Section IV - Metabolic Diseases and Endocrine Function

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Chapter 17. Chronic Complications of Diabetes

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Introduction - Before the discovery of insulin, the greatest threat to the diabetic patient was sudden death from coma caused by acidosis. From 1894 - 1915, 64% of all diabetic patients died in coma.[1] After insulin became generally available, diabetic coma as cause of death fell to 8.3% between 1922 - 1936, and to 1% between 1950 - 1968.[2] However, diabetic coma has been more than supplanted by the composite category of cardio-renal disease, which now accounts for about 80% of total deaths of diabetics.[3] The effects of long-term diabetes were thus unmasked, and, by 1950, it was evident that, whilst prolonging life, insulin treatment cannot prevent the appearance of disabling complications of chronic diabetes,[4] such as retinopathy, nephropathy, neuropathy, cataracts and generalized atherosclerosis.

Diabetic Microangiopathy - One of the most striking features of diabetes is the slow and progressive development of vascular abnormalities, particularly in the small blood vessels.[5] Diabetic retinopathy and nephropathy are, thus, rarely found at the onset of the disease.[6,7] The slow, progressive development of vascular changes during the years of incompletely normalized metabolism suggests that diabetic angiopathy is secondary to the metabolic abnormality(ies) characterizing diabetes mellitus.[5] According to McMillan,[8] the development of diabetic microangiopathy proceeds through several stages: at the onset, blood flow is disturbed in several body areas, and dilatation of small veins increases slowly until, in established diabetes, it becomes irreversible. Later, periodic arteriolar vasoconstriction sets in. As diabetes becomes long-standing, sclerosis of the vessels of the entire microcirculation develops which, finally, results in progressive decompensation of the microcirculation.

The following categories of alterations appear to contribute to diabetic angiopathy: (1) Basement membrane thickening, although the role remains unclear; however, hydroxylysine-linked glucosylgalactose units in basement membranes appear to be greatly increased in diabetes.[9,13] (2) Functional alterations, e.g. impaired phagocytosis,[14] abnormal lymphocytes,[15] and increased levels of lysosomal enzymes,[16] may affect the microcirculation by altering passage of blood, vascular tone and removal of basement membranes. (3) Altered cell metabolism, e.g. increased activity of the polyol pathway (see below).[17] (4) Altered blood flow characteristics, e.g. enhanced erythrocyte aggregation, increased plasma viscosity,[18] and increased resistance to blood flow.[8] (5) Increased sensitivity of platelets to aggregation correlating with elevated levels of von Willebrand's factor,[19] possibly due to excess of growth hormone (GH). (6)

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Impaired oxygen transport, e.g. by $HbAI_c$, a minor variant of hemoglobin with greater avidity for oxygen than normal hemoglobin; $HbAI_c$ is about twice as abundant in insulin-treated diabetics as in control subjects and accounts for about 10% of total erythrocyte hemoglobin.[20,21] Increased erythrocyte 2,3-diphosphoglycerate, directly related to plasma phosphate, can compensate for impaired oxygen release by decreasing the oxygen affinity of HbA.[22,23] (7) Altered hormone production, e.g. of GH,[24] whose levels are 3-4 times higher in juvenile diabetics than in normal subjects.[5] The significance of increased glucagon levels in diabetic hyperglycemia is still controversial.[25] In addition to increasing glucose output by the liver, glucagon stimulates the formation of "acute phase" proteins,[26] thus possibly contributing to altered blood viscosity.

The pattern of deterioration of the microcirculation in diabetes is, however, not satisfactorily explained by any single category of these alterations. The slow progression of diabetic microangiopathy favors a mixture of adaptation and degeneration in response to several strains placed upon the microcirculation by the diabetic state.[8]

Diabetic Retinopathy is present in 60-80% of long-term diabetics. Five to 10% of diabetics surviving 20 years from the time of diagnosis will be blind, mostly from retinopathy, which ranks as leading cause of blindness in Great Britain[28] and the U.S.[29] In 1970, in the U.S., 8.5/100,000 persons were reported to be blind from diabetic retinopathy.[30] The prevalence of retinopathy increases with the duration of diabetes. Retinopathy is conventionally divided into a simple or non-proliferative, and a proliferative category. Non-proliferative retinopathy is characterized by alterations occurring in the original retinal vessels, e.g. microaneurisms, hemorrhages, exudates, and changes in retinal veins. Changes superimposed on the simple variety constitute proliferative retinopathy, e.g. new vessel development, vitreous hemorrhage and fibrous tissue proliferation, leading to traction retinal detachment. Proliferative retinopathy has a poor prognosis for retention of vision and, after five years, 43% of juvenile-onset and 60% of adult-onset diabetics become blind.[31] Proliferative retinopathy is associated with other long-term vascular complications, such as nephropathy and coronary heart disease. The development of retinopathy is accelerated by high blood pressure and low intraocular pressure.[32] The cause of diabetic retinopathy is unclear, and the mechanism of the early breakdown of the blood-retinal barrier is unknown. Several mechanisms have been proposed to explain the development of capillary occlusions, e.g. increased platelet aggregation,[19] decreased fibrinolytic activity,[33] increased plasma viscosity,[18] elevated $HbAI_c$,[20] and increased microvascular protein passage and deposition in the walls of the arterioles.[34] Since the introduction of hypophysectomy for diabetic retinopathy, in 1953, attention has been placed on GH as a causal factor in the development of diabetic angiopathy;[5] however, GH levels were not higher in juvenile diabetics with proliferative retinopathy than in those with minimal, or no retinopathy.[35] The question requires further study.

Diabetic Nephropathy - The kidneys of the diabetic patient are a target for structural damage which mainly involves the small blood vessels, i.e.

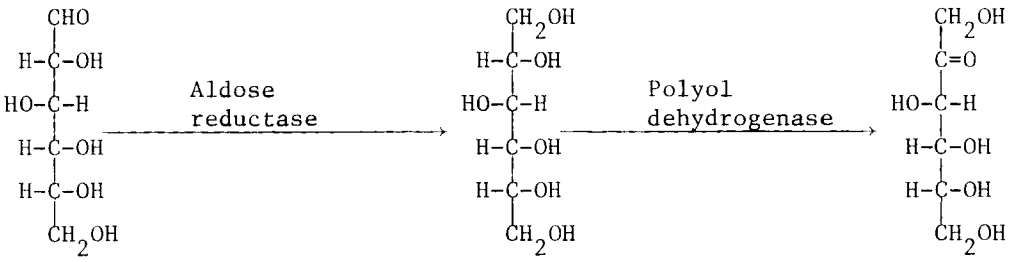
the glomerular capillaries and the associated arterioles, leading successively to proteinuria, impaired renal function and hypertension. There is a close correlation between the diabetic microvascular changes in the kidney and in the retina; however, while retinopathy is readily detected by ophthalmoscopy, renal involvement may cause few immediate clinical features until well advanced.[36] The earliest clinical feature of nephropathy is symptomless proteinuria. The time-interval between the detection of proteinuria and the deterioration of renal function varies considerably. In a recent retrospective analysis,[37] nephropathy accounted for 53% of deaths among juvenile diabetics; the mean duration of diabetes to the onset of proteinuria was 17.3 years and the duration of life after the onset of proteinuria was 4.8 years. The first symptom of nephropathy usually consists of peripheral edema, probably worsened by vasomotor defects caused by peripheral neuropathy; finally symptoms characteristic of renal failure develop, with fluid retention as one of the major problems.[38] In man, diabetic nephropathy is irreversible: once the clinical signs of nephropathy become evident, the natural course is inexorably progressive to death. In the later stages, the rate of progression is accelerated by the appearance and progression of other complications of diabetes, such as retinopathy, neuropathy and cardiovascular disease.[37] The factors causing diabetic nephropathy and those determining its progression are still unknown, and there is no convincing evidence that poor glucose control causes diabetic nephropathy or in any way alters its course.[39]

Diabetic Neuropathy of varying degree probably afflicts the majority of people with recognized diabetes mellitus. Clinically manifest problems which accrue from diabetic neuropathy are evident in over 50% of the American diabetic population.[40] The varying underlying pathogenic mechanisms and the resulting diversity of clinical manifestations suggest that, in diabetes, there are neuropathies - rather than a single entity of neuropathy. The spectrum of involvement is wide, with virtually every organ system at risk.[41] Ellenberg has broadly divided the manifestations of diabetic neuropathy into peripheral and visceral, and their subdivisions.[41] While peripheral neuropathy is the most common form, visceral neuropathy is also highly significant and may affect every part of the gastrointestinal tract, the genitourinary tract,[42,43] sexual function,[44] as well as the autonomic[45] and, possibly, the central nervous system.[46] Possible explanations for the development of diabetic neuropathy are based on theories of either microangiopathy and occlusive vascular disease, on abnormalities of metabolism, or on both.[47] Recent investigations suggest that chronic metabolic disturbances[48] are an underlying factor in nerve affection.[41] The most prominent lesion of the peripheral nerve fibers affected by diabetic neuropathy is segmental demyelination.[49] Since the myelin sheath is formed by spiral folding of Schwann cell membranes, diabetic neuropathy may, in fact, result from a metabolic defect of the Schwann cell.[49] The characteristic decrease in conduction-velocities of peripheral motor and sensory nerves may be due to segmental demyelination. Recently, it has been postulated that Schwann cell loss and abnormalities may be caused by increased aldose reductase activity resulting in intracellular accumulation of sorbitol (see below).[17] An interesting relationship between impaired motor-nerve-conduction-velocity and decreased

myoinositol concentration has been found in the nerves of streptozotocin-diabetic rats.[48] Furthermore, decreased myoinositol and increased sorbitol levels have been found in cerebrospinal fluid of patients with diabetic polyneuropathy.[50]

Diabetes and Cataract - Although it is generally believed that diabetes causes cataracts, there is no scientific study supporting this view.[51] Nevertheless, in contrast to the lack of data on a correlation between diabetes and prevalence of cataracts, several hospital surveys indicate that diabetics undergo cataract extraction 5 to 9 times more frequently than non-diabetics.[51,52,53] It thus appears that the rate of cataract development in the diabetic is increased, thus resulting in cataract extraction at an earlier age.[54] In Britain, approximately one diabetic becomes blind from cataract for every three becoming blind from retinopathy;[55] in Canada, the proportion is one to four.[56] Recent evidence implicates aldose reductase as the key factor in the initiation of diabetic cataract (see below.)[53]

Role of Aldose Reductase - The clinical expression and the development of diabetic complications depend mainly on the duration of diabetes; current means of therapy are therefore, at best, only partly effective. It is pertinent that the tissues (lens, nerve, retina, kidney, blood vessels and islet cells) afflicted by diabetic manifestations do not require insulin for uptake of glucose. These tissues are thus exposed to any circulating levels of glucose without a protective barrier.[17] Recent experimental evidence suggests that the metabolic disposition of excess glucose in some of these tissues proceeds via the polyol pathway, and that the polyol produced initiates the changes leading to the development of diabetic complications. The polyol pathway consists of two enzymes: aldose reductase (AR), catalyzing the NADPH-dependent reduction of glucose and other aldoses to the corresponding polyol, and polyol dehydrogenase, catalyzing NAD-dependent oxidation of sorbitol to fructose.



D-glucose Sorbitol D-fructose

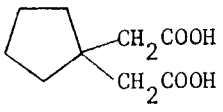
The polyol pathway was first identified in seminal vesicles,[57] and later in lens[58] and other tissues.[59,60,61] The physiological function of the polyol pathway in these tissues remains unknown. The possible role of AR in the development of diabetic complications is based largely on the role of AR in the initiation of sugar cataracts.

The lens is uniquely vulnerable to diabetic conditions for the following reasons:[51] (1) since glucose uptake does not depend on insulin,[62] the lens is exposed to ambient glucose concentrations; (2) metabolism of glucose via the glycolytic pathway is controlled by hexokinase,[63] whose activity is low, but avidity for glucose is high:[64] hexokinase is thus easily saturated, making any excess glucose available to AR;[58,62,65] (3) as affinity of AR for glucose is low,[66] appreciable AR activity is attained only at high intracellular concentrations of glucose, as in diabetes; (4) sorbitol is not efficiently metabolized, e.g. by polyol dehydrogenase,[67] and does not readily diffuse through cell membranes, hence accumulates. The resulting increased osmotic pressure within the lens causes water uptake and lens swelling leading to loss of transparency, i.e. cataract. These events form the basis of Kinoshita's osmotic hypothesis,[68] which attributes the association between increased polyol levels and cataractogenesis[58,65] to the osmotic effects of increased polyol levels in a lens exposed to high sugar concentrations.[69] The concept has been substantiated by biochemical studies in vitro[51] and in laboratory animals by the use of AR inhibitors.[70,72] The identification of sorbitol in the lens of the human diabetic, whether cataractous or not, suggests that the sequence of events postulated by the osmotic hypothesis also occurs in man.[73]

The intriguing question is whether the consequences of increased AR activity in hyperglycemia also play a role in the development of other diabetic complications. In neuropathy, the case for the osmotic hypothesis is supported by the presence of AR in Schwann cells of peripheral nerves,[74] and the finding that, both in diabetic[75,76] and galactosemic rats,[77,78] polyol accumulates in the sciatic nerve, and that the accumulation was prevented by an AR inhibitor.[71] Furthermore, the defect in motor-nerve-conduction-velocity, occurring in both human[79] and experimental diabetes,[80] is controlled with insulin, and occurrence of a similar defect in galactosemic rats was delayed by an AR inhibitor.[80] Osmotic damage resulting from sorbitol accumulation has been suggested to be responsible for diabetic capillary disease in the retina.[81] AR has been found in the retina,[60] and sorbitol was found to accumulate in the retina of diabetic rats, albeit at low levels.[82] In addition, tissue cultures of mural cells from human retinal capillaries contain AR and accumulate sorbitol when incubated in high glucose medium.[83] Except for the localization of AR in the papilla of the kidney,[60] no information is available on the possible role of AR in nephropathy. Thus, the presently available evidence supports the postulate that AR is involved in the initiation of diabetic cataracts and, possibly, diabetic neuropathy.

AR Inhibitors - If AR is indeed responsible for initiating the development of some diabetic complications, then inhibition of AR may represent a pharmacological approach to their delay and, possibly, prevention. The approach is attractive because AR appears to play an important role only in a non-physiological state, such as created by high blood glucose levels. The first compounds reported to inhibit AR in vitro were medium-chain aliphatic fatty acids (C_6-C_8)[66] and, later, tetramethyleneglutaric acid (1), which was used to corroborate the osmotic hypothesis in vitro.[70]

Alrestatin (AY-22,284) (2), an orally active AR inhibitor, decreased polyol accumulation in lens and sciatic nerve of galactosemic and diabetic rats,[71] and suppressed cataract formation when administered either orally,[71] or topically.[84] AR inhibitory activity *in vitro* has also been reported for a series of flavonoids,[85,86] and the most potent compound, quercitrin (3), delayed the appearance of cataracts in the diabetic degu,[87] a South American rodent prone to rapid cataract development. AR inhibitors are thus useful to further elucidate the role of AR in the development of chronic diabetic complications.



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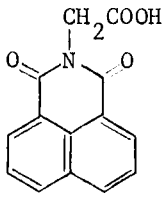

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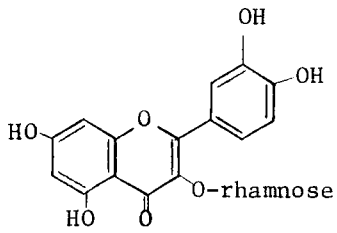

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