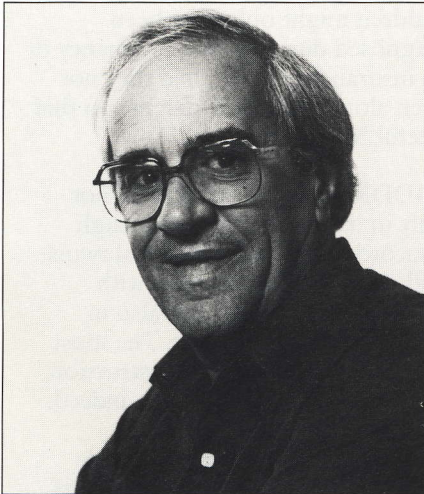


Diabetes Mellitus: III Non-insulin-dependent diabetes mellitus

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Curriculum vitae

Dr LI Robertson studied at Cape Town University where he received the MB ChB in 1954. He did some post-graduate training at Mc Cord Zulu Hospital (Durban) and St Monica's Home (Cape Town), received the MFGP (SA) in 1975 and has been in Private Family Practice in Durban since 1957. He has a wide interest in different fields of medicine, and at the moment still holds the following posts: Senior Medical Officer - Diabetes Dept (Addington Hospital), Medical Director - Child Guidance & Research Centre (Durban/Westville), Medical Director - Institute of Human Sexuality. He also makes time to serve on several committees. He is Vice-chairman of the council of SA Academy of Family Practice/Primary Care; he is an elected member of the SA Medical and Dental Council and gives time to many other committees serving the community. Dr Robertson has presented many papers at Medical Conferences, has published several scientific papers and contributed to two medical textbooks. He is married to Barbara and they have 4 children.

Summary

A review of non-insulin-dependent diabetes mellitus or Type II diabetes, wrongly referred to as "maturity-onset diabetes" or "mild diabetes". Patient reports illustrate why these names are indeed misconceptions of the disease. A few aspects dealt with, are the varying prevalence rates in different parts of the world, hereditary and environmental factors, clinical features, prognosis and outcome of the disease.

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Also known as Type II diabetes, (these terms having replaced the older 'maturity-onset diabetes'), non-insulin-dependent diabetes (NIDDM) is the larger subgroup of primary diabetes, accounting for close to 80% of the diabetic population. The essential aspect differentiating NIDDM from IDDM is the fact that the former group's lives are not dependent on exogenous insulin, even though, in the course of time, a high percentage will come to require insulin for improved control. Initially, however, most NIDDM patients can achieve adequate glycaemic management with a combination of dietary restriction and an increase in simple, recreational exercise.

Gestational diabetes and the badly-named (and, to my mind, dubious)

'maturity-onset diabetes in the young' (or MODY), first described by Tattersall¹ are probable variants of NIDDM, but the type following on the use of large doses of steroids does not deserve a separate category as this almost certainly merely represents the early subclinical phase in a patient on the way to NIDDM, whose clinical onset of diabetes has been brought forward some months or years by the temporary excess of circulating counter-regulatory hormones.

One of the common misconceptions pervasive in both lay and medical circles is that NIDDM is a milder form of the disorder. In terms of natural history it is anything but mild. As we shall see, the clinical onset is undramatic in most cases so that, like essential hypertension, it may have been present for months or many years before detected, so that it is common to find complications already present at the time of diagnosis. Large-vessel disease is particularly severe and accelerated in NIDDM, with considerable early mortality from ischaemic heart disease, and morbidity from angina, stroke, claudication and foot problems. There are two additional factors which compound the situation and indeed, the effect on our health care system, and these are the already mentioned fact that NIDDM constitutes the bulk of the diabetic problem, and, secondly, that there is a vast reservoir of as yet undiagnosed cases, many of them in their early teens.

Prevalence rates vary enormously in different parts of the world, ranging from a rate of 50% in a group of North American Indians, the Pimas in Arizona, down to a low of about 0,75% in Europeans. Between these

... Non-insulin-dependent diabetes

extremes we have Naureans in Micronesia with a rate of 30%, Mauritians (of all ethnic groups) about 18% and migrant populations from the Indian subcontinent including our own South Africans of Indian descent with a prevalence of about 15%. Our Zulu Royal family also has a very high prevalence.

Heredity and NIDDM

In IDDM the pathogenesis appears to depend on a genetic susceptibility (conferred by an association with certain HLA types, such as the HLA DR3 and DR4 antigens) acting together with certain environmental factors, in particular, certain viral infections, to start a cascade of autoimmune destruction of Beta-cells, which, when it reached a critical mass, resulted in the clinical manifestation of the disease. David Pyke's famous twin studies have, however, demonstrated that heredity *per se* was not a dominant factor, and that less than 50% of identical twins were concordant for IDDM². That

NIDDM is wrongly called "mild diabetes"

NIDDM was far more likely to be hereditarily determined, was illustrated by the fact that over 90% of identical twins were concordant for the disease, even if they happened to be separated from birth and therefore exposed to different environmental factors. This has certainly been our experience in our Indian patients. There are many families with diabetes on both sides of the family tree, and in these there is a high and increasing frequency of

early presentation of a rather more severe form of the disease. We have started to investigate these 'double chromosomal inheritance' families

Clinical onset is undramatic and can be missed for years

and are coming up with some startling results, of which the following Family study is typical.

Family study

Mr and Mrs Naidoo, both NIDDM. She has recently had to be put on insulin for better control, he is well-controlled on diet alone. Three of their parents had NIDDM, all deceased.

14th May. 18:30 hours.

They arrive for their joint appointment having just picked up their two children from the tennis courts where they have been participating in a school tournament. The youngsters are persuaded, sweating and hungry, into my consulting room where I have just been expounding on the risk of inherited NIDDM. Random, (in fact, virtually fasting), blood-glucose levels of 19,8mmol/L and 15,4mmol/L are found in 13 year-old Devashnee and 11 year-old Surendren respectively.

27th June.

By now Devashnee has been put on basal/bolus insulin as diet and sulphonylureas have not touched the hyperglycaemia. Suren is under reasonable glycaemic control on a small dose of glibenclamide.

It is frightening to realise that the

children might only have been diagnosed during a first pregnancy or an insurance medical, had they not been along with their parents on that fateful May evening.

NIDDM differs from IDDM not only in its genetic features – high concordance rates in identical twins and absence of association with specific HLA types – but also in other important respects. The most striking is that Beta-cell destruction does not occur in NIDDM; indeed, the pancreatic islets can be microscopically indistinguishable from those of non-diabetic subjects and contain normal or near-normal amounts of insulin, though the total islet and Beta-cell mass is reduced to about 50-60% of normal.³ Recently, there has been renewed interest in a discovery first described at the turn of the century.⁴ This was the demonstration of the presence of an interesting amyloid deposited in the islets of man and other mammals. Formerly called 'hyalin', now known as 'islet amyloid polypeptide' or 'amylin', it consists of 37 amino acids

Probably a vast reservoir of as yet undiagnosed teenage patients

and shares more than 40% sequence homology with calcitonin-gene-related-peptide (CGRP). It is confined to the islets and there is evidence that it originates in the Beta-cell secretory granules,⁵ and is present in most insulinomas, but not in other endocrine tumours of the pancreas.⁶ There is speculation that amylin might play an important role in the pathogenesis of NIDDM.⁷

... Non-insulin-dependent diabetes

Clinical features of NIDDM

It is useful to divide NIDDM patients into two subgroups, which differ in both pathophysiology and management. These are *obese* and *non-obese* NIDDM. Obesity is a common feature in NIDDM, with some 54% of males and 73% of females over 120% of their ideal body weight at presentation.⁸ Reduced insulin secretory capacity is thought to be the major defect in non-obese NIDDM, whereas insulin resistance is generally considered to be the hallmark of obese NIDDM;⁹ indeed, such patients are often actually hyperinsulinaemic as measured by conventional radioimmunoassay.¹⁰ As we shall see in a later article on management, the therapy of the two types varies as well. The non-obese patient should initially be treated with a normo-caloric diet excluding refined carbohydrate, and if this does not achieve control, a low dose of a sulphonylurea is added. For the obese

Often complications already present when first diagnosed

patient, initial treatment is a weight-reducing diet (also sugar-free), with metformin often used as second-line treatment.

Most patients with NIDDM present later in life, especially in Europids, but in our Indian patients (as in the Arizonan Pima Indians), it is by no means unusual to find that much younger individuals are affected, witness our Family study.

The classical symptoms of IDDM,

thirst and polyuria and weight-loss are not often present in NIDDM, and the onset is an insidious one, with fatigue a common presenting feature. Most cases are discovered indirectly, at insurance or pre-employment examinations, or during

No Beta-cell destruction in NIDDM

hospital or clinic visits for unrelated disorders, or intercurrent infections, (usually genital candidiasis or urinary tract infections). As previously indicated, it is by no means uncommon to find that advanced microvascular complications are already present at the time the diagnosis is made. In our sexual dysfunction clinic the initial diagnosis of NIDDM is not infrequently made in males referred for erectile problems. Our patient story illustrates a typical presentation.

Patient History: Non-insulin-dependent diabetes mellitus

B N 42-year old Building Society manager.

6th August.

Referred to an ophthalmologist by his GP for sudden and severe drop in visual acuity. Found to have extensive background retinopathy, peri-macular proliferative retinopathy and a small right vitreous haemorrhage, and referred to our Diabetes unit.

7th August.

First, emergency visit to diabetes clinic.

- * Fasting blood glucose 14mmol/L. No ketonuria.

- * Mass 78kg, height 1,68m, BMI 27 (obese).
- * HbA1 15% (non-diabetic range 5,0 - 8,0%).
- * On questioning, polyuria, thirst for two months.
- * Triglycerides 4,12; Total cholesterol 7,2; HDL-cholesterol 0,89.
- * Weight-reducing diet prescribed by dietitian.
- * Basic diabetes education by diabetes nurse. Taught home blood-glucose-monitoring.

8th August.

Pan-retinal photocoagulation by ophthalmologist.

4th September.

Attended diabetes clinic.

- * Followed diet rigidly. Home blood-glucose levels 10 - 14mmol/L.
- * 1% glycosuria. Fasting blood-glucose 8,9mmol/L.

Obesity common in NIDDM

2nd October.

Attended diabetes clinic.

- * Mass 74kg. Home blood-glucose levels 7 - 10mmol/L.
- * Visual acuity improved.
- * Fasting blood-glucose 9,1mmol/L.
- * Prescribed glibenclamide 2,5mg before breakfast.

27th November.

Attended diabetes clinic.

... Non-insulin-dependent diabetes

* Mass 75,5kg. Home blood-glucose levels mostly under 8mmol/L.

* HbA1 7,9%

* For repeat visit in 3 months.

Natural history of NIDDM

Beta-cell function tends to deteriorate as the years go by and many who are controlled by diet and an increase in recreational physical activity initially may need oral hypoglycaemic agents, whilst some who need these may graduate to needing insulin for adequate control. Poor compliance, unfortunately not uncommon, may contribute to this decision for a more aggressive therapeutic approach. In the poorly controlled obese NIDDM patient the decision to use insulin (which will further aggravate the obesity) is a difficult one and here it is useful to know what the patient's residual Beta-cell function is like (ie the C-peptide level), because high endogenous insulin plus unnecessary exogenous insulin greatly increases the atherogenic risk, and is unlikely to improve glycaemic control anyway. Currently about 20% of our Addington diabetes clinic NIDDM patients are on insulin.

Outcome and prognosis

Both IDDM and NIDDM carry the risk of long-term complications, including the specific microangiopathies (retinopathy and nephropathy), neuropathy and the non-specific macrovascular problems of occlusive atherosclerotic disease affecting heart, brain and legs.¹⁰ As NIDDM affects older individuals generally, large-vessel disorders are a special problem, aggravated by the fact that these patients often have other arteriosclerotic risk factors, as obesity, hyperlipidaemia, hypertension and smoking.

Peripheral vascular disease may cause intermittent claudication and gangrene which may require amputation, and, together with neuropathy, is a major cause of the diabetic foot syndrome, the cause of considerable morbidity and cost to the health care system. At least one third of male NIDDM patients have some degree of impotence.

Cerebrovascular disease presents as transient ischaemic attacks or stroke which is commoner than in the non-diabetic population, but it is coronary artery disease, however, which is the main scourge of NIDDM. Angina afflicts 17% or more¹¹, and ultimately nearly 60% die from ischaemic heart disease as compared with 15% of patients with IDDM.¹² Overall mortality in NIDDM is increased 2 – 3 fold and life-expectancy is reduced by 5 – 10 years compared with the general population.¹³ It is particularly in female NIDDM patients that the increased mortality risk from ischaemic heart disease is a striking feature, given the fact that the (non-diabetic, non-smoking, pre-menopausal) female has an inherent protection against this scourge.

The error in regarding NIDDM as 'mild diabetes'¹¹ is now well-recognised, as is its importance as a major cause of disability and premature death. The high prevalence in the elderly poses special logistic challenges for our health services. Finally, an interesting but ominous observation in our clinic is the marked increase in prevalence in our Zulu population; interesting, in that a high percentage of these patients requires exogenous insulin for control, and ominous, given the paucity of adequate health services in the rural areas.

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