INTERNAL MEDICINE GRAND ROUNDS

UNIVERSITY OF TEXAS SOUTHWESTERN

MEDICAL CENTER AT DALLAS

DIABETIC NEUROPATHY:

A FEEL FOR THE INTERNIST

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INTRODUCTION

Diabetic neuropathy is probably the most clinically important complication of diabetes mellitus. Depending on how one views diabetic neuropathy, either clinically apparent or the subclinical form, the prevalence of diabetic neuropathy varies from 10% to 100%.

PREVALENCE OF DIABETIC NEUROPATHY

REPORTED PREVALENCE OF SYMPTOMS AND SIGNS OF NEUROPATHY IN DIABETES

Source	Measurement	No. Patients	Neuropathy %
Cleveland 1953	Subjective Complaints	261	62
Salford, Eng. 1953	General Findings	100	57
Brussels 1965	Objective Signs	1,175	21
Stockholm 1950	Objective Signs	150	49
Rochester, Mn. 1961	Electromyography,	103	42
	Objective Signs	198	55
Philadelphia 1958	Impotence	16	44
New York 1952	Skin vessel dilatation	337	20
London 1960	Abnormal Valsalva maneuver	100	52
Toronto 1961	Objective Signs	77	35
Chicago 1966	Objective Signs, motor nerve conduction velocity	107	10
Aarhus, Denmark 1968	Motor conduction velocity	14	100
London 1971	Motor conduction velocity	39	100
Edinburgh 1977	Motor conduction velocity; autonomic vascular tests	10	100

From: U.S. Dept of HEW: Diabetes data DHEW Publ (NIH) 78-1468, 1978.

There are various ways to classify diabetic neuropathy. I have chosen one that I feel is most clinically useful.

CLASSIFICATION OF DIABETIC NEUROPATHY

SOMATIC NEUROPATHY

1. DISTAL SYMMETRIC DIABETIC NEUROPATHY

   - Predominantly Sensory

     Small fiber (pain and temperature sensory function)
     Large fiber (proprioception, vibration, sensory function, and muscle reflex)

     Mixed large and small fiber

2. PROXIMAL SYMMETRIC DIABETIC NEUROPATHY

3. ASYMMETRIC DIABETIC NEUROPATHY

   - Predominantly Sensory
     - Intercostal radiculopathy
     - Truncal radiculopathy

   - Predominantly motor
     - Cranial neuropathy
     - Peripheral neuropathy
     - median (Carpal tunnel syndrome)
     - ulnar
     - popliteal

   - Proximal neuropathy

AUTONOMIC NEUROPATHY

1. CARDIOVASCULAR
   - Exercise intolerance
   - Cardiac denervation syndrome
   - Orthostatic regulation

2. GASTROINTESTINAL
   - Gastric emptying abnormalities
   - Constipation
   - Diabetic diarrhea
   - Incontinence

3. GENITOURINARY
   - Bladder dysfunction
   - Sexual dysfunction
     - impotence
     - retrograde ejaculation

4. SUDOMOTOR

5. COUNTER-REGULATORY

(from: Med Clin N Amer 72:1439, 1988)

Listed below are the most common clinical syndromes of diabetic neuropathy. Although diabetic neuropathy can have almost any clinical presentation and sometimes the diagnosis is one of exclusion, there are several characteristic syndromes in most patients with diabetic neuropathy.

CLINICAL SYNDROMES OF DIABETIC NEUROPATHY

A. SOMATIC NEUROPATHY

Distal Symmetrical Polyneuropathy

- Parathesias (tingling, numbness)
- Pain (dull ache, burning, lancinating, etc)
- Impaired sensation (vibratory, pain, etc)
- Nocturnal exacerbation
- Absent knee and ankle reflexes
- Motor involvement variable

Neuropathic Ulcer

- Major source of morbidity
- Caused by loss of protective sensation and repetitive trauma (i.e., walking)
- Over areas of increase pressure (i.e. metatarsal heads or under calluses)
- Hammer-claw toe deformity of foot causes increased pressure on metatarsal heads.

Neuropathic Arthropathy (Charcot's Joint)

- Occurs in presence of impaired pain and proprioception but intact motor power.
- Painless
- Non-edematous swelling of the foot
- Abnormal gait

Cranial Neuropathy

- Abrupt onset usually in older patients
- Cranial nerve III lesion most common
    - ptosis and ophthalmoplegia
    - pupil usually spared
- Other lesions include cranial nerve VI and VII, cranial nerve IV rarely involved
- Recovery spontaneous in 6-8 weeks
- Not related to level of diabetic control

Mononeuropathy

- Ulnar, medial, radial, femoral, peroneal, and lateral cutaneous nerves of thigh
- Carpal tunnel syndrome
- Usually motor neuropathies

Diabetic Amyotrophy

- Pain
- Severe muscle atrophy in limb girdle distribution
- Fasciculation of muscles
- Often acute onset
- Older patients with mild diabetes
- Improves spontaneously (1-3 years)

B. AUTONOMIC NEUROPATHY

1. CARDIOVASCULAR

Cardiac Denervation

- Resting tachycardia (due to decreased parasympathetic tone)
- Dysfunction of both left ventricular filling and systolic ejection
- Painless myocardial infarction

Exercise Intolerance

- Blunted increase in heart rate at low work loads due to impaired withdrawal of parasympathetic tone
- Blunted increases in heart rate at high work loads due to impaired sympathetic chronotropic effect
- Predisposition to orthostasis due to decrease vascular resistance

Orthostatic Hypotension

- Fall in systolic BP $\geq$ 30 mmHg and/or diastolic $\geq$ 10 mmHg upon assuming the upright position
- May not result in an increase in heart rate

2. GASTROINTESTINAL

Gastric Emptying Abnormalities

- Postprandial nausea, vomiting, and early satiety
  - "Asymptomatic" gastroparesis may cause wide unexplained blood glucose swings
  - Diagnosis made using the "Feldman Test"

- Constipation

- Most common complaint of diabetic patients
- Treated with high fiber diets, stool softeners and/or laxatives

Diarrhea

- Watery diarrhea lasting hours to days
- Nocturnal exacerbation
- Must rule out other causes, i.e., celiac sprue, pancreatic insufficiency, etc.
- Can be extremely debilitating

3. GENITOURINARY

Bladder Dysfunction

- Symptoms include straining, hesitation, incomplete emptying, overflow, overflow incontinence, and decreased urinary stream
- Can result in urinary stasis and recurrent urinary tract infections
- Diagnosis made by finding a 150 ml post void bladder residual; confirmation with cystometrogram

Impotence

Retrograde Ejaculation

Just as the case with the other late complications of diabetes the development of diabetic neuropathy tends to be multifactorial. Listed below are some of the "risk factors" for the development of diabetic neuropathy.

RISK FACTORS FOR THE DEVELOPMENT OF DIABETIC NEUROPATHY

- Genetic Predisposition
- Male Gender
- Height
- Alcohol
- Hyperglycemia

TABLE 1

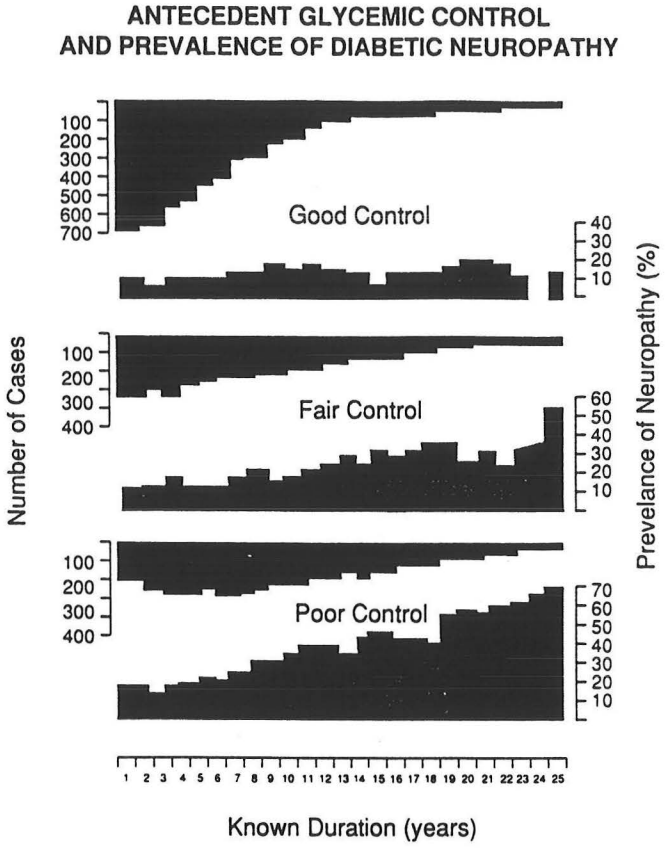
CHARACTERISTICS OF IDDM SUBJECTS UNAFFECTED WITH NEUROPATHY

	Unaffected	Affected
N	169	109
Age(yr)	23 ± 8	26 ± 8
Gender (% male)	42	58*
IDDM duration (yr)	6 ± 4	8 ± 4*
Cigarette smoking (%)	17	22
Diabetes diagnoses after onset of puberty (%)	47	22
Height (cm)	168 ± 10	171 ± 10
Body weight (%ideal)	101 ± 14	102 ± 13
Diastolic blood pressure (mmHg)	69 ± 10	68 ± 10
Presence of retinopathy (%)	57	72*
HbA1c	9.0 ± 2	9.0 ± 2
Stimulated C-peptide (pmol/ml)	0.09 ± 0.11	0.06 ± 0.90
Albumin excretion (mg/24 h)	21 ± 21	25 ± 38

Where range is indicated, values are means ± SD
* $p<.05$ vs unaffected subjects

From: Diabetes 37:476:81, 1988

Figure 1



(From: Pirart, Diabetes Care 1:168, 1978)

POTENTIAL PATHOPHYSIOLOGICAL MECHANISM OF DIABETIC NEUROPATHY

- Increased Polyol Pathway Activity
- Abnormal Myoinositol Metabolism
- Glycosylation of Tissue Protein
- Abnormal Vascular Structure and Permeability

Figure 2

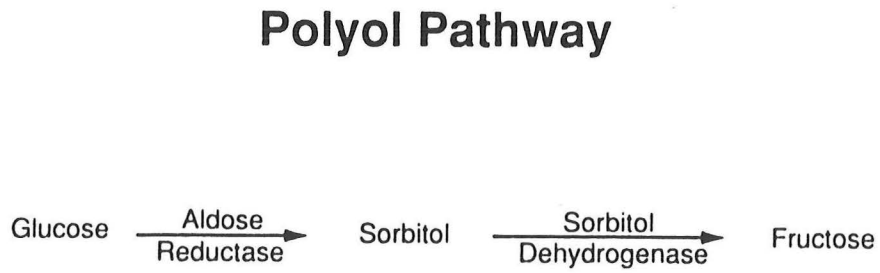
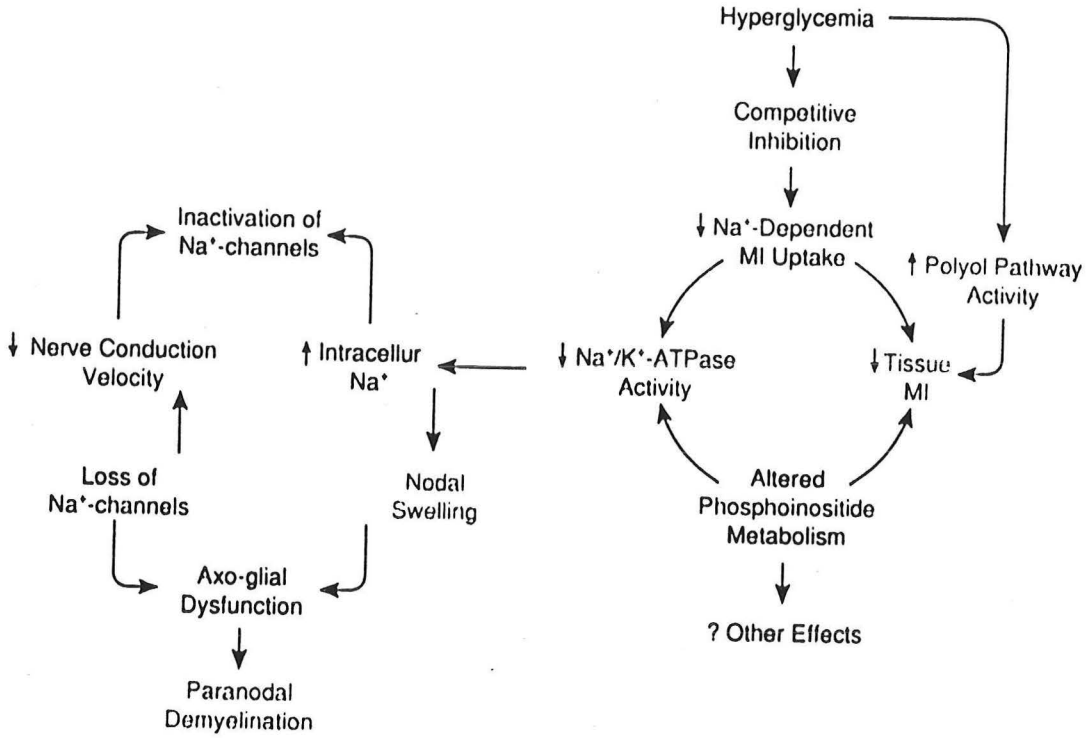


Figure 3

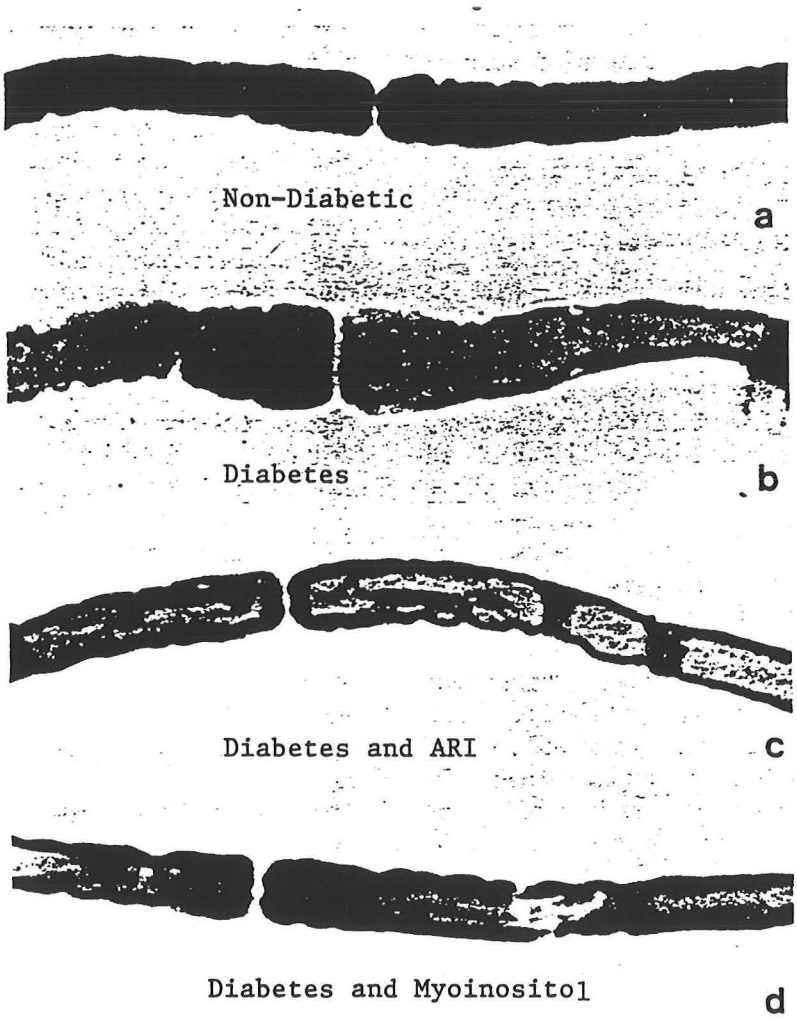
Postulated Relationship between Hyperglycemia, Polyol Pathway Myo-inositol, Na+/K+ ATPase and Nerve Conduction in Diabetes



(From: Green and Brown, Seminars in Neuro 7:18-29, 1987)

Figure 4

Effect of Insulin Deficiency, ARI Treatment, and MI Supplementation On The Appearance of the Node Ranvier of Large Myelinated Fibers From The Sural Nerve of Spontaneously Diabetic BB rats.



(from: Greene et al JCI, 1479, 1987)

The evaluation of a patient with diabetic neuropathy includes a careful history and physical examination. In addition there are a series of electrophysiological, quantitative sensory, and autonomic nervous system tests that can be done to define the severity of the neuropathy. Finally, as a last resort, a nerve biopsy can be done to establish the diagnosis and to evaluate the effect of treatment.

Electrophysiological Tests for the Evaluation of Diabetic Neuropathy

- Motor nerve conduction velocity
- Sensory nerve conduction velocity
- Amplitude and latency of evoked sensory or motor response
- Measurement of motor nerve F wave

SAMPLE PROTOCOL FOR ELECTRODIAGNOSTIC TEST

Motor Nerve Conduction Studies

Unilateral studies of either ulnar of median nerve, including F waves in the upper limbs

Unilateral studies of peroneal nerve, including F wave in the lower limb

Measurement of muscle action potential amplitude and latency at each site of stimulation and calculation of segmental conduction velocity

Sensory Nerve Conduction Studies

Unilateral studies of either ulnar or median nerve in the upper limb

Unilateral studies of either medial plantar or sural nerve in the lower limb

Measurement of nerve action potential, amplitude, and latency at each site of stimulation and calculation of segmental conduction velocity

Studies of Additional Nerves

May be necessary to characterize abnormalities based on the distribution of clinical symptoms or signs

Quantitative Sensory Tests for the Evaluation of Diabetic Neuropathy

- Vibratory Perception Threshold
- Thermal Perception Threshold
- Tactile Perception Threshold
- Electrical Threshold

Value of Quantitative Sensory Tests

- Allows for longitudinal noninvasive assessment of subclinical or clinical neuropathy
- Administers reproducible algorithms for objective testing and assessing thresholds
- Employs a forced choice method of testing
- Sensory threshold is the minimum stimulus correctly detected 50% of the time
- Coefficient of variation ranges from 15-50%

Vibratory Perception Threshold

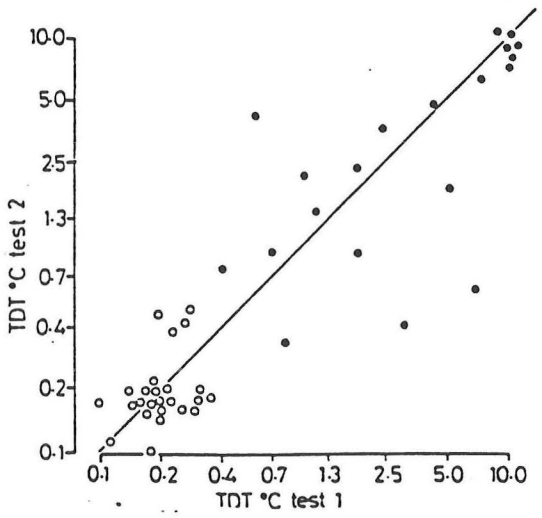
- Measures large nerve fiber integrity
- Poorer in lower extremities than upper extremities
- Abnormal in absence of clinical signs or symptoms
- Sensitive index of subclinical neuropathy

Thermal Perception Threshold

- Measures large nerve fiber integrity
- High coefficient of variation
- Has important clinical implications

Figure 5

Correlation of Thermal Perception Thresholds on Repeat Testing

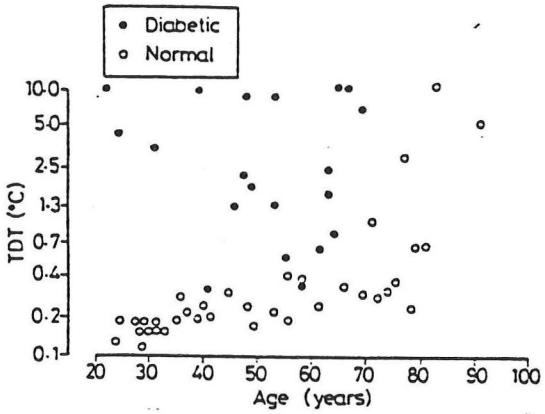


o - non-diabetic (<70 yrs old)
• - diabetic neuropathy

(from: Bertelsmann, J. Neurol, Neurosurg, & Psych 48:686, 1985)

Figure 6

Relationship of Thermal Perception Threshold and Age



(from: Bertelsmann, J. Neurol, Neurosurg, & Psych 48:686, 1985)

TACTILE PERCEPTION THRESHOLD

- Simultaneously measures combined integrity of two populations of large nerve fibers that mediate light tough and vibratory sensation
- Has a high coefficient of variation
- Reflects a patient's ability to "feel"

Table 3

NEUROFUNCTIONAL VALUES OF STUDY SUBJECTS*

	Subjects		
Neurofunctional	Diabetic (n-100)	Nondiabetic (n-20)	P value
Vibration Sensitivity Tester, U	5.9 ± 0.5	3.0 ± 0.3	<.001
Biothesiometer, U	20.8 ± 1.3	9.4 ± 0.7	<.001
Thermal Sensitivity Tester, degrees	6.3 ± 0.6	1.7 ± 0.2	<.001

*Means ± SEM

(from: Sosenko, et al, Arch Int Med, 147:1741, 1987)

Table 4

NEUROFUNCTIONAL VALUES FOR CONTROLS AND FOR PATIENTS ACCORDING TO SYMPTOM STATUS

		PATIENTS			
Neurofunctional Test	Controls (n=30)	No Symptoms (n=46)	Paresthesias (n=12)	Hypesthesia Plus Paresthesias (n=29)	Hypesthesia (n=13)
Vibration Sensitivity Tester, U	3.0 ± 0.3	4.4 ± 0.4†	3.7 ± 0.5	8.0 ± 1.0††	9.0 ± 1.3††
Biothesiometer, U	9.4 ± 0.7	16.3 ± 1.3††	17.3 ± 3.8§	27.4 ± 2.6††	25.2 ± 3.8††
Thermal Sensitivity Tester, degrees	1.7 ± 0.2	4.0 ± 0.7†	5.5 ± 1.4††	10.4 ± 1.9††	

*Mean ± SEM. All P values represent comparison with values of controls

† $p<.01$
†† $p<.001$
§ $p<.05$

(from: Sosenko et al Arch Int Med 1987)

Autonomic Nervous System Tests

- **Cardiovascular Function**
  - **RR variation to both respiration and valsalva**
  - **Blood pressure changes on standing**
- **Adrenomedullary**
  - **Erect and supine renins**
- **Pupillary Function**
  - **Light reflex latency and velocity**
  - **pupil cycle time**
- **Sudomotor Function**
  - **Bioelectric skin potential**
  - **Quantitative sudomotor axon reflex test**

Pathological findings in Diabetic Neuropathy

Triopathy of Diabetic Neuropathy

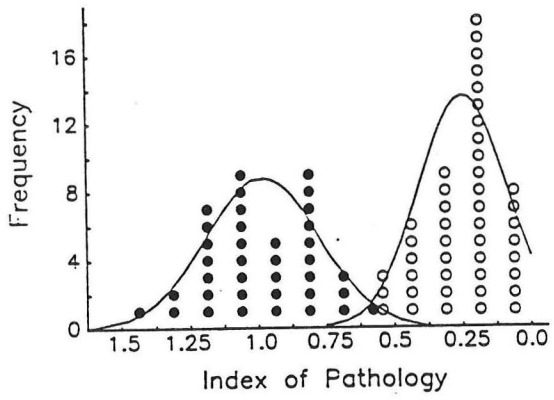
- **Fiber Loss**
- **Fiber Atrophy**
- **Specific Fiber Lesions**

Duration-Dependent Morphometric Abnormalities in Diabetic Sural Nerve Biopsies

- **Fiber Loss:** decreased fiber density
- **Fiber Atrophy:** decreased mean fiber size
  increased myelin wrinkling
- **Specific Fiber Lesions:** decreased normal fibers
  increased axo-glial dysjunction
  increased remyelinated nodes

Figure 7

Index of Pathology of Sural Nerves from Diabetic and Nondiabetic Individuals

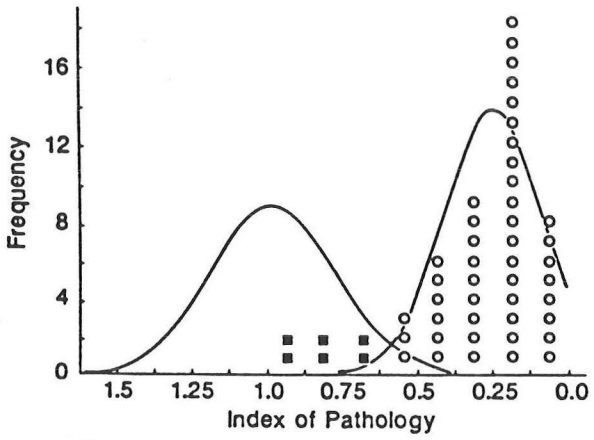


• non-diabetic
o diabetic

(From: Diabetic Neuropathy, Dyck P, ed. 1987)

Figure 8

Index of Pathology of Sural Nerves from Diabetic Patients With and Without Neuropathy

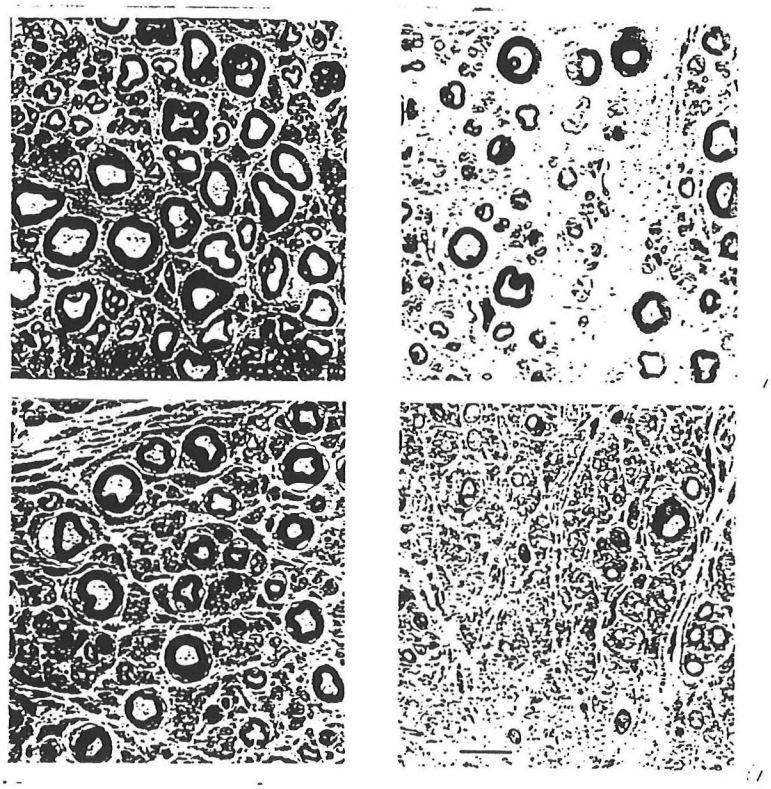


+ No neuropathy
o Neuropathy

(From: Diabetic Neuropathy, Dyck, P., ed. 1987)

Figure 9

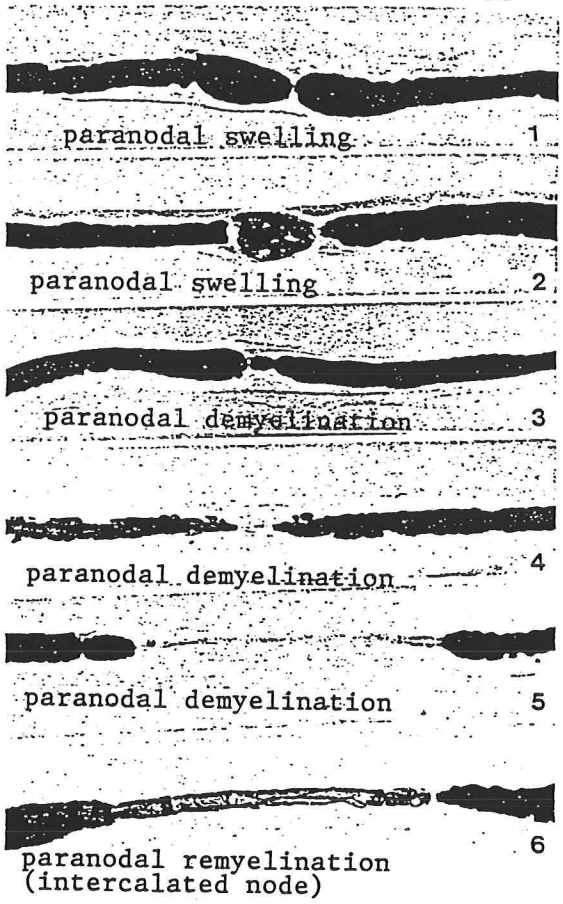
Electron Micrographs of Sural Nerves From Normal Subjects and Subjects with Diabetic Neuropathy



(from Britland et al Diabetes 39:900, 1990)

Figure 10

Effect of Diabetes on the Paranoidal Apparatus of Myelinated Fibers



(from: Sima et al JCI 81:349, 1988)

The treatment of diabetic neuropathy is less than satisfactory. Below are listed the usual treatment modalities for diabetic neuropathy as well as the presently experimented aldose reductase inhibitor drugs.

TREATMENT OF DIABETIC NEUROPATHY

- Improved Glycemic Control
- Dietary Myoinositol
- Drugs Alone or In Combination

    Amitriptyline (Elavil®)
    Carbamazepine (Tegratol®)
    Fluphenazine (Prolixin®)
    Imipramine (Trofranil®)
    Desipramine (Norpramin®)
    Analgesics

- Aldose Reductase Inhibitor Drugs (Experimental)

DALLAS DIABETES PROSPECTIVE TRIAL

Table 5

The Effect of Diabetes Control on Nerve Conduction Velocity in Insulin Dependent Diabetes

	Initial	1 year	Change	*P*
Median motor NCV				
CSII	50.7 ± 3.3	53.0 ± 3.6	+2.3	<0.01
Control	52.3 ± 3.6	52.2 ± 4.9	−0.1	>0.05
P	>0.10	>0.10		
Ulnar motor NCV				
CSII	53.6 ± 4.7	55.6 ± 4.2	+2.0	<0.03
Control	53.2 ± 4.8	53.1 ± 6.5	−0.1	>0.05
P	>0.10	>0.10		
Peroneal motor NCV				
CSII	40.3 ± 4.6	43.6 ± 4.6	+3.3	<0.001
Control	39.8 ± 6.2	39.2 ± 7.2	−0.6	>0.05
P	>0.10	<0.05		

(from: Ehle and Raskin, J. Neurol Sci 74:191:1968)

Table 6

THE EFFECT OF DIABETES CONTROL ON THE PROGRESSION OF NEUROPATHY

	Intensive* Treatment	%	Conventional Treatment
Better	62		38
Stable	14		25
Worse	24		38

*p=<0.005 vs conventional treatment (Chi square)

(From: Ehle and Raskin, J. Neurol Sci 74:191, 1986)

Table 7

THERAPEUTIC TRIALS WITH *myo*-INOSITOL

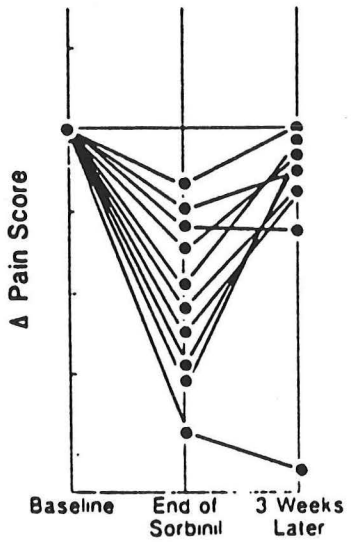
	Human Therapeutic Trials					Rat Dietary Supplementation
	Salway et al.[15] *1978*	*Gregersen et al.*[10] *1978*	*Clements et al.*[3] *1979*	*Greene et al.*[7] *1981*	*Gregersen et al.*[9] *1983*	*Greene et al. 1975*[3] *Gillon et al. 1983*[6]
Amount supplemented/day	500 mg × 2	1000 mg × 3	~1000 mg	2000–3000 mg	2000 mg × 3	1% or 650 mg/kg
Plasma inositol (mean values, μmol/1)						
Normals	58		50		20	30–70
Normals + supplementation			61		40	200
Diabetics	60	26*	38		20	30–70
Diabetics + supplementation	108	34*	46	100	60	200–250
No. treated patients	7	30	20	4	14	
Treatment period	2 wk	24 wk	16 wk	6 mo	2 mo	
Double-blind	Yes	Yes	No	Yes	Yes	
Significant improvement of nerve action potential	Yes	—	—	No	No	
Motor conduction velocity	No	No	No	No	No	
Sensory conduction velocity	No	—	Yes	No	No	
Vibratory perception threshold	—	No	—	—	No	
Clinical effect	—	No	Yes	Yes	No	

*Measured 14 hours after last drug intake.

(from: Diabetic Neuropathy, P. Dyck 1987)

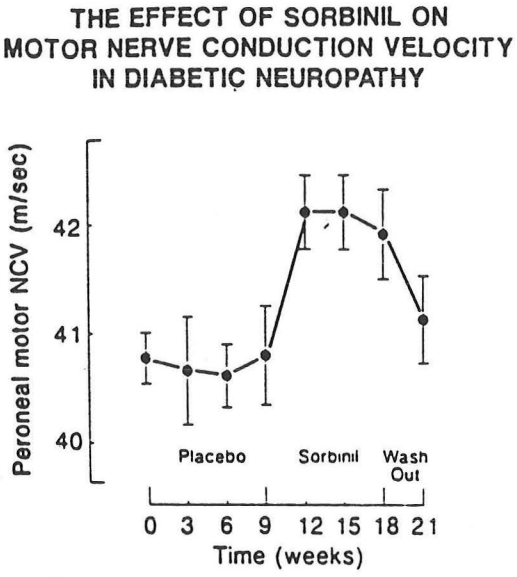
Figure 11

THE EFFECT OF SORBINIL
ON PAINFUL DIABETIC NEUROPATHY



(From: Jaspan et al Lancet 2:758-762, 1983)

Figure 12



(from: Judzewitsch, et al NEJM 308:119, 1983)

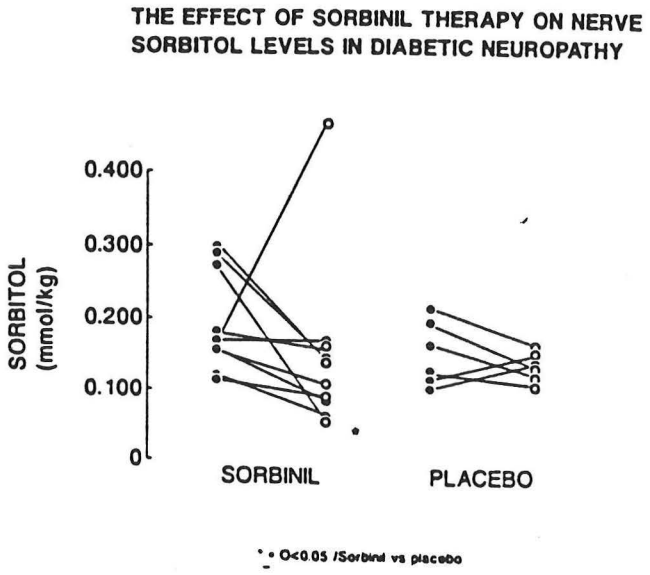
Table 8

EFFECTS OF ONO-2235 IN DIABETIC PATIENTS

	Baseline	12 Week Drug	4 week Washout
Ulnar nerve motor conduction velocity (m/s)	43.8 ± 1.8	48.9 ± 2.1	45.9 ± 2.4
Ulnar Nerve sensory conduction velocity (m/s)	47.5 ± 1.6	45.0 ± 1.3	41.3 ± 2.9
RBC Sorbitol (nmoles/gHb)	40.0 ± 6.3	23.1 ± 3.4	30.2 ± 2.9
HbA1c (%)	8.9 ± 0.8	7.3 ± 0.6	8.1 ± 0.5

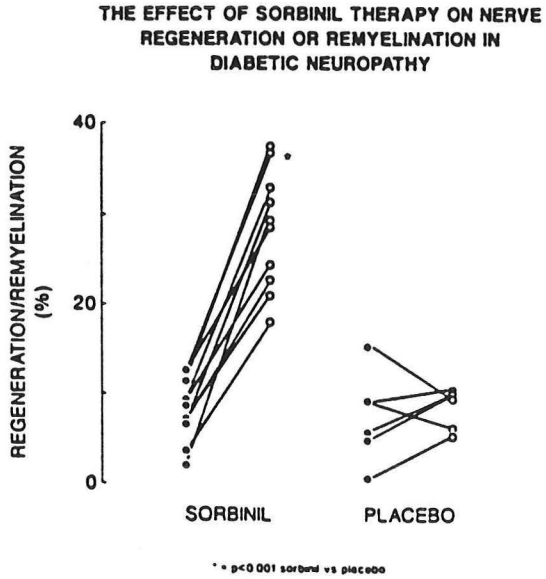
Adapted From Hotta et al. Diabetes 34(suppl 1):98A, 1985.)

Figure 13



(from Sima et al NEJM 319:548, 1988)

Figure 14



(from Sima et al NEJM 319 548, 1988)

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