Gastroparesis Diabeticorum

Thesis
Submitted for Partial Fulfilment of Master Degree in Internal Medicine

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1994

Acknowledgment

First of all thanks to God

I would like to express my deepest gratitude and sincere thanks to **Professor Dr. Mohammed Abdelfattah**, Professor of Internal Medicine, Ain Shams University, for providing me the opportunity to work under his guidance and for his generous support, valuable observations and advice throughout this study.

I was fortunate to carry this work under the guidance of **Professor Dr. Hussein El Damassy**, Professor of Internal Medicine, Ain Shams University who offered me a lot of his experience.

Greatly acknowledge **Professor Dr. Heba Khalil El Dib**, Professor of Radiology, Ain Shams University, for generous help and kind care she offered me throughout the practical part of this work.

Many thanks to **Dr. Mohammed Hammed**, Lecturer of Internal Medicine and Endocrinology, Ain Shams University, for his kind help and support.

Finally, I would like to thank every one who extended a helping hand during the process of this research especially **Professor Dr. Raouf Wahba**, Professor of Radiology in Military Medical Academy, who offered much of his time, experience and support to accomplish this work.

Manal Boulos

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INTRODUCTION

Diabetic neuropathy is now regarded as the most common cause of neuropathy in the Western World. (Green et al ,1990)
Diabetic neuropathy contributes to many cases of limb amputation and erectile impotence in diabetic patients, and as such remains unsolved medical problem of enormous proportions.
Diabetic neuropathy is actually composed of several distinct syndromes with different anatomical distribution , clinical course and possibly underlying pathogenetic mechanisms (Green et al , 1990) .

The overall prevalence of diabetic neuropathy is uncertain but appears to parallel the duration and severity of hyperglycaemia in both insulin dependent diabetes (IDD) and non insulin dependent diabetes (NIDD) . It's rarely found before the fifth year of diabetes except in NIDD where preexisting asymptomatic hyperglycaemia is difficult to exclude and it ultimately affects up to 50% of patients with long-duration diabetes mellitus (Sima et al ,1990) .
Diabetic neuropathy complicates the secondary forms of diabetes such as those resulting from pancreatectomy , non alcoholic pancreatitis and hemachromatosis (Thomas et al ,1987); A finding that supports a common pathogenetic mechanisms for diabetic neuropathy involving hyperglycaemia and / or insulin deficiency .

A close link between severity and / or duration of hyperglycaemia with the development of diabetic neuropathy would support intensified diabetic control as potential preventive measure and implicate glucose or insulin related metabolic factors as important pathogenic elements in the disease process .

Gastric neuropathy secondary to diabetes was first described by Rundles in 1945 , and became widely recognized after 1958 when Kassander dubbed the condition "Gastroparesis Diabeticorum" (Kassander , 1958) .

Patients with gastric motility problems usually have an associated peripheral neuropathy or combined peripheral and autonomic neuropathies (Glouberman , 1977) ; However , gastroparesis may be the only manifestation of their neuropathy.

Before making the clinical diagnosis of gastroparesis diabeticorum mechanical gastric outlet obstruction or presence of gastric bezoar should be excluded (Green et al ,1990) .
It's the emptying of indigestible solids that seems to demonstrate the most profound abnormalities in gastric emptying (Feldman et al 1984) ; Thus troublesome post-prandial hypoglycaemia and then hyperglycaemia are more likely to occur with solid foods in cases of diabetic gastroparesis (Green et al , 1990)
This occurs because of abnormalities of the interdigestive migratory motor complex , a finding similar to that found after surgical vagotomy (Malagelada et al , 1980) .
Pharmacological and histological evidence for vagal denervation has been demonstrated in patients with diabetic gastroparesis (Feldman et al , 1983) ; Although other contributory factors as hyperglycaemia and hormonal changes have been suggested . (Malagelada et al , 1986)

Ultrasound has been used to measure gastric volume providing non- invasive determination of gastric emptying time .

The medical management of patients with gastric hypomotility usually includes the administration of prokinetic agents ; Although antiemetic phenothiazines or bethanechol may provide some relief ; The latter don't accelerate gastric emptying in the vast majority of patients and often produce unacceptable side effects (Sleisenger, 1989)

AIM OF THE WORK

The aim of this work is to study the effect of diabetic control and the prokinetic drugs on the gastric motility in diabetic patients .

DIABETIC NEUROPATHY

PATHOGENESIS
(A) Biochemical , pathobiology and pathophysiology of diabetic neuropathy (Metabolic hypothesis)

Neuropathy and other long term complications of diabetes are now generally thought to result from the interaction of multiple : metabolic, genetic and environmental factors (Green et al , 1990).

The observations that poorer metabolic control is a risk factor for the development of neuropathy and that more vigorous metabolic treatment improves nerve function in diabetic subjects and that hyperglycaemia and its metabolic consequences have been linked to abnormal nerve function and biochemistry in laboratory animals, have lead to search for possible biochemical mechanisms by which insulin decrease and / or hyperglycaemia might adversely affect peripheral nerve (Green et al , 1990).

At present there are four distinct but not usually exclusive and possibly interrelated metabolic hypothesis for the pathogenesis of diabetic neuropathy which include :

(a) Sorbitol-myoinositol Na+-K+-ATPase hypothesis
(b) Hypoxia-ischaemic hypothesis
(c) Non enzymatic glycation hypothesis
(d) Insulin / neuronotrophism / axonal transport hypothesis .

(a) The sorbitol-myoinositol Na+-K+ ATPase hypothesis and the biochemical basis of acute conduction slowing

Glucose acts virtually as the sole source of energy in peripheral nerve as well as the brain , glucose enters the nerve cell through an insulin independent pathway and is used in production of ATP (Bays & Pfiefer , 1988).

Although ATP production does not appear impaired , experimental diabetic neuropathy demonstrates a reduction in ATP utilization thought to be secondary to decrease Na+-k+-ATPase activity (Geen et al , 1990) ; Decrease Na+-K+-ATPase activity has been shown to correlate to decrease myoinositol concentration within peripheral nerve in diabetic animals (Green et al , 1984).

Metabolic studies in diabetic animals have revealed a series of related biochemical and biophysical defects that may interact in cyclic re-inforcing fashion to provide a cogent link between acute hyperglycaemia and rapid reversible slowing nerve conduction (Green et al , 1987).

The evidence that the slowing of nerve conduction in acute experimental diabetes results from metabolic alternations caused by insulin decreasing and hyperglycaemia (Green et al , 1985) , is readily reversible with metabolic correction (Green et al , 1985) , and occurs in the absence of widespread evidence of demyelination of axonal degeneration (Fukuma et al , 1978) prompted a search for an underlying biophysical / metabolic mechanism (although subtle structural changes are indeed present) (Green et al 1987) .

Therefore early and reversible slowing of nerve conduction in animal diabetes has been attributed to acute metabolic disturbance that occur in axon , Schwan cells and /or their endoneurial environment due to acute insulin reduction .

Hyperglycaemia results in at least three major metabolic consequences deleterious to the nerve cell including : (Fig. 1-A).

(a) Glycosylation of cellular proteins, may result in structural and functional changes (Bays & Pfiefer, 1988).

(b) Competitive inhibition of myoinositol uptake results in decrease myoinositol concentration , altered membrane phospholipids metabolism and so, abnormal cellular response : one of these abnormal responses is reducing Na+-K+-ATPase activity which not only results in nerve cell dysfunction but also decrease the active myoinositol uptake resulting in self re-inforcing cycle (Fig. 1-B)

(c) Finally enhanced aldose reductase activity may also play a role in nerve cell myoinositol concentration (Bays & Pfiefer , 1988).

The polyol related defects in metabolism results in structural abnormalities (Sima et al , 1988).
Aldose reductase enzyme increase the activity of polyol pathway and converts glucose into sorbitol utilizing NADPH which leads to depletion of reduced glutathione (GSH) that protects against oxidation inactivation of critical membrane proteins i.e. Na+-K+-ATPase

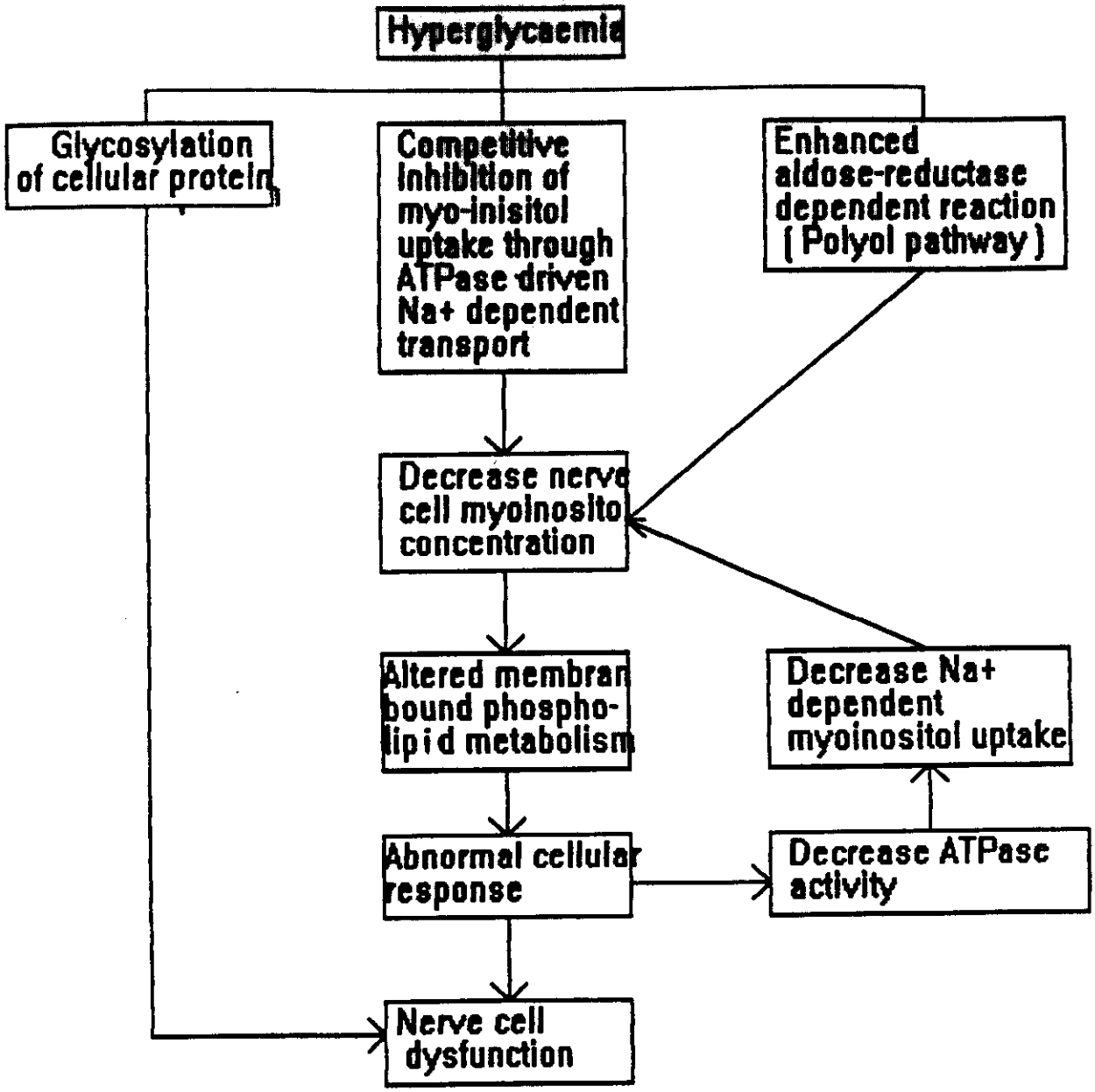


Fig. 1 - A (Bays and Pfiefer 1988)

(Showing a metabolic scheme of diabetic neuropathology , hyperglycaemia results in at least three major consequences deleterious to the nerve cell.)

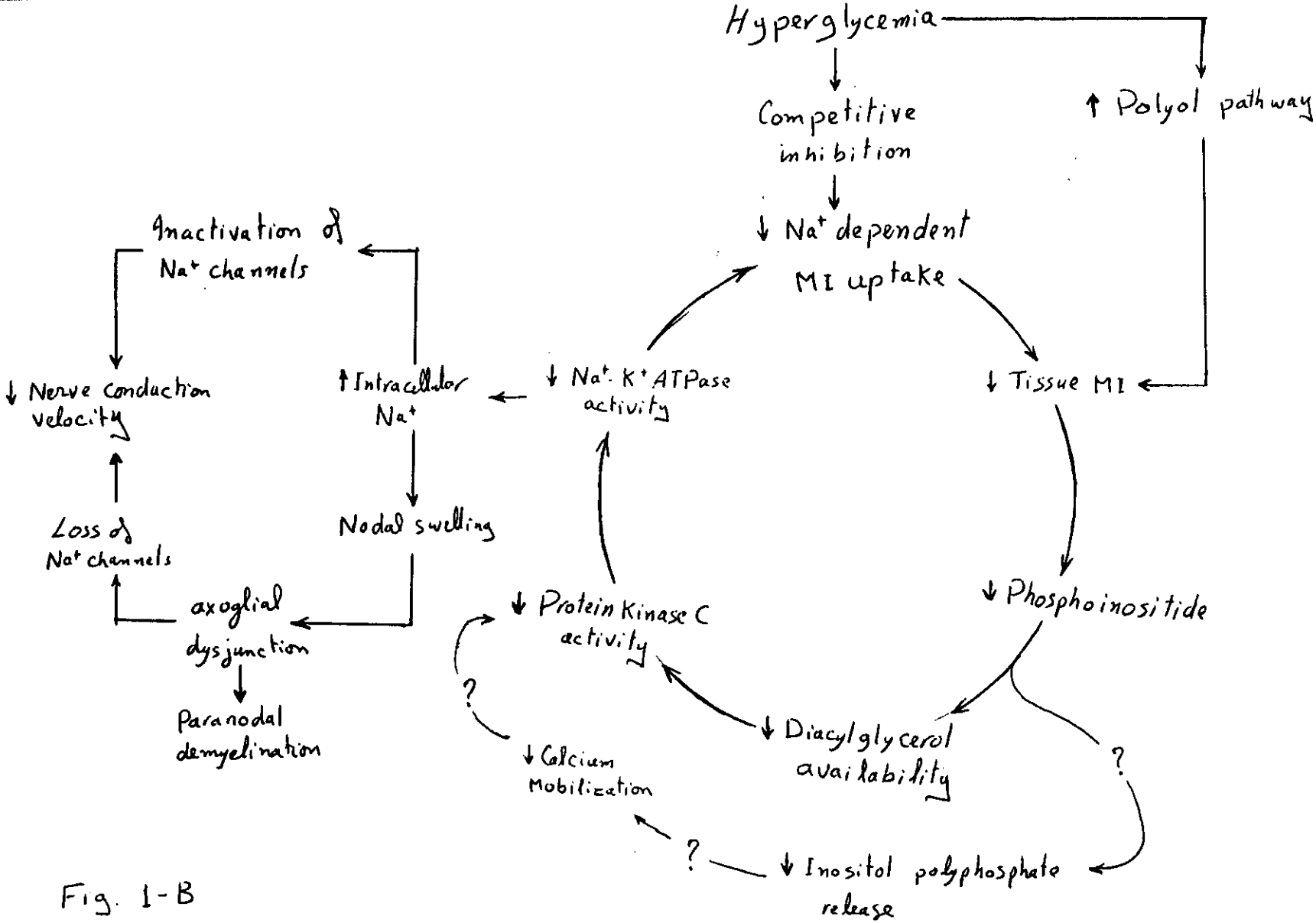
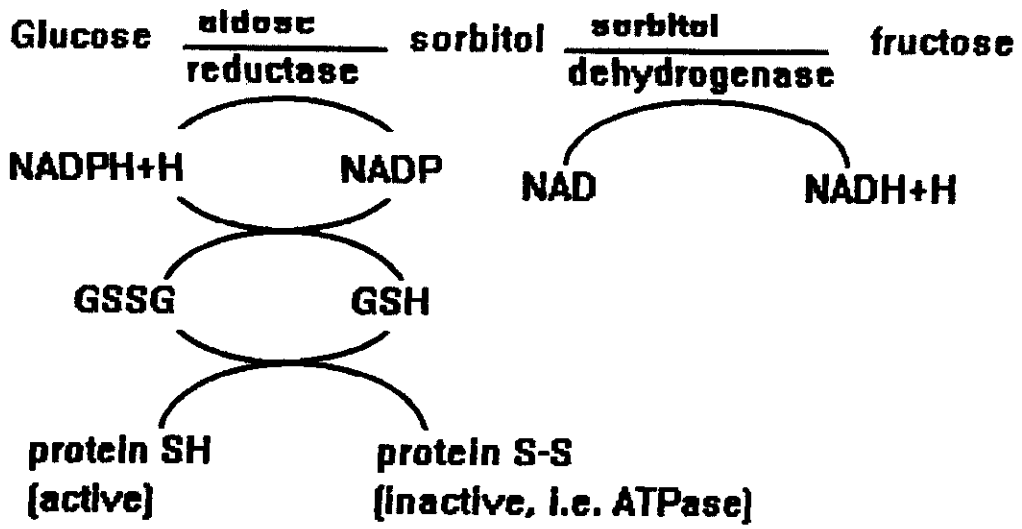


Fig. 1-B

Shows proposed self-re-inforcing metabolic defect involving polyol pathway activity, phosphoinositide metabolism, protein Kinase C and sodium-potassium ATPase (Na^+-K^+-ATPase).

MI = myoinositol

(Green et al., 1990)



(The polyol pathway)

For the last point, the aldose-reductase inhibitor was able both to reduce the accumulation of sorbitol and fructose in the sciatic nerve and to prevent the fall in tissue myoinositol concentration suggesting an important metabolic interaction in improving nerve function in human and animal diabetes (Green et al , 1984) .
Furthermore dietary myoinositol supplementation to diabetic rats prevents myoinositol depletion in nerves and normalizes nerve conduction and Na+-K+-ATPase activity (Green et al 1987).

Osmotic hypothesis :

While there's good evidence that accumulation of sorbitol (which diffuses poorly across cell membrane) in the lens results in osmotic over-hydration leading to Cataract formation (Gabbay, 1973) ; The qualities of sorbitol , glucose and fructose in diabetic nerve would only lead to osmotic effect harmful to peripheral nerves , if the accumulation of sorbitol occurred solely in the Schwan cell itself .

Direct extrapolation of this osmotic hypothesis from the lens to diabetic peripheral nerve is problematic for several reasons : (Green et al , 1990) .

1) The diabetic peripheral nerve accumulate only micromolar rather than millimolar concentration of sorbitol which are unlikely to be directly osmotically significant unless high localized anatomically (Clements , 1979).
2) The correlation of accompanying depletion of myoinositol reverses most of the effects of increase polyol pathway in diabetic nerve without influencing nerve sorbitol concentration (Green et al , 1987) .

Lipid metabolism :

Peripheral nerve myelin is a complex of lipid consisting of triglyceride , cerebrosides , cholesterol and sphingomyelin .
There's quantitative changes in myelin composition and altered myelin synthesis (demyelination) because of abnormal lipid metabolism (Hosking et al , 1978).

The enzyme system acetic thiokinase was found to be deficient in diabetic neuropathy (Field & Adams , 1964) ; This enzyme is necessary for acetylation of CoA as a first step in synthesis of fatty acid from acetate , so it does seem that in the diabetic neuropathy fatty acid synthesis is impaired ; The consequence is the decreasing levels of lipids and altered patterns of lipid composition with accumulation of complex lipid inclusion bodies in cytoplasm of Schwan cells (Bishoff , 1968) .

Abnormalities in the lipid composition of diabetic nerves include reduction in cholesterol , cerebrosides , phosphatidyl serine and inositol ; Since myelin is rich in these lipids , any changes in their composition would be expected to affect myelin synthesis (Scarpello , 1984) .

(b) Ischaemic-hypoxic hypothesis

Fagerberg 1959, described the presence of arteriolar lesions in sural nerve specimen, obtained either by biopsy or an autopsy, in which the caliber of vessel was decreased and the walls thickened , hyalinized as a result of accumulation of PAS+ve material. Similar changes were also found in the peripheral autonomic nerves .
These abnormalities are those of non atheromatous "diabetic angiopathy" defined by Goldenberg et al , 1959.

All of patients with diabetes for twenty years or longer had capillary basement membrane thickening (Williamson , 1971)

Endoneurial capillaries of patients with diabetic neuropathy exhibit increase endothelial cell proliferation and increase capillary closure that correlates with the severity of neuropathy (Dyck et al , 1986).

The endoneurial blood flow of diabetic rats has been shown to be 33% that of healthy rats, and endoneurial oxygen tension is less (Tuck et al , 1984).

The potential causes include :

a) The vasculopathy just described.
b) Hyperviscosity related to dehydration or hyperfibrinogenemia.
c) Decrease deformability in diabetic erythrocyte.
d) Increase adherence of diabetic erythrocyte to endothelial lining of capillaries.
e) Shunting of blood because of autonomic changes in the vasculature.
f) Platelets and fibrin plugging . (Tuck et al , 1984).

Because of this pathology and because of hypoxia may reproduce many of the abnormalities found in diabetic neuropthy,

some investigators believe that capillary pathology may be a primary factor in diabetic neuropathy (Tuck et al , 1984).

A concurrent reduction in creatine phosphate energy stores and an increase in tissue lactate is consistent with endoneurial hypoxia and a partial compensatory switch to non oxidative glycolytic metabolism.

However in-vitro studies by Green and Winegard using defined nerve preparation from acutely diabetic rabbits had previously demonstrated that reduced creatine phosphate levels and increase lactate concentration in diabetic nerve persisted during in-vitro incubation in 95% oxygen (Green and Winegard , 1981).

Detailed morphometric analysis of endoneurial vessels in nerve biopsies from diabetic patients and carefully age matched control biopsies revealed no increase in frequency of capillary closure by endothelial swelling or endothelial cell proliferation in diabetic nerves, versus age matched control nerves. However both diabetic and control nerves showed an increase in the frequency of capillary changes with advanced age .

On the other hand vascular perfusion distance (the distance across the vascular wall) are significantly increased in diabetic subjects as compared with age matched controls (Sima et al , 1988).

Endothelial-cell-tight junctions, the structural substrate for the blood nerve barrier, appear to be decreased in diabetic nerves, possibly suggesting an increase permeability of endoneurial vessels in diabetes, these findings suggest that changes as capillary closure due to swelling and proliferation of endothelial cells are not diabetic related but age related (Sima et al , 1988).