ABSTRACT SERVICE
Childhood Diabetes Mellitus (CDM)

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Childhood Diabetes Mellitus (CDM) is a global problem affecting all races and nations, people both rich and poor. However, wide geographic and temporal variations in CDM incidence has been observed, lending credence to the involvement of "environmental" factors in the disease pathogenesis. Also, there has been a trend towards a rise in the incidence of this disease , worldwide. Studies of CDM in immigrant populations are beginning to yield interesting results.

The precise incidence and prevalence of this disease is not available in several economically underdeveloped countries. Deficient health care resources/facilities lead to death before diagnosis in a majority of instances, leading to underestimation of the burden of this problem. Optimal management (including availability of insulin) is often nonexistent, and long term prognosis is very dismal, with only a minority of children surviving beyond a decade or two with this disease. Also, distinct variations in clinical presentation of CDM have been reported from these populations.

On the global front, recent advances in the field of CDM include: recognition of type I IDDM as a 'classic' autoimmune disease (with MHC association), identification of a long preclinical phase of IDDM (characterized by detection of ICAb and decline in B-cell function), feasibility of prevention or cure of this disease in animal models of IDDM (BB/W rat, NOD mouse) with extension to pilot immunotherpay trials in women. The existence and nature of the "environmental trigger(s)" for islet cell autoimmunity and B-cell distinction remain completely elusive (despite the incrimination of certain infectious agents and dietary factors-complex proteins).

Even with all this scientific promise, the priority in CDM in developing countries remains the best possible diabetes health-care , including awareness and health education. Some important abstracts from the literature are now presented.

Geographic patterns of childhood insulin-dependent diabetes mellitus Diabetes Epidemiology Research international Group. Diabetes 1988; 37:1113-9.

Population-based registries of insulin-dependent diabetes mellitus (IDDM) worldwide have reached the critical mass needed to investigate global patterns of the disease. International collaboration of 24 registries form 15 countries resulted in the first set of standardized incidence measures among divergent areas and ethnic groups. The average annual age-adjusted incidence under age 15 yr ranged from 1.7/100,000 person-yr in Hokkaido, Japan, to 29.5/100,000 person-yr in Finland during the years 1978-1980. The geographic differences in IDDM in childhood are rarely seen among chronic diseases . It appears that the risk for IDDM is determined by factor(s) correlated to the average yearly temperature of environment and to the ethnicity of the population at risk.

Rewers M, Stone-RA , LaPorte-RE . Drash AL, Becker DJ, Waiczak M, Kuller –LH.

Poisson regression modelling of temporal variation in incidence or childhood insulin-dependent diabetes mellitus in Allegheny Country, Pennsylvania, and Wielkopolska,Poland, 1970-1985. Am-J-Epidemiol 1989; 129: 569-81.

Contradictory observations have accumulated regarding a secular trend and/or and epidemic pattern in the incidence of insulin-dependent diabetes mellitus. In this study, insulin-dependent diabetes mellitus incidence below age 15 years was examined in Allegheny Country. Pennsylvania and in Wielkopolska, Poland, two areas diverse in terms of their geography and average risk for this disease. Numerator data are extracted form individual patient records, and annual denominator data were available for the years 1970-1985. Poissonregression models were used to disentagle the contributions of country, race ,sex, age, period, and cohort effects to the observed variation in incidence. Poles and Allegheny Country non whites were at greatly and moderately reduced risks, respectively, relative to Allegheny country whites. An increase in risk with age was significant and proportional in all three groups . There was significant time variability in Wielkopolska, where an epidemic began in 1982 and continued through 1985. This was a period rather than a cohort phenomenon and was a result of a recent outbreak of the disease rather than a long trend. In Allegheny Country, changes in risk over the 16-years period were insignificant, although incidence doubled among whites age 0-9 years during 1982-1983. The Poisson regression modeling provided a quantification and formal comparison of determinants of the incidence of insulin-dependent diabetes mellitus.

Xu-Y-F, Hours M , Collet-U.P., Sun-G.J., Guin-X.J., Guin-X.J., Francois-R Fabry-J.
Juvenile insulin-independent diabtes in Wuhan Province, People's Republic of China. Incidence rate from 1971 to 1985. Rev-Epidemiol-Sante-Publique 1989; 37:227-31.

The average incidence rate of juvenile diabetes in Wuhan (People's Republic of China) between 1971 and 1985 was 0.6/10(5) in children less than 14 years of age. This incidence rate is close to that observed in Japan but seven times lower than the French rate and much lower than the incidence rate in other occidental countries. This is the second study to show a lower incidence rate of juvenile diabetes among Asian populations as opposed to occidental populations. However, interpretation of the results must be cautious with regard to the method of data collection.

Another illustration of low-incidence of IDDM in certain oriental populations.

Insulin-dependent juvenile diabetes. Descriptive study in the Rohne department (France).
Rev-Epidemiol-Sante. Publique 1984; 32:107-12.

A systematic study of juvenile onset diabetes cases observed in the Rhone department between 1960 and 1979 indicates an annual incidence of 4.7/10(5) children from 0 to 15 years of age. This incidence is lower than that which has been reported for Great Britain and some Scandinavian countries. There was a surprisingly high incidence among immigrant children from North Africa (10.2/10(5) children) and also in some urban areas (middle-sized cities and the southeast suburb or Lyon). Farmer's children seem more often affected that others). The seasonal trend cited in earlier studies was also noted here for children between 5

Matter in italics are author's comments

and 15 years of age. These findings are compatible with the concept that environmental factors play some role in the onset of juvenile diabetes.

The precise quantitation of the incidence of CDM in native North African children would be highly informative.

Kalits I, Podar T Incidence and prevalence of Type 1 insulin dependent diabetes in Estornia in 1988 Diabetologia 1990; 33:346-9.

(Estonian soviet social public: East of Baltic sea)

In 1988, 35 new cases of Type I DM were diagnosed among children aged 0-14 years (incidence of 10.3 per 1,00,000) and 131 among the population over 15 years. The highest incidence of Type I diabetes(31.1 per 100,000) was found in all group 15-19 years. These data suggest that risk of Type I DM in Estonia is not low but certainly not so high as in Finland where the population is ethnically and linguistically similar and where highest incidence of type I DM is found.

Historically divergent evolutionary patterns in IDDM incidence? Understanding the reasons for differences in IDDM incidence between Finland (highest incidence in world) and Estonia would be both fascinating and crucial.

Rao-R.H., Vigg-B.L., Fao-K.S.
Suppressible glucagon secretion in young, ketosis-resistant, type "J" diabetic patients in India.
Diabetes 1983; 32:1168-71.

Plasma glucagon levels were measured in young individuals with severe, insulin-dependent, juvenile-onset diabetes mellitus to study whether difference in glucagon secretion were related to ketosis proneness and resistance. Fasting glucagon levels were similarly elevated in both classical, ketosis-prone, type I diabetic subjects and ketosis-resistant, type "J" subjects (70 +/-7 pmol/L(mean +/-SEM) and 81 +/-10 pmol/L, respectively) compared with nonobese, nondiabetic controls (36+/-3 pmol/L P less than 0.01). After oral glucose administration, however, glucagon responses were strikingly dissimilar in the two groups. In type I diabetic individuals, glucagon rose paradoxically during OGTT, by 21 +/-4 pmol/L, an increase of 33+/-10%. On the other hand, glucagon levels in type "J" diabetic individuals fell by 28 +/-7 pmol/L, a decrease of 33+/-5%. There was no measurable increase in plasma free insulin during OGTT in either group. Postprandial glucagon suppressibility may be relevant to the ketosis resistance that is characteristic of type "J" diabetes.

Over the last two decades several investigators working in developing countries have reported a clinically variant form of IDDM in the young characterized by (i) evidence of severe malnutrition (ii) insulin requirement without proneness to severe ketoacidosis (upon insulin withdrawal) (iii) low socio-economic status, and (iv) absence/unelicitable family history. This clinical entity has been labelled as ketosis-resistant diabetes of the young (KRDY) or "J" type of diabetes . In these diabetics, a relatively better preserved endogenous residual B-cell function with C peptide reserve has been documented. Onset is usually in 2nd or 3rd decade. The above interesting paper documents yet another metabolic characteristic of KRDY or J type of diabetes i.e. a decline in immunoreactive glucagon levels in OGTT (ef: elevation in classic type I diabetes). This might reflect the paracrine effect of the residual endogenous insulin secretion in this variant subset of diabetes mellitus.

Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual B-cell function : observation during eligibility testing for the diabetes control and complications trial(DCCT)

THE DCCT RESEARCH GROUP J Clin Endocrinol Metabl 1987; 65:30.

To examine the effect of age, duration and treatment of insulin-dependent diabetes(IDDM) on residual B-cell function, fasting and Sustacal stimulated serum C peptide levels in 610 conventionally treated IDDM patients (age 13-39 yr; duration of diabetes, 1-15 yr) during eligibility screening for the Diabetes Control and Complications Trial (DCCT) were studied. Fasting and stimulated C-peptide values were closely correlated (r=0.83 P < 0.001) and both declined with increasing duration of disease. However, among patients who had been diabetic for more than 5 yr, 11% (33 of 296) of adults compared with 0 of 75 adolescents (P < 0.001) retained substantial insulin secretory capacity. Patients with stimulated C-peptide levels greater than 0.2 pmol/ml had a significantly lower mean fasting plasma glucose level (177+6(+SEM) vs 222+6 mg/dl P < 0.001) a smaller rise in glucose after sustacal administration (151 + 5 vs 184 + 3 mg/dl, P < 0.001), and lower hemoglobin A (84+0.2% vs 9.3+0.1% P < 0.001) than the patients with a stimulated C-peptide level of 0.05 pmol/ml or less even though the C-peptide secretors were receiving less insulin (0.52+0.02 vs 0.78+0.02 U/kg day: P < 0.001).

To determine the effects of treatment of B-cell function, 33 patients with stimulated C-peptide values between 0.2 and 0.5 pmol/ml. At entry in the DCCT were restudied 1 yr after randomization to standard treatment (n-15) or an experimental (n-18) treatment designed to achieve and maintain near normal glucose levels. Although C-peptide levels declined in both groups, experimental treatment was associated with slightly less of a decline in stimulated C-peptide values compared to standard treatment.

The results of C-peptide measurements in the large and well defined population of IDDM patients demonstrate residual B-cell function continues for a longer period of time in adults compared to adolescents with IDDM. This endogenous insulin secretion contributes significantly to metabolic control and may be prolonged by intensive insulin treatment regimens.

Several other studies have also documented the association of C-peptide positivity in IDDM children with lower HbA1 concentration, lower insulin requirement, later age of onset, and shorter duration of diabetes than children who were C-peptide negative (Diabetes Care 1987; 10:33-8).

Todj JA, Bell JI, McDevit HO (Stanford Univ)
HLA-DQB Gene Contributes to Susceptibility and Resistance to insulin –Dependent Diabetes Mellitus
Nature 1987; 329:599-604. Oct. 15, 1987.

The 4 major expressed polymorphic class II gene products isolated from 3 patients with insulin-dependent diabetes and from several controls were sequenced. A rapid method was used to produce enough target gene sequences from RNA by complementary DNA synthesis and in vitro DNA amplification. The gene segments encoding the first domains of DRB, DQ AND DQB chains-which contain most of the polymorphism-were cloned and sequenced.

No unique class II sequences were found only in patients with insulin-dependent diabetes. However, the DQ-B-Chain amino-acid sequence correlated directly with a disposition to insulin-dependent diabetes. Susceptibility and resistance were largely dependent on the identity of amino-acid residue 57 of the B-chain

of the heterodimer. All DQB alleles positively associated with diabetes had Ala, Val, or Ser at position 57. All alleles that were neutral or negatively associated with disease had Asp at this position.

It appears that the amino acid at position 57 subserves a critical function of the DQ molecule in insulin-dependent diabetes. The murine homologue of DQB isolated from a nonobese spontaneously diabetic mouse strain, also has a unique Ser 57 residue, supporting this correlation. It may be that DQB allelic polymorphisms especially at position 57-determine the specificity and extent of the autoimmune response to islet cell antigens through T cell help or suppression, or both.

These observations may be true at least in Caucasions; but this association of IDDM susceptibility with HLA-DQB-57 non-Asp, has not been observed in a recent Japanese study (Diabetologia 1989; 32:762-4). Insulin-dependent diabetes involves the selective destruction of insulin-producing pancreatic islet cells. It may reflect a T cell-mediated autoimmune response to an islet antigen. The disorder is polygenic in inheritance; it is estimated that the human leukocyte antigen (HLA)-D region, which influences immune responsiveness, contributes more than 50% of the heritability. About 95% of patients have either HLA-DR3 or HLA-DR4, compared with 45% to 54% of the normal population. The HLA-DQ genes, which are in linkage-disequilibrium with HLA-DR, are more closely associated with insulin-dependent diabetes than are the DR genes.

Baisch JM, Weeles T, Ciles R. Hoover M. Stastny P, Capra JD Analysis of HLA-DQ Genotype and susceptibility to insulin Dependent Diabetes Mellitus.
N Engl J. Med. 1990; 322: 1836-1841.

Using allele specific oligonucleotide probes and polymerase chain reaction, authors studied 216 patients with IDDM and 203 unrelated normal subjects for eight HLA DQB gene alleles. Two major findings emerged. First, the presence of an HLA DQW 1.2 allele was protective. Only 6 at the 266 patients with IDDM (2.3%) were positive to HLA.DQW 1.2 as compard with 74 of the 203 normal subjects (36.4%; P<0.001). These persons with th HLA DQA1.2 allele, which is one of the polymorphic form of B-chain of HLA DQ molecules, rarely had IDDM, no matter which other HLA.DQ-B. chain allele they inherited ("dominant protection"). Second, the presence of HLA DQ W8 allele increased the risk of IDDM. The relative risk IDDM was 5.6 in persons homozygous for HLA DQW8, ad it was similar in persons with HLA DQW1.1 DQW8 or HLA. DQW 2/DQB haplotype ("dominate susceptibility"). However the relative risk of IDDM in persons who had HLA DQW1.2/DQW8 haplotype was 0.37, so that the protective effect of HLA DQW 1.2 predominated over the effect of HLA DQW 8.

It was thus concluded that presence of HLA Class II antigen DQ W1.2 is strongly protective against the development of IDDM, and complete HLA DQ typing is necessary for accurate assessment of susceptibility to IDDM.

E, Bhatia, Mehra NK, Tavia V, Vaidya MC Ahuja MMS DR Antigen Frequencies in north Indian Type I Diabetic population.
Diabetes 1985;34:565-67.

88 North Indian patients with Type I IDDM and 113 unaffected individuals were typed for HLA-DR. antigens from DR 1 to DR7. The frequency of HLA. DR 3 was significantly increased in the patients as compared to the controls (78.4% vs 25.7% corrected $P=1.68X10^{-12}$), the relative risk (RR) of 10.52 being much higher than that reported in the Western IDDM population. HLA-DR 2 showed a significant negative association (RR=0.18; Corrected $P=1.03x10^{-5}$) but DR 4 had no relationship with IDDM in the present study (RR-1.12, p=0.12). These results emphasize the difference in HLA-IDDM associations among different ethnic groups.

Studies from India and other populations have confirmed similar HLA association (both positive and negative): HLA-DR3 and DR4 conferring susceptibility and DR2 protection. Multiplex family studies have shown similar HLA haplotype association from India.

Srikanta S, Ganda Om P, Rabizadeh AD, Soelduner JS, and Eisenbarth GU:
First degree relatives of type I DM: ICAb and abnormal insulin secretion).
N Engl J Med 1985; 313:416-4.

In a prospective study to evaluate the prevalence and predictive potential of circulating ICAb, authors screened 1723 "normal" firs degree relatives (parents, siblings and off spring) of patients with IDDM. The prevalence of ICAb on initial screening was 0,9% (16 of 1723). Over a maximal follow-up peiod of 2 years IDDM developed in 2 of 16 relatives with ICAb and in 1 of 1707 without antibodies.

In addition, 6 to 12 non-diabetic relatives with ICAb had abnormally low insulin responses-below the third percentile in 6 and below the first percentile in 4-on the initial challenge. Thus prospective ICAb screening of high risk-first degree relatives in combination with IV glucose tolerance testing is capable of identifying immunologically abnormal persons with profoundly diminished B-cell function, who are presumably at risk of IDDM.

Several long term prospective studies of high risk subjects (discordant monozygotic twins, I relatives of IDDM probands), reported in this decade have established the presence of long prodromal/preclinical phase this chronic autoimmune disease is characterized by presence of serologic markers like islet cell antibodies (ICA), subtle B-cell dysfunction and progressive loss of early phase insulin response to IV glucose. Besides, in high risk subjects, ICA have proved to be accurate predictive marker for IDDM even in general population at large as exemplified by the studies in normal school children of Florida, USA.

Tarn AC, Thomas JM, Dean BM, Ingram D, Schwarg G, Bottazzo GF, Gale EAM.
Predicting insulin-dependent diabetes.
Lancet 1988; (1): 845-850.

719 first –degree relatives of diabetic children were followed to assess the value of HLA haplotype sharing , and of islet-cell antibodies (ICA) for prediction of IDDM. Within a maximum of 8 years follow-up (3384 patient-years of observations), 16 unaffected relatives (5 patients and 11 siblings) became insulin-dependent. The cumulative risk of becoming insulin-dependent by age 25 was 16% for siblings sharing two HLA-haplotype with the proband, 9% for those sharing one haplotype and zero for those sharing none. 13 of 24 (54%) subjects positive for complement-fixing ICA on 3 or more occasions became insulin-dependent, as against 1 of 30 (3%) with noncomplement-fixing ICA alone and 2 of 665 (0.3%) ICA-negative subjects by life-table analysis the risks after 8 years of known ICA–status are 76%, 3% and 0.6% respectively. In terms of total time at risk, ICA–positive family members had a relative risk of 75.2 compared with ICA-Negative individuals with positivity for complement fixing ICA, the relative risk was 188.5.
The ability to predict IDDM in the pre-clinical phase have raised hopes for possible prevention (immunoprophylaxis).

Atkinson MA, Maclaren NK, Scharp DW, Lacy PE, Riley WJ: 64000.
Mr. Autoantibodies as predictors of Insulin-dependent diabetes.
Lancet 1990;335: (8702):1357-1360.

The occurrence of autoantibodies to an islet-cell protein of 64000 Mr (64KD) was examined in relation in relation to development of IDDM. 64K, were absent in 26 normal controls and present in only 1 of 41 first degree relatives who lacked islet-cell cytoplasmic autoantibodies (ICA) and insulin-autoantibodies (IAA). Among first degree relatives at high risk for IDD 64K were identified in 23 of 28 persons positive for ICA and 4 to 5 with IAA but no ICA. Among 31 patients with newly diagnosed IDD, 64K were found in 26. 64KD were identified in 23 of 28 persons studied upto 75 months before clinical onset of IDD. Of these 23 64KD positive prediabetic subjects, 5 were ICA negative and 10 lacked IAA. 64KD were most predictive in those who became diabetic before age 34 (22/24). In several individuals, 64KD were detected before the other autoantibodies appeared. These findings suggest that 64KD may be an early and useful predictive marker for IDD.

IDDM in man, in the biobreeding rat (BB) and in NOD mouse is characterized by autoantibodies directed against an immunoprecipitable islet cell protein of relative molecular mass 64000. 64KD may be the earliest and potentially best marker of impending IDD yet identified. This 64KD islet cell antigen has recently been shown to be related to the Mr 64 family of heat shock proteins (hsp), a group of highly evolutionarily conserved protein, from microorganism to vertebrates with potential roles in the induction of autoimmune responses through a mechanism like molecular mimicry. Interestingly the expression of 64KD islet cell protein is stimulated by high glucose concentration suggesting a potential physiologic role in islet glucose recognition/regulation.

Besides this 64KD protein, certain islet cell glycolipids are also being evaluated as possible candidates for target islet cell autoantigen(s).

Notsu-K, Note-S, Nabeya-N, Kuno-S, Sakurami-T
Antinuclear antibodies in childhood diabetes .
Endocrinol-Jpn 1983; 30:49-73.

Antinuclear antibodies (ANA) were detected both in type I diabetic children and in control subjects. The incidence of ANA in eighty of these diabetics was 16.3% as determined using two different substrates, human pancreas and human peripheral leucocytes. The incidence and the patterns in the detection of ANA were the same . Four hundred and seventy three children and one thousand one hundred and twenty-five adults served as the controls. The incidence of ANA in non-diabetic children was 0.8% and that in one adult population was 1.1%. Therefore, the incidence of ANA in childhood diabetics was significantly higher.

Increased prevalence of antinuclear antibodies in type I IDDM is yet another marker of autoimmunity in this disease. It overlaps between organ specific (Type I diabetes, autoimmune thyroid disease. Addison's disease, pernicious anemia) and non-organ specific (SLE, PSS, Rheumatoid arthritis, Sjogren's syndrome) clusters of autoimmune disorders, often associated with immunogenetics (HLA) association.

Bodansky HJ, Beverley DW, Gelsthorpe K, Saunders A, Bottazzo GF, Haigh D,
Insulin-dependent diabetes in Asians.
Arch Dis child 1987; 62:22-30.

Type I diabetes is said to be extremely rare in children in India, where diabetes treated with insulin may be due to chronic pancreatic disease or malnutrition. To see whether typical Type I DM occurred in Asian children in UK, all known Asian children with diabetes in industrial West Yorkshire were ascertained. A total of 17 such children were studied. Of these 7 were from 3 multiplex families prone and developed diabetes while resident in the UK. There were significant increases in HLA-B8 and DR. 3 and increases in HLA-DR4 and HLA-DR. 3/DR4, while HLA-B15 was absent. ICAb, either IgG or complement-fixing , were present in 4 of 18 subjects tested all of who had disease of short duration. The prevalence of type I DM in Asian children 15 years or less in West Yorkshire was 36/1000, assuring complete asscertainment. It is concluded that typical type I DM occur in Asian children and this condition may be more common in families who have migrated to UK.

In other study of Type I DM in Asian Indians of Leicester, Samanta et al (Diabetic Medicine 4:65; 1987) determined similar prevalence among 20000 Asian and 44000 white Caucasian 0-15 years old of 54 and 99/100000 respectively, an insignificant difference .It was suggested that Asian children who have the established HLA association will develop IDDM at comparable rates to white Caucasians if exposed to comparable environmental factors. Data is also available on IDDM in Indians migrant to South Africa. Critical comparison of the epidemiology and profile of IDDM in native vs migrant Indians can be informative.

Matsuda-K, Asakura-T, Nakayama-M, Terada-K, Maeda-Y, Hamada-H
Coma at the onset of young insulin-dependent diabetes in Japan. The results of a nationwide survey. Japan and Pittsburgh Childhood Diabetes Research Groups.
Diabetes 1985; 34:1241-6.

The descriptive epidemiology of diabetic coma at onset was investigated in a nationwide survey of insulin-dependent diabetic (IDDM) children (age at onset less than 18 years) throughout Japan for the year 1970-81. Of the 1172 cass, 148 (12.6%) were unconscious at onset. Diabetic coma was highly associated with abnormalities in the biochemical variables. There was no sex difference in the frequency of coma; however, there was an inverse association with age wherein children under 5 years , of age were approximately two times more likely to present in coma than older children. There was a strong association with reported infections wherein patients with coma were more than twice as likely to report infection tan patients without coma. It seemed that the frequency of coma did not decline during the study period. The risk of dying at onset was very high; diabetic children in coma (4.7%) were 12 times more likely to die than patients without coma.

These are the results from one of the most economically affluent and prosperous nations. Results from economically under privileged societies can be expected to be much worse. That deaths due to DKA are fully preventable can never be overemphasized.

Childhood diabetes mellitus in Ethiopians.
Diabetic-Med 1986; 3:278-80.

Of 1088 consecutive Ethiopian diabetic patients registered over 9 years, 80 (7.4%) were diagnosed at or before age or before age 15 years. There were 48 girls and 32 boys, with mean age of onset of 10.1 years. Diabetes had been present 10 years or less in 62 , 11 to 20 years in 15 , and more than 20 years in only 2. twenty-two were rural, 27 had poverty certificates. Twenty-three have known diabetic relatives. The original mode of presentation could not be

verified in 16 , 7 presented in ketoacidosis, 5 were diagnosed by a diabetic relative, and the rest presented with the rapid onset of classical symptoms. To date, 43 have been ketaocidotic at least once. No pancreatic calcification was seen in 34 abdominal radiographs. Three of 6 newly diagnosed patients tested had islet cell surface antibodies . Three cases , initially suggestive of tropical malnutrition diabetes, evolved into typical type I diabetes. Serious complicating illnesses were tuberculosis (6), bacterial endocarditis (1) and rhinocerebral mucormycosis (1). Six patients have had metabolic cataracts. Ten patients (12%) have died, 4 of ketoacidosis and 4 of diabetic nephropathy. Childhood diabetes mellitus in Ethiopians in clinically very similar to type I diabetes elsewhere.

This represents the prototype of the saga of CDM in the face of economic impoverishement. The only available mortality data on childhood onset DM from India highlights these remarks.

CR Stiller, J Dupre, M Gent, MR Jenner, PA Keown A Laupacis, R Martell, NW Rodger BV Grafenried BMJ Wolfe. Effet of cyclosporine Immunosuppression in insulin dependent diabetes mellitus of recent onset. Science , 23;1362:1365,1984.

Type I diabetes may be an autoimmune disorder, although the evidence is largely circumstantial. The natural history of the disease after diagnosis includes partial remission in most patients, but only 3 percent achieve transient insulin independence. Beta cell function, as indicated by the plasma concentration of C-peptide , is lost over 6 to 30 months and islet cell antibodies disappeared over 1to2 years. This article describes a pilot study in which 41 patients were treated with the immunosuppressive agent cyclosprorine for 2 to 12 months. Of 30 patients treated within 6 weeks of diagnosis, 16 became insulin independent with concentrations of plasma C-peptide in the normal range and decreasing titers of islet cell antibodies. Of 11 patients who entered the study 8 to 44 weeks after diagnosis, two achieved this state. These results indicate that a controlled trial of the effects of cyclosporine in type I diabetes should be conducted.

G. Feutren R. Assan , G, Karsently , H. DuRostu , J. Sirmai, L. Papoz, B. Vialetts, P. Vexall, M. Rodier, A. Lallenaxd, Cyclosporine increases the rate and length of Remissions in insulin Dependent Diabetes of recent onset Results of a multicentre Double blind Trial, Lancet 1986; 2:119-123.

In a double-blind trial 122 patients aged 15-40 years with insulin-dependent diabetes of recent onset were randomly assigned to cyclosporine 7.5 mg/kg per day or placebo. At the sixth month 25.4% of the cyclosporine ground 18.6% of the placebo group were in complete remission (not a significant difference). Treatment was continued in those patients with complete or partial remission (insulin requirement < 0.25 u/kg per day and 106 patients were followed to nine months at which stage 24.1% of the original cyclosporine group and 5.8% of the original placebo group were in complete remission (P <0.001). For those patients whose whole blood trough cyclosporine levels in the first three months averaged 300 mg/ml or more, the rates of complete remission at six and nine months were 37.5% and 37%. The rates of partial remission were also higher in the cyclosporine group and at six months the rate of complete or partial remission was 46% in the whole cyclosporine group and 65.6% in those with an average blood level exceeding 300√mg ml in the first three months, versus 28.8% in the placebo group. The principal side-effect of cyclosporine was a modest and reversible increase in plasma creatinine. These results indicate that cyclosporine promotes the remission of type I diabetes and suggest the need for new controlled protocols aimed at evaluating the length of the effect and selecting the best drug regimen.

The above two reports represent the results of the 2 well designed pilot immunotherapeutic trials in autoimmune IDDM. The salient messages are : I) nonspecific (blanket) immunosuppression with agents like cyclosporine A given over a period of 1 yr. can protect residual B-cell function when administered to new onset IDDM subjects, associated with suppression of autoimmune response. ii) discontinuation of immunosuppressive therapy is associated with relapse of islet-cell autoimmuity B cell destruction and IDDM (ICAbs may reappear and rebound in higher titers). Thus to be effective these drugs have to be given life long. iii) the practical question may be long term toxic effects of cyclosprone A (hepatotoxicity, malignancy) vs the prognosis with current forms of insulin therapy. Iv) preclinical (before significant destruction of B-cells) and selective (antigen specific desensitization; antidiotype antibodies) immunomodulation might be essential for this approach to be clinically useful.