 mgm.%, with diet and 10 units of insulin the blood sugar was readily maintained under 160 mgm.%. He complained of paraesthesiae over the dorsum of the feet, worse at night. Examination and skin temperature tests were carried out on April 2 and 9, 1953. His blood pressure was 150-85 sitting, 130-80 lying. The pupils reacted slowly but in the normal way. The right fundus showed arterio-sclerotic changes only, the left was obscured by a cataract.

The posterior tibial and dorsalis pedis pulsations were faintly palpable. There were no colour changes and the nutrition of the skin and nails appeared normal. The feet were cool. There were no tendon reflexes in the arms. The knee jerks were present, the left ankle jerk was faintly present, the right absent. Touch sensation was absent in the toes. Sensation to touch and pain was diminished below the ankles, and there was a patchy diminution of sensation over the lower leg. Vibration sense was absent below the iliac crests, position sense in the toes was absent. The patient had evidence of a moderately extensive sensory impairment, without definite clinical evidence of arterio-sclerosis obliterans.

8. Mrs. J.Z. Winnipeg General Hospital. O.P.D. No. 75030.

A 66 year old white female who first attended the outdoor clinic in January 1952, at which time she was found to have mild diabetes. Her fasting blood sugar was 218 mgm.%. The diabetes was readily balanced on a 1200 caloric diet. She complained of pain and burning in both feet, which was said to have been present periodically for 10 years. Examination and skin

temperature testing were carried out from May 7 to May 23, 1952. The blood pressure was 160-80 sitting, 170-80 lying. The pupils and fundi appeared normal. The dorsalis pedis pulses were readily palpable, but the posterior tibial pulses could not be felt. Slight rubor on dependency was observed. The feet were warm and dry. The skin and nails showed early atrophic changes. All the tendon jerks were absent. Sensation to pin-prick and to touch was diminished over the feet and the lower one-third of the legs. Vibration sense was diminished over the same area. Position sense was impaired in the toes. The patient had a moderately severe sensory loss; there was clinically also early obliterative arteriosclerosis.

9. Mrs. P.B. Winnipeg General Hospital, No. A 62790.

A 68 year old white female who was admitted to the hospital on March 11, 1953. She had known that she was diabetic for 20 years. The diabetes was not carefully supervised; she had been taking insulin units 20 daily for 7 years. Following an elective cholecystectomy in November 1952 she developed a watery diarrhoea, dizziness on standing and numbness in the legs and hands. Despite the lack of care, the fasting blood sugar was only 154 mgm.% an

admission to the hospital. Examination was carried out on March 19, 1953 and skin temperature tests from March 10 to April 10, 1953. The blood pressure was 120-60 lying down, fell to 60 -? on standing, when the patient became very dizzy. The pupils reacted normally, the fundi could not be visualized. The posterior tibial pulses were not palpable, the dorsalis pedis pulses were faintly discernible. The feet were warm, the skin dry and scaling below the knees. The right great toe nail, was markedly thickened. There were no colour changes on dependency. The strength in the hands and lower legs was poor, but there was no localized weakness or wasting. The knee and ankle reflexes were absent, the tendon reflexes in the arms faintly present. Sensation to touch and pin-prick was lost below the knees and elbows. Vibration sense was lost below the knees and wrists, position sense was absent in the toes, impaired in the fingers. With rest and careful supervision of the diabetes which was balanced on 35 units of insulin daily the sensory defect receded considerably, but the weakness, vasomotor impairment, and diarrhoea remained.

The patient was considered to have a severe diabetic peripheral neuropathy, without definite evidence of impaired blood supply to the feet despite the poor quality of the pulses at the ankle. A year later, however, she developed extensive gangrene of the right foot, and x-ray showed marked calcification of the inter-digital arteries. The extensive sensory defects, postural hypotension and diarrhoea were still present.

10. Mr. E.S. Winnipeg General Hospital No. A 62672

A 24 year old white male who gave a history of sudden onset of thirst, polyuria, and weight loss at the age of 20. Over the ensuing year he lost 60 lbs. (180 lbs. to 120 lbs.). He required approximately 100 units of insulin daily to manage the diabetes and he only administered this periodically. In September 1952 he noticed that his feet were numb below the ankles. During the following winter they became cold easily and when cold were difficult to get warm. He was admitted to the hospital on March 14, 1953 in a state of chronic ketosis. Skin temperature tests were carried out over the period of March 18 to April 3, 1953. The blood pressure was 130-90. The pupils and fundi were normal. The pulses at the ankle were easily palpable. The skin below the knees was dry and scaly, but otherwise normal. All the

tendon reflexes were absent. All types of sensation were absent below the knees, and impaired in the hands and forearms. Vibration sense was absent to the iliac crests. With treatment of the diabetes sensation rapidly returned, so that at the end of a week, no definite impairment could be detected. The knee jerks returned, but not the other tendon reflexes. No improvement was noticed in the vasomotor responses during the period of observation. The patient was considered to have a severe neuropathy due to chronic diabetic imbalance. There was no evidence of arteriosclerosis. The diabetes proved exceedingly difficult to control, requiring approximately 200 units of insulin daily. The patient subsequently died at his home of diabetic coma.