PROCEEDINGS OF XII INTERNATIONAL DIABETES FEDERATION CONGRESS, MADRID

September 23-28, 1985

The enormous effort being directed to resolve the various hitherto unknown facets of diabetes provides optimism and hope for the future. More than 5000 scientists from all over the globe meet every three years and recount their successes and failures in this endeavour upto date.

September 1985 witnessed this event in the land of Espana, South west of Europe, but least European in appearance. Countrywise historically, there still exists the nostalgia of once being an Imperial Power in Europe. Its cultural expositions were abundantly felt by the majestic museums at Pedro, manly sports such as bull fights and gay amusements such as the Flamingo dances.

Presented here is an account of scientific deliberations as one could perceive from an International Congress. Realizing that in this Congress, orations, plenary sessions and oral presentations were spread over five days, one can naturally present only a resume of the areas where one could physically attend and grasp the new information being presented. This has further been rearranged to provide a cognent profile of the disease -clinical, therapeutic and basic aspects.

(I) Clinical Aspects

Reconaissance of epidemiological data on diabetes mellitus was presented in the Kelly West lecture. Populations identified with maximal prevalence of diabetes mellitus included Pima Indians (25%), Nauru Micronesiari (25%), Mexican Americans (17%). In contrast, recent data from the People's Republic of China provides a figure of 0.7%, while diabetes mellitus seems to be non-existant in the highlands of Papua New Guinea. Longitudinal studies on IDDM indicate that its incidence is increasing all over the world.

The need for application of standardized methodology and means for identification of special characteristics with specific environmental attributes was emphasized. Nutrition related attributes were significantly contributing to prevalence of diabetes mellitus. . If such interrelationship could be substantiated, preventive measures based on diet would prove rewarding.

A number of presentations related to recognition of premanifest stage of diabetes. In insulin dependent diabetes mellitus (IDDM) detection of islet cell antibodies (ICA) by ELISA technique, IgG and IgM, HLA DR typing, T lymphocyte subpopulation and pattern of insulin secretion can provide prediction for development of IDDM. In noninsulin dependent diabetes mellitus (NIDDM) glucose clamp studies bring out the inheresnt insulin resistance and failure of adaptation by the beta cell as regards sensitivity to glucose:

A long term follow up of children in Leister (UK) was presented. Since 1968 (ie for 17 years) there were 325 index cases (diabetics diagnosed within one month), 168 cases (from other clinics in Leister) and 48 cases (originally diagnosed elsewhere and then referred to Leister), total of 533 children were profiled. 85.5% of these were managed on domiciliary treatment throughout, hospitalization being required only in 18.5%. Of these, 11.77% (48) were admitted with ketosis. Complications, duration wise, were as follows (actual cohort since 1930):

	Proliferative Retinopathy	
Duration (yr)	percentage	Persistent proteinuria
Percentage		
0-10	-	2
11-20	7	4
21-30	28	9
31-40	34	14
>40	24	5

Mortality was : ketosis 7, hypoglycaemia l, renal failure 6, ischemic heart disease 9, others 14.

The study is creditable and shows that competent, intimate and compassionate liason can provide control of metabolic state, improve the natural history and prevent a lot of human suffering in a chronic disease.

Long term complications : Cardiovascular system

Ample statistical data was presented to show increased atherosclerotic vascular disease among diabetics. In Western countries at least 50% of the diabetic mortality is due to cardiovascular events. WHO statistics in 1980 related mean annual mortality from coronary artery disease with the degree of glucose intolerance in diabetics.

Schwabing's study indicated that age, duration and SBP (sex, smoking, BP) cholesterol or diabetic therapy were not significantly correlated, whereas triglycerides and plasma insulin in some studies were related significantly to mortality from coronary artery disease.

Some aspects of hypertension in diabetes were elucidated : 30% of diabetes have hypertension (> 160/95). Most of the antihypertensive agents available cause sufficient side effects which result in poor compliance. The choice of a specific antihypertensive agent is to be arrived at most judiciously, taking into consideration individual factors.

One interesting observation was that among patients following a clinic protocol, loss in follow up was only seven percent in contrast to 45% of those attending the same clinic routinely. Regarding lipids in macrovascular disease, abnormalities were observed in total triglycerides (in both IDDM and NIDDM), Apo B (in IDDM), LDL (in both IDDM and NIDDM), and HDL cholesterol and total cholesterol (in NIDDM).

There is increased VLDL synthesis in NIDDM while abnormalities in lipoprotein lipase or receptor may be contributing to hyperlipoproteinemia in patients with IDDM. Interpretation of lipid profile in a diabetic should only follow after achieving glycemic control.

Renal complications were addressed under the title 'From microproteinuria to kidney transplantation'.

The definition of microproteinuria seemed to vary in different studies (immuno assay method). Guy's Hospital > 30 mg/24 hours, Steno Hospital > 70 mg/24 hours and Aarhus Hospitat > 15 mg/24 hours. This is presumed to indicate development of diabetic nephropathy later. Persons with high glomerular filtration rate initially were considered to be at risk for the development of nephropathy later.

A distinct relationship between structural changes in the basement membrane and its functional capability has been demonstrated.

In follow up studiss, five years after the onset of diabetes, basement membrane thickening can be related to the further duration of the disease. In advanced cases GFR was also related to the number of occluded glomeruli, being inversely proportional to the filtration surface of nephrons.

Circulatory parameters show alterations in the balance of afferent and efferent glomerular resistance and subsequent changes in transcapillary hydrostatic pressure. The hemodynamic status of glomeruli affects the rate of development of glomerular lesions.

Autopsy data on kidneys in the UDGP study show that diabetic glomerulosclerosis was present in 55 out of 84 instances, nodular lesions in 17, mesangial thickening and diffuse changes in 26. In another four, there were abnormal glomeruli but not diabetes related and normal changes due to aging were found in eight. The control group showed changes suggestive of diabetes in seven, abnormal but not diabetes related in two and normal for aging in six (total 15). Except for the initial high glucose tolerance and duration, other factors such as SBP, serum creatinine, qualitative albuminuria, treatment did not seem to be related. Management policy recommended was to initially seek to delay the progression of nephropathy. This is achieved by optimizing btood gtucose, lowering blood pressure and instituting low protein diets.

With the onset of deterioration in renal function, dialyis in some form should be initiated. This is done, keeping in view the need for transplantation at a later stage (preferably from a living donor). Recent figures on transplantation show survival rates of 90%. Fifty percent among these survivors return to full work, while another 17% are fit for at least part time work. Combined kidney and pancreatic transplant is now being carried out more frequently. Of 24 recipients 23 are alive and well.

Studies on *autonomic nervous system* (ANS) in diabetes have gained more significance. It appears that involvement of the ANS accounts for a number of manifestations not well recognised so far.

Besides the nervous, cardiovascular; gastrointestinal and genito-urinary systems, respiratory, vasomotor and peripheral vascular systems are also involved, : Morphological changes in gangliosides as the basic and consistant pathological lesions are now well recognised.

The parasympathetic abnormalities affecting the cardiovascular system appear first. Heart rate variation (HRV) with a single deep breath is consistently present. HRV in supine resting position is predominantly affected by parasympathetic involvement, while orthostatic tachycardia is affected by both sympathetic and parasympathetic involvement, particularly the former. In autonomic neuropathy, inactive renin levels are elevated. Thus conversion of inactive to active renin in the kidneys appears to be under autonomic regulation. Again, catecholamine clearance is decreased in such instances, probably resulting from defective neuronal reuptake.

(II) Treatment

Treatment is discussed under three headings :

* Modificafions in diet.

* Scope of new hypoglycaemic agents, combined therapy and

* Advaneed technology far constant insulin delivery systems.

New strategies in dietary management were focussed on bringing changes in life style. It can be achieved by appropriate modifications in attitude, habits of food. intake advise about alcohol and inducement for exercise. Knowledge from caloric reckoner flexibility in diets individualization in planning attributed for a better compliance. Basic calorie requirement , depends on activity, while resting metabolic rate is 0.9 Kcal/min for obese persons 1246 calories, it is 0.7-0.75/K cal/min for lean persons, 1152 calories, for activity another 700-1200 calories are required.

The nemesis for *all weight reduction protagonists* came from a number of studies indicating that glycaemic control would precede any actual reduction in weight. There seemed to be no evidence now that the incidence of CAD decreased with weight reduction in NIDDM. The highlight of a symposium on diet was a simple explanatory talk on diabetic diets by a dietitian. Here I only reproduce her simple, naive yet so-far-unrecognised advise to diabetics about the virtues of drinking six to eight glasses of plain water a day. Benefits from this, she said, included simplifying kidney problems, reducing gastric acidity, improving skin function (moisture), regulating bowel function and reducing the sense of hunger. Wonder-all this, without costing anything !

Recent information on the use of omege 3 fatty acids adds further to the armamentorium for affecting lipids at the cellular level. In eight weeks, three grams (6 caps) of fish oil per day or one herring in NIDDM would bring about changes in insulin sensitivity, lower plasma triglycerides, without any changes in erythrocyte membrane fluidity (membrane lipid changed, i.e., phospholipid unsaturation and sphingomyelin content are increased). Use of upto 15% of total calorie as simple sugars by diabetics was not universally accepted.

Alcoholic beverages provide on an average 7 Kcal/gm. Their free usage in diabetics was not favoured. Medium term effect of high fibre in diet (2 months) resulted in normalization of intermediary metabolites, plasma aminoacids and lipids. This contributed to improvement in insulin sensitivity and better utilization of aminoacids.

As *regards new hypoglycaemic* agents, two main avenues are being investigated in great detail :

1. Drugs that affect the gastrointestinal tract, Gaur, glycosidase inhibitors, e.g. Bayer's second generation compound, i.e. Bay 1248, Bay 1099.
2. Drugs that affect the peripheral tissues, e.g. receptors.

A number of oral presentations provided results of the Bay 1248, Bay 1099, new alpha glucosidase inhibitors. Bay 1099 was dose dependent, more effective in reducing insulin requirement and its effect lasted for longer duration (all 3 main meals). Besides reduction in the rate of nutrient absorption, disaccharidases are inhibited. Hormonal changes include reduction in insulin, gastrin inhibiting polypeptide (GIP), an increase in gastrin, while glucagon and motilin showed no alteration.

Other - agents (not sulphonylurea or biguanides) undergoing human trials giglitazone, linogliride, seem to act by increasing endogenous insulin secretion.

Combined therapy

a) In Insulin requiring Type II diabetics, addition of glipizide may decrease insulin needs mostly by enhancing the endogenous insulin secretion and in some instances also by increasing peripheral tissue sensitivity to insulin:

b) In secondary failure with sulphonylureas, insulin therapy alone even in high dose or insulin therapy usually in low dose when combined with sulphonylureas provides evidence for pancreatic and extra-pancreatic actions of sulphonylureas. Continuation of sulphonylureas in secondary failure together with low dose insulin was beneficial in secondary failure. This avoided hyper-insulinaemia and provided better metabolic control.

3. In secondary failure with sulphonylureas, combination with metformin did not however achieve glycaemic control compared to that in combination with soluble insulin.

4. In 50% of secondary failure with oral sulphonylurea, short term (10 days) strict blood glucose control by optimized insulin therapy could restore the efficacy of sulphonylureas. This improvement was however not related to increased residual insulin secretion.

New innovation

Continuous administration of insulin, depending on the blood glucose levels would require a glucose sensor, application of computer analogue and requisite infusion of insulin or glucose. Glucose sensor : This contraception is now shaped like a needle. This provides a continuous monitoring of glucose values in the tissue implanted. As the sensing membrane loses sensitivity in 3-7 days, it must be replaced about every fourth day.

Computer analogue system: This has been miniaturized and the programme utilizes insulin glucose algorithms. There is provision of an alarm system for indicating technical problems with the pump or an empty reservoir.

Insulin glucose delivery system is in a wearable format or as implantable form and this completes the closed loop system. The feed back control system is self adjusted.

In comparable studies, protagonists imply that a closed loop glycaemica control is essential to overcome the fluctuations in glycaemia characteristics, such as variations with meal ingestion, rate of absorption or insulin insensitivity.

In citing experience with usage of CSII system, wherein indications included diabetic ketoacidosis, surgery, transplantation, or calculation of insulin dose for subcutaneous use in certain diabetics or for induction of a remission phase, consensus is on its merit and usefulness in states destabilising diabetes control.

Continuous subcutaneous insulin provides excellent metabolic control of diabetes: Yet it is expensive, requires a great deal of physician and patient's care and supervision. However 45% of patients seem to develop problems with it. Intraperitoneal administration of insulin seems more physiological. There is 75% absorption though it is not as fast as the IV route. This insulin transverses the enterohepatic circulation as occurs physiologically. In

comparative studies, intraperitoneal administration provides better metabolic control and mean normal free insulin in IDDM patients than by the continuous subcutaneous insulin infusion.

A new computer simulation is now available wherein varied strategic situations of metabolic control are programmed and effective treatment plans are offered for all the biochemical in parameters.

Bio-artifical pancreas is devised by allogenic transplantation of living islets. This is contained in a semi-permeable membrane thus providing an implantable closed loop system. The limitations are short survival of islets cells and variable membrane integrity that need to be improved further.

(III) Basic Physiopathology

Insulin Receptor

The three main functions of the insulin receptor are : (a) membrane events that initiate the glucose transfer, (b) enzyme activation leading to phosphorylation and (c) intracellular metabolic effects that result in macromolecular biosynthesis through RNA/DNA.

The insulin receptor is 50 kilobase, located on chromosome 19 and has multiple insulin messenger RNA; its function depends on the affinity. Monoclonal antibodies can be raised against the receptor which can block the action of insulin. Reduction in the number of receptors or increased receptor degradation results in 'down regulation' of the receptor. This is observed in obesity and NIDDM (Type II diabetes). Insulin resistance could be due to decrease in receptor synthesis (genetically determined) as seen in acanthosis nigricans Type A and leprechanism, or a down regulation of receptor as seen in some hyperinsulinaemic states.

Immunological Studies in Diabetes

Interferon gamma and a potent lymphoregular (released by activated T lymphocytes) regulate the expression of the major histocompatibility antigens (MHC) on islet beta cell during an immune response. Susceptibility of the beta cells to immune injury in IDDM depends on MHC antigen. Antibodies to an apparently beta cell specific integral membrane protein seem to be early markers of an aberrant immune reaction against the beta cells. In the pre-diabetic stage, in 80 percent patients of IDDM, autoantibodies have been detected.

Anti-insulin receptor antibodies (AIRA) are the hallmark for insulin resistance in adult diabetics with acanthosis nigricans, though they are present in all cases of severe insulin resistance. In patients with polyendocrine disorder who are ICA(+), T cell subpopulation studies showed decrease of total T cell population, Ta cells or increase of TS/C. N/NK cells or activated lymphocytes do not show significant alterations, indicating heterogeneity in IDDM and polyendocrine diabetes.

Family studies were done at Oxford and Bart's Windsor for a period of 6 years, based on 100 subject years. The results showed that the risk of getting diabetes by age 25 was 12% for persons who are HLA identical, and 8.6% for haplopoidentical subjects for ICA : IgA positive. 0.94 for CFI CA positive 8.5.

Pathogenesis of lDDM/NIDDM

In IDDM, the predisposing factor is genetic, initiating factor a virus and the precipitating factor an autoimmune response. The presence of ICA can precede manifest IDDM (especially in high risk subjects, monozygotic twins or first degree relatives); again in such cases insulin release following IV glucose is impaired, even though IV arginine, tolbutamide or glucagon or oral glucose may still give a normal response

In NIDDM, the hallmark of pathogenesis is a state of insulin resistance, the defect being at the receptor or postreceptor level. Steady state studies indicate high basal insulin levels and decreased glucose disposal rates in IGT and DM group of patients. The glucose transfer system being affected, lipid oxidation and glucose oxidation are inversely correlated and hepatic gluconeogenesis is increased which also contributes towards insulin resistance.

Death of Beta cell-'Homicide or Suicide' was elaborated in a lecture where the role of genetic, environmental and immunological factors was analysed. Chromosome 6 provides the major histocompatibility complex, DR_3/DR_4 (RR DR_3 DRx 5.4, DR_4 DRx 6.8, DR_3 DR_4 14.2 while absence of DR_2 and C_4AB seem to be protective). Other evidence e.g. (a) DNA sequence flanking the chromosomal 11 insulin gene probably contributes to susceptibility, (b) Chromosome 14, Gm heavy chain immunoglobulin, or (c) chromosome 2 Kapa light chain relating to KIDD blood group have yet not been proved to be confirmatory for increased risk of IDDM.

Autoactive Lymphocytes-IgG

Complement activation is→ cytotoxic cells seems to be the sequence for the slow process of autoimmunization in genetically predisposed individuals.

Proinsulin and C peptide

Characterization for biological effectiveness reveals proinsulin : insulin ratio of 20 : l. Proinsulin has a prolonged metabolic clearance rate, delayed onset of action and greater hepatic effect than peripheral metabolic action (50-70% cleaved in liver compared to 10 % C-peptide). Proinsulin excess indicates abnormalities in beta cell secretion. Instances with hyperinsulinaemia are recognized (in Japanese, autosomal dominant and resulting in diabetes, while families recognized with hyperproinsulinaemia in USA are not diabetics).

Raised proinsulin levels are also found in chronic renal failure. In insulinoma, proinsulin value may be diagnostic irrespective of the degree of hypoglycaemia. In some instances with NIDDM, proinsulin secretion may be affected wherein inerease in hepatic glucose uptake contributes to hyperglycaemia.

C-peptide studies have provided insights in to the natural history of IDDM. C-peptide reflects the status of metabolic control and efficacy of therapy. It is also an indicator of the status of beta cells in the neonate of a diabetic mother.

Endocrine Control of Carbohydrate Metabolism

Experimental studies in depancreatized dogs employing the insulin clamp technique and evaluation of secretion of insulin have provided new information on the following aspects :

* Stomach, upper to lower intestines are the sources for extrapancreatic glucagon in decreasing order. GLI found in hypothalumus is also involved. It regulates the hepatic production of glucose.

* Epinephrine and endorphins interact and potentiate hyperglycaemia. Again exercise in a metabolically controlled diabetic inhibits glucose production and the blood glucose value improves. However, in an uncontrolled diabetic, glucose utilization is poor and exercise may further worsen the glycaemic status. With exercise, there is a suppression of glucagon without an increase of counter regulatory hormones.

  Key enzymes of the glycolytic and gluconeogenic pathways are depressed by high glucagon levels.

* Somatostatin decreases production as well as clearance of glucose while inhibition of somatostatin is accompanied by increased glucagon response.
  Beta blockers do not suppress the glucose production.