ABSTRACT SERVICE:

R.G. Naik P. Shah
"Non Insulin Dependent Diabetes Mellitus"
Dept. Endocrinology Metabolism & Diabetes, All India Institute of Medical Sciences

Diabetes mellitus was considered a disease of the rich and lazy until some time ago. It was really not a wrong concept an alarmingly high prevalence of type II diabetes in developing populations, reported from all over the world bears testimony to it. Similar epidemics of obesity and insulin resistance have also been reported. With well known effects of obesity-hyperinsulinemia-diabetes syndrome, mortality and morbidity patterns of such recently 'prosperous' populations are likely to change.

This environmental onslaught on background genetic predisposition precipitates type II diabetes. The exact "genetic predisposition", however, is not clear at all. Attempts to look for specific genetic defects in insulin synthesis, processing or action have not been fruitful. The metabolic defects are being unravelled, however.

Whatever the precise pathogenetic mechanism, "Coco colaisation" of everything, from philosophy to life pattern, may well be responsible for this oncoming burden to poorly developing medicare system in our societies.

Mather HM, Keen H.
The Southall Diabetes Survey: prevalence of known diabetes in Asians and Europeans.
Br Med J 1985; 291: 1081-4. (From: Ealing Hospital, Southall, Middlesex and Guys Hospital Medical School, London).

A house to house inquiry for patients with known diabetes was carried out in a defined area of Southall, west London, which contained over 34,000 Asians and 27,000 Europeans in the 1981 Census. 1143 diabetic patients were ascertained, of whom 761 were Asian and 324 European. The prevalence, adjusted for age of known diabetes in Asians, was at least 3.8 times higher than that in Europeans. For patients aged between 40 and 64 years it was at least five times higher, was over 12% in Asians aged 60-69, and over 8% in those aged 50-59. These data are important in planning for the care of diabetic patients in health districts with large Asian communities. The causes and consequences of this exceptionally high prevalence requite further study.

Ramchandran A, Jali MV, Mohan V, Snehalatha C, Viswanathan M.
High prevalence of diabetes in an urban population in South India
Br Med J 1988; 297: 587-90. (From Madras Diabetes Research Centre, Madras and Kudremukh Iron ore Company Hospital, Kudremukh).

An urban population in a township in south India was screened for diabetes with an oral glucose tolerance test. Every fifth person aged 20 and over registered at the local iron ore company's hospital was screened. Of 678 people (346 men and 332 women) who were tested, 34 (5%; 20 men and 14 women) had diabetes and 14 (2%; 8 men and 7 women) had impaired glucose tolerance. Thirteen subjects were already known to be diabetic. Diabetes was present in 21% (37/179) of people aged over 40. The peak prevalence (41%; 7/17) was in the group aged 55-64. A family history of diabetes was present in 16 of the 34 subjects with diabetes and nine of the 15 with impaired glucose tolerance. Diabetes was significantly related to obesity in women but not in men (57% (8/14) v 5% (1/20)). The plasma glucose concentration two hours after glucose loading was correlated to body mass index, age, and income in both sexes. The prevalence of diabetes was significantly higher in subjects whose income was above the mean.

When the overall prevalence of diabetes was adjusted to the age distribution of the Indians living in Southall, London, and in Fiji, it increased to 10% and 9%, respectively. The prevalence of diabetes is high among urban Indians and is comparable with the high prevalence seen in migrant Indian populations.

Dowse GK, Gareeboo H, Zimmet PZ, Alberti KG, Tuomilehto J, Fareed D, Brissonnettee LG, Finch CF.
High prevalence of NIDDM and impaired glucose tolerance in Indian, Creole and Chinese Mauritians
Diabetes 1990; 39: 390-6. (From WHO Collaborating Centre, Epidemiology of Diabetes Mellitus, Lions International Institute, Melbourne, Australia.)

Mauritus, a multiethnic island nation in the south-western Indian Ocean, has one of the world's highest diabetes mortality rates. The prevalence of both impaired glucose tolerance (IGT) and non-insulin dependent diabetes mellitus (NIDDM) was investigated in 5080 Muslim and Hindu Indian, Creole (mixed African, European, and Indian origin), and Chinese Mauritan adults aged 25 to 74 years who were selected by random cluster sampling. Based on a 75-g oral glucose tolerance test and World Health Organization criteria, the age standardized prevalence of IGT was significantly greater in women (19.7%, 95% confidence interval (CI) 18.1-21.2) than in men (11.7%, CI 10.5-12.8). By contrast, the prevalence of NIDDM was similar in men (12.1%, CI 10.9-13.4) and women (11.7%, CI 10.5-12.8) for all ethnic groups combined. The gender difference in IGT prevalence was seen in all ethnic groups, but for NIDDM, the gender difference was not consistent across ethnic groups. However, age and gender standardized prevalence of IGT and NIDDM was remarkably similar across ethnic groups (16.2% and 12.4% in Hindu Indians, 15.3% and 13.3% in Muslim Indians, 17.5% and 10.4% in Creoles, and 16.6% and 11.9% in Chinese, respectively). Three new cases of diabetes were diagnosed for every 2 known cases. The high prevalence of abnormal glucose tolerance in Indian subjects is consistent with studies of other migrant Indian communities, but the findings in Creole and, in particular, Chinese subjects are unexpected. Potent environmental factors shared between ethnic groups in Mauritius may be responsible for the epidemic of glucose intolerance.

Verma NPS, Methta SP, Madhu F, Mather HM, Keen H.
Prevalence of known diabetes in an urban Indian environment: the Daryaganj diabetes survey Br Med. J 1986; 293: 423-4. (From: New Delhi).

Information was obtained from 6878 residents (3643 men and 3235 (47%) women) in a home-to-home survey within a defined area in Darya Ganj. New Delhi: A total of 213 people were reported to be diabetic, giving an overall crude prevalence of 3.1%.

This survey showed an unexpectedly high prevalence of known diabetes in this fairly affluent population. The prevalence is much higher than that found in previous Indian surveys, although direct comparison is difficult owing to different methods of ascertainment.

Matter in italics are author's comments.

The high prevalence in Daryaganj may relate to socioeconomic state, improved relative survival of patients with diabetes, more intensive screening of the population, or all of these factors. The true prevalence can be ascertained only by systematically applying standard diagnostic techniques. The age specific prevalences reported are strikingly similar to those found in Asians in Southall and at least five times as high as those in Europeans in Southall aged 40-64. More complete diagnostic ascertainment would be unlikely to negate these major differences. Although Asians in Southall comprise mainly Punjabi Sikhs, the economic state of the Southall and Delhi samples is probably comparable. A high prevalence may therefore occur within Indian as well as in migrants elsewhere if the population is exposed to appropriate environmental factors. Indian people would seem to rank high in terms of ethnic susceptibility to diabetes.

Ahren, Corrigan CB
Prevalence of diabetes mellitus in North-Western Tanzania Diabetologia 1984; 26: 333-6. (From Ramachumu and Bugando Hill Hospital, Mwanza, Tanzania).

The prevalence of diabetes mellitus in 3,145 Tanzania Africans living in three different areas of the country was studied. Fasting capillary blood glucose concentrations were measured by dextrometer and if the levels were > 5.5 mmol/L oral glucose tolerance test was performed. When using the WHO criteria (8) for diagnosis, the overall diabetic prevalence was 0.7%. Prevalence increased with age, and in the population > 20 years of age it was 1.6%. In a rural area inhabited by the Haya tribe, the prevalence in the population > 20 years was 2.5%, and in a similar area populated by Sukuma tribe it was 0.5%. In the urban area of Mwanza town it was 1.9%. Obesity was seen in 3.7% of the population and in 9.1% of the diabetic subjects. Sixty eight percent of the diabetic patients were female compared with 53% in the general population. None of the diabetic patients discovered had any symptoms. Thus, the overall prevalence of diabetes in Tanzania is rather low but shows geographical variability and is strongly associated with age.

Winter WE, Maclaren NK, Riley WJ, Clarke DW, Kappy MS, Spilar, RP.
Maturity -- Onset Diabetes of Youth in Black Americans N Engl J Med 1987; 316: 285-91. (From Univ. of Florida, Gainesville).

Maturity-onset diabetes of youth is a subtype of non-insulin-dependent diabetes that is often inherited in an autosomal dominant pattern. An atypical diabetes syndrome was identified in young black Americans that has features of maturity-onset diabetes of youth.

The study group included 129 unrelated black patients who were initially thought to have insulin dependent diabetes. In 12 of these patients the disease took an unusual clinical course, with apparent insulin dependence at the time of presentation followed by absence of dependence months to years later. This atypical form of diabetes was found in at least two generations in 9 of the 12 families of the propositi. Because of this, 14 of the diabetic relatives, as well as the 12 propositi were studied.

Islet cell autoantibodies were not identified in any of the patients, and thyroid microsomal autoantibodies were identified only in one. Furthermore, the frequencies of the insulin-dependent-diabetes-associated antigens HLA-DR3 and DR4 were not increased among the propositi, and diabetes did not cosegregate with HLA haplotypes in the informative families. Insulin secretion was found to be intermediate between secretion in non-diabetic controls and that in patients with classic insulin-dependent diabetes. The peripheral blood monocytes expressed increased numbers of insulin receptors as well as decreased empty site affinities. This atypical from of diabetes in black Americans can be distinguished from classically defined insulin dependent diabetes and may be best classified as a form of maturity onset diabetes of youth.

Omar MAK, Seedat MA, Dyer RB, Rajput MC, Motala AA, Joubert SM.
The prevalence of diabetes mellitus in a large group of South African Indians
S Afr Med J 1985; 67: 924-6. (From University of Natal, South Africa).

The prevalences of diabetes mellitus and impaired glucose tolerance (IGT) among 866 Indians living in the Chatswoth area of Durban were determined. The study group was selected by cluster sampling and the participants underwent a modified glucose tolerance test (GTT) (determination of fasting and 2-hour plasma glucose levels after a 75 g glucose load). On the basis of the revised World Health Organization criteria the overall prevalence of diabetes mellitus was 11% and of IGT 5.8%. Of the 368 men, 7.6% were found to have diabetes mellitus and 7.1% IGT, the prevalence of diabetes mellitus was much greater among women (13.5%), while there was less IGT (4.8%). Subjects with diabetes mellitus were significantly older (mean 50.7 years) than those with a normal GTT (mean 30.9 yearsbersm

genetic background" (see also Perspectives in diabetes: Archeology of NIDDM, Excavation of the "thrifty" genotype. Wendorf, M and Goldfine, ID. Diabetes 1991; 40: 161-65). The remarkably high prevalence forecasts a dim future for most NIDDMs in such developing populations in their home lands if the preventive and medicare systems do not grow adequately.

Rotwein PS, Chirgwin J, Province M, Province M, Knowler WC, P.H., Pettitt DJ, Cordell B, Goodman HM, Permutt MA.
Polymorphism in the 5' Flanking Region of the Human insulin Gene: A Genetic Marker for non-insulin-dependent Diabetes N Engl J Med 1983; 308: 65-71. (From: National Institute of Arthritis, Diabetes and digestive and Kidney Diseases, Phoenix).

Authors sought to determine whether differences in the human insulin gene or its immediate flanking sequences could be found in diabetes. Peripheral leukocyte DNA from 217 unrelated persons, including blacks, whites, and Pima Indians, was analyzed by restriction enzyme digestion, blotting to nitrocellulose filters, and hybridization to cloned (P) insulin gene probes. A region of length variation including deletions (0.1 to 0.2 kilobase pairs) or insertions (0.6 to 5.5 kb) of DNA was found only in the immediate 5' flanking region in 33 per cent of the genes examined. A 1.6-kb insertion accounted for 80 per cent of the polymorphism. This variant was found more often in subjects with non-insulin-dependent diabetes than in non-diabetics, regardless of race (P=0.011). Length polymorphism in the 5' flanking region of the insulin gene may provide a genetic marker for non insulin-dependent diabetes.

Hitman CA, Karir PK, Mohan V, Rao PV, Kohner EM, Levy IC, Mather H.
A Genetic Analysis of Type 2 (Non-insulin-dependent)
Diabetes Mellitus in Punjabi Sikhs and British Caucasoid patients
Diab Med. 1987; 4: 526-30. (From: Tandon Hospital, Whitechapel and Ealing Hospital, London).

A genetic analysis of diabetic and non diabetic Punjabi Sikhs (n=164) was made for markers of non insulin dependent diabetes mellitus using insulin receptor Insulin, and HLA-D gene probes. Additionally British Caucasoids (n=163) were studied using the insulin receptor probe. Insulin receptor gene restriction fragment length polymorphisms were defined using Southern blot techniques and the restriction enzyme Bgl II and Bam HI. In Punjabi Sikhs and British Caucasoids neither of the restriction fragment length polymorphisms distinguished non-insulin-dependent diabetes mellitus subjects from controls. In the Sikhs no association with non-insulin-dependent diabetes mellitus was seen with the hypervariable region of the insulin gene or with HLA- DR/DQ/DX chain restriction fragment length polymorphism. Therefore is concluded that despite the high prevalence of non insulin dependent diabetes mellitus in Asians authors were unable to find any genetic markers for this disease using the available cloned gene probes.

Raben N, Barbetti F, Cama A, Lesniak MA, Lillioja S, Zimmet P, Werjeantson SS, Taylor SI, Roth J.
Normal Coding Sequence of Insulin Gene in Pima Indians and Nauruans, Two Groups with Highest prevalence of Type II Diabetes
Diabetes 1991; 40: 118-22. (From: National Institute of Diabetes and Digestive and Kidney diseases, NIH, Bethesda).

The nucleotide sequence of the insulin gene was determined in American Pima Indians and Micronesian Nauruans, two populations in whom the prevalence of non insulin dependent (type II) diabetes mellitus is the highest in the world. The insulin gene was amplified by the polymerase chain reaction to generate single stranded DNA suitable for direct sequencing. The nucleotide sequence of the coding and adjacent regions of the insulin gene in six Pima Indians and two Nauruans with type II diabetes were identical to previously published insulin gene sequences of non-diabetic subjects.

In an attempt to clinch the "gene" involved in the pathogenesis of type II diabetes many polymorphisms have been described in studies on small groups of patients. It often appeared as though the riddle would be solved either as a defect in proinsulin gene, proinsulin processing, insulin receptor gene or glucose transporter gene. But none have stood the test of time. In actuality, the genetic key may be lying somewhere else and is "hidden" as yet. Newer paradigms need exploration.

Kirk RL, Ranford PR, Serjeantson WS, Thompson AR, Munirathnam Chetty SM, John L, Mohan V, Ramchandran A, Snehalatha C, Viswanathan M.
HLA, Complement C2, C4, properdin factor B and glyoxalase types in South Indian diabetics
Diabetes Research and Clinical Practice 1985; 1:41-7. (From: John Curtin School of Medical Research, Canberra, CMC, Vellore and Diabetes Research Center, Madras).

A series of diabetic patients from 3 centres in South India have been tested for HLAA, HLAB, BF, C2, C4A, C4B and GLO types. For insulin dependent diabetes mellitus (IDDM) patients there was a significant increase in HLA B8 of BF F and decrease of C4, A6. No significant variation in HLA, BF, C2 or GLO frequencies was found in non-insulin dependent diabetes mellitus (NIDDM) patients.

Omar MAK, Hammond MG, Seedat MA, Asmal AC.
HLA antigens and non-insulin-dependent diabetes mellitus in young South African Indians
S Afr Med. J 1985; 67:130-2.(From: Univ. Natal.)

HLA A, B and C antigens were determined in 84 South African Indian patients with non insulin dependent diabetes mellitus (NIDDM) in whom age of onset was under 35 years and in 760 healthy Indian controls. The findings in this study serve to emphasize the heterogeneity of diabetes mellitus....

With detection of a very high (initially, 100%) frequency of Aspartic acid negative homozygosity at amino acid 57 of HLA beta chain of type II molecule, we seemed to have solved the problem of HLA and type I diabetes. However the coexistence of IDDM and non-homozygosity of Asp (at position 57) has put this in doubt. No correlation has been found between NIDDM and HLA types. However, HLA typing can be used to determine the race of an individual, though restriction fragment length ploymorphism "finger printing" may be a better tool.

Modan M, Halkin H, Karasik A, Lusky.- The Israel study of glucose intolerance, obesity and hypertension.
Effectiveness of glycosylated hemoglobin, fasting plasma glucose and a single post load plasma glucose level in population screening for glucose intolerance
Am J Epidemiol 1984; 119: 431-4. (From: Dept. of clinical Epidemiology and Medicine, Chaim Sheba Med. Center Israel).

Five shortcut methods of population screening for glucose intolerance (impaired glucose tolerance and non-insulin-dependent diabetes mellitus) were assessed for effectiveness: 1) glycosylated hemoglobin concentration (HBA1), 2) fasting plasma glucose level, 3) combinations of fasting plasma glucose and HbA1, 4) plasma glucose one hour post oral glucose load, and 5) plasma glucose two hour post oral glucose load. In a sample of the Israeli Jewish population aged 40-70 years, 2040 participants in the Israel Study of Glucose Intolerance, Obesity and Hypertension, who were not known to be diabetic, underwent an oral glucose tolerance test based on three blood samples (fasting, one hour, and two hour post oral glucose load). In 1058 of the subjects, HbA1 was also

measured, and was found to increase significantly ($p<0.001$) with increasing glucose intolerance, but with extensive overlap of ranges, even between normals and newly found diabetics. Fasting plasma glucose was more effective than HbA1 in screening for both impaired glucose tolerance and diabetes by its higher specificity and predictive value of a positive test at comparable sensitivity levels. Combinations of HbA1 and fasting plasma glucose did not improve prediction over fasting plasma glucose alone. As observed in other studies, the screening effectiveness of fasting plasma glucose was also unsatisfactory, either post load glucose level being more effective. Plasma glucose level two hour post load was better for detection of diabetes alone. Plasma glucose level one hour post load was more effective at detecting the total group of glucose intolerance, but did not discriminate well between impaired tolerance and diabetes. A cost risk benefit evaluation suggests that a full three sample oral glucose tolerance test is the best method in screening for both intolerance categories.

Epidemiologic tools for diagnosis of diabetes or IGT is far from ideal. Though HbA1c can be used as a single test and does not require the glucose loading, its effectivity for screening is doubtful. Despite "WHO criteria" (Technical report series 727, World Health Organisation, Geneva, 1985 p11) many people prefer additional blood glucose samplings also for diagnosis of impaired glucose tolerance (Harris M, Cahil G. (Members of NIH Diabetes Date Group workshop). A draft classification of diabetes mellitus and other categories of glucose tolerance. Diabetes 1979; 28:1039-57).

Nagi DK, Hendra TJ, Temple RC, Clark P, Schneider A, Hales CN, Yudkin JS.
Insulin deficiency as a cause of non-insulin-dependent diabetes mellitus- a study using immunoradiometric insulin assays in Asian and Caucasian subjects
Diab Med. 1989; 6 Suppl 2: 2A. (From: London Addenbrooke's Hospital, Cambridge).

Hyperinsulinaemia and insulin resistance are common features of NIDDM. Using highly specific monoclonal antibody based immunoradiometric assays (IRMA) authors had previously shown that in fasting NIDDM subjects as much as 70% of "immunoreactive insulin" (IRI) comprises 32-33 split pro-insulin and intact pro-insulin, with IRMA insulin levels only 30% of those measured by radioimmunossay. Their hypothesis is that insulin deficiency may play a more important role in the aetiology of NIDDM than previously thought. They have used homeostatic model assessment (HOMA) to calculate insulin resistance (IR, normal = 1.0) and islet B-cell function (BCF, normal = 100%) using fasting insulin levels measured by IRI and by IRMA, employing the observation that IRMA insulin comprises 76 (SD 3%) of all insulin like molecules in non obese non-diabetic subjects in order to adapt the HOMA equation for use with IRMA insulin levels. 50 NIDDM subjects (24 Asian, 26 Caucasian) with mean duration of diabetes 3 (0.5-16) Y were assessed. Mean fasting glucose was 9.4 (SD 3.2) mmol/l and glycosylated haemoglobin 9.1 (SD 1.9%). Insulin resistance (IR) calculated using IRMA insulin was 3.8 (SD 2.6) compared to 8.3 (SD 6.5) using IRI ($p<0.0001$). B-cell function (BCF) using IRMA insulin was 41.4 (SD 35.2%) compared to 86.1 (SD 74.2%) using IRI ($P<0.0001$). Asian subjects demonstrated elevated levels of IR compared with Caucasians using IRMA estimates ($p=0.04$), but BCF was similar in the two groups. Insulin deficiency may therefore play a major role in the aetiology of NIDDM.

Lillioja S, Mott DM, Howard BV, Bennett PH, Yki-Jarvinen H, Freymond D, Nyoma BL, Zurlo F, Swinburn B, Bogardus C.
Impaired Glucose Tolerance as a Disorder of Insulin Action: Longitudinal and Cross-Sectional Studies in Pima Indians N Engl J Med. 1988; 318: 1217-25. (From: Natl. Inst. of Diabetes and Digestive and Kidney Disorders, Phoenix).

Impaired glucose tolerance often portends the development of non-insulin-dependent diabetes mellitus (NIDDM). Study of the determinants of impaired glucose tolerance should lead to better insulin action were thus assessed in 25 Pima Indians, representative of a population having a high prevalence of diabetes, before and after the development of impaired glucose tolerance and in 254 individuals having a wide range of glucose tolerance.

The transition from normal to impaired glucose tolerance was associated with a decrease in insulin stimulated glucose uptake form 0.018 to 0.016 mmol/minute. During an oral glucose tolerance test, the mean plasma insulin concentrations rose from 1,200 to 1,770 pmol/L. In 151 individuals with normal glucose tolerance the insulin concentration measured during an oral glucose tolerance test correlated with the plasma glucose concentration. The insulin concentration predicted from this relationship in normal individuals was nearly identical to that observed in patients with impaired glucose tolerance, suggesting that these individuals had normal insulin secretion. In contrast, the plasma insulin concentrations in diabetic patients decreased as glucose concentrations rose; this suggests deficient insulin secretion. Relative insulin deficiency first appeared at the lower end of the second diabetic mode seen in population frequency distributions of plasma glucose concentrations.

In this study population impaired glucose tolerance appears to be caused primarily by impaired insulin action. In contrast, impaired insulin action and insulin secretory failure are both present in patients with NIDDM.

Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, Group L.
Early Metabolic Defects in Persons at Increased Risk for Non-Insulin Dependent Diabetes Mellitus
N Engl J Med 1989; 321: 337-43. (From:Helsinki Univ).

It is estimated that 43% of the first degree relatives of patients with non-insulin dependent diabetes mellitus (NIDDM) will ultimately have diabetes. To identify early metabolic defects in persons at increased risk for NIDDM, insulin sensitivity and insulin secretion were measured in 26 first degree relatives of patients with NIDDM, 14 healthy controls with no family history of NIDDM, and 19 patients with NIDDM. The euglycemic insulin clamp technique, indirect calorimetry, and infusion of (3-H) glucose were used to assess insulin sensitivity.

Total body glucose metabolism was significantly impaired in relatives of patients with NIDDM compared with controls. Relatives of patients with NIDDM had the same degree of disturbance in glucose metabolism as patients with manifest NIDDM. The defect in total body glucose metabolism was almost completely accounted for by impaired non oxidative glucose metabolism, primarily the storage of glucose as glycogen. The relatives with normal glucose tolerance had a similar degree of impairment in non-oxidative glucose metabolism as the relatives with impaired glucose tolerance. Only the patients with manifest diabetes had significant impairment in insulin stimulated glucose oxidation. During hyperglycemic clamping, first phase insulin secretion was absent in patients with NIDDM and severely impaired in their relatives with impaired glucose tolerance. Insulin secretion was normal in the relatives with normal glucose tolerance.

Metabolic abnormalities leading to NIDDM begin much earlier than previously thought. Impaired glucose metabolism is common in first degree relatives of patients with NIDDM despite normal glucose tolerance. Both insulin resistance and impaired insulin secretion are necessary for the development of impaired glucose tolerance in these individuals.

Ramachandran A, Snehalatha C, Mohan V, Bhattacharyya PK, Viswanathan M.
Decreased Insulin sensitivity in offspring whose both parents have type 2 diabetes.
Diabetic Med 1990; 7:331-4. (From: Diabetes Research Centre, Madras, India).

Offspring of 2 type-II diabetic parents have a high prevalence of diabetes and impaired glucose tolerance. Studies in normoglycemic offspring have shown abnormal insulin responses. Twenty four non-obese offspring having normal oral glucose tolerance were investigated by the insulin tolerance test for abnormalities of insulin sensitivity. Plasma insulin responses were measured during an oral glucose tolerance test. Although the plasma glucose responses during the oral glucose tolerance test were similar to the control values, the corresponding insulin responses were higher. The mean area under the insulin curve was 121+29 (+SD) mU/l/h in the control subjects and 203+73 mU/l/h in the offspring ($p<0.001$). The mean KITT value in the offspring was 4.3+1.9/min. X 100 which was significantly lower ($P<0.01$) than the value of 6.2+2.0/min. X 100 in the control subjects. The results suggest that some offspring of 2 type-II diabetic parents have low insulin sensitivity and the presence of hyperinsulinism may be a compensatory phenomenon.

Osei K.
Increased basal glucose production ad utilization in non-diabetic first-degree relative of patients with NIDDM Diabetes 1990; 39: 597-601. (From: Ohio State University Hospital, Columbus, USA).

To characterize the abnormalities in basal glucose homeostasis in people who are at increased risk for non insulin dependent diabetes mellitus (NIDDM), the authors measured the rates of basal hepatic glucose output (HGO), glucose disappearance, and metabolic clearance of glucose (MCR) in 27 non diabetic first degree relatives of NIDDM patients and 16 age, gender, and weight matched healthy control subjects with no family history of NIDDM. Mean fasting plasma glucose was significantly lower ($p<0.05$) in control subjects (mean + SE 77+2 mg/dl) than in relatives (84+2 mg/dl). Mean basal insulin levels were not significantly different between relatives and control subjects (10.0 +1.5 uU/ml vs. 7.7+1.0 uU/ml). Mean basal HGO was significantly lower in control subjects compared with relatives (1.83 + 0.7 mg/kg/min. vs. 2.20 + 0.10 mg/kg/min., $p<0.05$). Mean MCR was similar in relatives (2.58 +0.12 mg/kg/min.) and control subjects (2.35 + 0.9 mg/dg/min.). In summary, this study demonstrates that basal hepatic glucose productions and glucose utilization are increased in glucose tolerant first degree relatives compared with healthy control subjects. The authors conclude that impaired basal hepatic glucose regulation rather than glucose disposal is present as an early defect in glucose tolerant first degree relatives of NIDDM patients.

Rahilly SO, Turner RC, and Matthews DR.
Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes
N Engl J Med 1988; 318: 1225-30. (From: Diabetes Research Laboratories, Radcliffe infirmary, Woodstock, UK).

In fasting non-diabetic subjects, insulin is secreted in regular pulses every 12 to 15 minutes, but patients with non insulin dependent diabetes lack regular oscillatory insulin secretion. To investigate whether abnormal insulin oscillations are an early feature of diabetes, authors studied 10 minimally glucose intolerant first-degree relatives of patients with non insulin dependent diabetes and controls matched for age and obesity. They performed a pre-series analysis of fasting plasma insulin levels in blood samples obtained at 1minute intervals for 150 minutes. Fasting plasma glucose levels were higher in the natives than in the controls (mean + SD, 5.4 + 0.7 vs. 14.03 mmol per liter). Autocorrelation of pooled data moved no regular oscillatory activity in the relatives but a 1 minute cycle in the controls ($r=0.23$, $P<0.001$). Similarly, Fourier transform analysis showed no significant peak in the relatives but the expected significant peak at 13 to 14 minutes in the controls ($p<0.05$). First phase (0 to 10 minutes) insulin secretory responses to glucose administered intravenously were not significantly impaired in the relatives (geometric mean, 188 pmol per liter (26.2 mU per litre), range of SD, + 103 to-67 pmol per liter (+14.4 to -9.3 mU per liter), as compared with the controls (geometric mean, 231 pmol per liter (32.2 mU per liter); range of SD, +131 to-83 pmol per liter (+18.2 to - 11.6 mU per liter).

We conclude that abnormal oscillatory insulin secretion may be an early phenomenon in the development of non insulin dependent diabetes.

Johnston C, Ward WK, Beard JC, McKnight B, Porte DJr.
Islet function and insulin sensitivity in the non-diabetic offspring of conjugal type 2 diabetic patients
Diabetes Med 1990; 7: 119-25. (From: Department of Medicine, University of Washington, Seattle, USA).

To determine whether the genetic predisposition towards type-II diabetes was associated with a defect in either islet-cell function or insulin action, 12 non-diabetic offspring each of whose parents both had type-II diabetes were studied, together with 12 control subjects matched for age, gender, and weight. Fasting plasma glucose was higher in the offspring (5.5+0.1 mmol/l (mean ± SE) than in the matched controls (5.1+0.1 mmol/l) ($P < 0.05$). Using an IVGTT insulin sensitivity was not significantly lower in the offspring compared with their controls (3.1+0.5 10-41/min./mU vs. 3.8+1.0 10-41/min./mU). There was no significant difference in any of the measures of insulin secretion (first and second phase response to IV glucose, slope of glucose potentiation, and maximal glucose regulated insulin secretory capacity). Glycogen secretion measured before and after a stimulus of IV arginine at varying plasma glucose concentrations was virtually identical in the offspring and their controls. Among a total of 28 non diabetic subjects of differing body weights there was a significant inverse relationship between insulin sensitivity and insulin secretion. When adjusted for their generally lower insulin sensitivity, maximal insulin secretory capacity was reduced in the offspring ($P=0.038$. one tailed t-test). The results suggest that the genetic predisposition to type-II diabetes is not associated in young adults with any major premorbid impairment in insulin secretion or insulin action but the relationship between the two may be abnormal. A-cell function appears to be normal.

The teleological sequence of events during evolution of the syndrome of "obesity-hyper-insulinemia-hyperglyceamia" is not very clear (see 'Etiopathogenesis of type II diabetes' in his issue of Bulletin). Moreover Nagi et al show that "hyperinsulinemia" may not really be a state of increased insulin in circulation because conventional RIAs may be measuring pro-insulin, and its non-insulin fragments also as "insulin."

But resistance to the action of insulin is apparent in per-diabetic first degree relatives of NIDDM. The insulin-mediated glucose uptake at the level of skeletal muscles is defective even in normal glucose tolerant first degree relatives of NIDDM. The impairment of insulin mediated stimulation of oxidative utilisation of glucose is associated with manifest diabetes. It appears that non-suppressibility of (otherwise also excessive) hepatic glucose output (HGO) by insulin may be one of the prime metabolic defects contributing to hyperglycemia of diabetes. An abnormal HGO has been recently demonstrated in first degree relative of NIDDM (Osei K et al).

Mckeigul PM, Shah B, Marmot MG.
Diabetes, Insulin Resistance and central obesity in South Asians and Europeans

Diab Med. 1989; 6 Suppl 1: A41-42.

South Asians (Indians, Pakistanis and Bangladeshis) have high prevalence of NIDDM and high mortality from ischemic heart disease compared with other populations. Preliminary results from a study testing the hypothesis that insulin resistance underlies this has been reported. 567 men aged 40-64 in industrial workfores in West-London have been examined. Prevalence of NIDDM was 14.8% in South Asians compared with 3.8% in Europeans. Serum insulin levels in South Asian men compared with European men were 20% higher in the fasting state and 66% higher at 2 hr. after a glucose load. Plasma triglyceride levels were 17% higher and HDL cholesterol levels were 0.1 mmol/L lower in South Asian than Europeans ($p<0.01$). South Asians showed a striking tendency to central obesity average waist hip circumference ratio 0.97 compared with 0.92 in Europeans which accounted for most of the ethnic difference in insulin levels. These results confirm that the high prevalence of diabetics in South Asian is part of a pattern f metabolic disturbances related to insulin resistance. It shows for the first time that this is associated with central obesity.

Mckeigue PM, Marmot MG, Syndercombe Court YD, Cottier DE, Rahman S, Pariemersma RA.
Diabetes, hyperinsulinaemia and coronary risk factors in Bangladeshis in East London
Br Heart J 1988; 60:390-6.
(From: Department of Community Medicine, University College and Middlesex School of Medicine; Department of Haematology, London Hospital Medical College and the Cardiovascular Research Univ. George Square, Edinburgh).

Immigrants from the Indian subcontinent (South Asians) in England and Wales have higher morbidity and mortality from coronary heart disease than the general population; this seems to apply to both Hindus and Muslims. Studies in north west London and Trinidad found the increased risk of coronary heart disease in Indians was not explained by dietary fat intake, smoking, blood pressure, or plasma lipids. In the present study the distribution of coronary factors was measured in an East London borough where the mortality and attack rate from coronary heart disease are higher in the Asian population, predominantly Muslims in Bangladesh, than in the rest of the population. In a sample of 253 men and women aged 35-69 from general practice, mean plasma cholesterol concentrations were lower in Bangladeshi than European men and women. Mean systolic blood pressures were 10 mm Hg lower in Bangladeshis. Plasma fibrinogen concentrations were similar in Bangladeshis and Europeans and factor VIII coagulant activity was lower in Bangladeshi than in European men. In contrast with the finding in Hindus in north west London, smoking rates were high in Bangladeshi men and the ratio of polyunsaturated fatty acids to saturated fatty acids in plasma lipids was lower in Bangladeshis in Europeans. Diabetes was three times more common in Bangladeshis than in Europeans. Diabetes was three times more common in Bangladeshis than in Europeans. Serum insulin concentrations measured after a glucose load were twice as high in Bangladeshi. High insulin concentrations in Bangladeshis were associated with high plasma triglyceride and high-density lipoprotein cholesterol concentrations.

Insulin resistance, leading to diabetes, hyperinsulinaemia, and secondary lipoprotein disturbances, is a possible mechanism for the high rates of coronary heart disease in South Asian Britain and overseas.

Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M, Shitrit A, Fuchs Z.
Hyperinsulinemia a link between hypertension, obesity and glucose intolerance
J Clin Invest 1985; 75:809-17. (From Departments of Clinical Epidemiology and Medicine, Clinical Pharmacology Unit, and Institute of Endocrinology, Chaim Sheba Medical Center, Israel).

Hypertension and glucose intolerance, determined in a random population sample (n=2, 475), showed a highly significant ($P < 0.001$) association from the mildest levels of both conditions, independent of the confounding effects of age, sex, obesity, and antihypertensive medications. Summary rate rations for hypertension were 1.48 (1.18-1.87) in abnormal tolerance and 2.26 (1.69-2.84) in diabetes compared with normal tolerance. Altogether, 83.4% of the hypertensives were either glucose- intolerant or obese-both established insulin resistant conditions. Fasting and post load insulin levels in a representative subgroup (n=1.241) were significantly elevated in hypertension independent of obesity, glucose intolerance, age, and antihypertensive medications. The mean increment in summed 1-and 2-h insulin levels (milliunits per liter) compared with non obese nor-motensives with normal tolerance was 12 for hypertension alone, 47 for obesity alone, 52 for abnormal tolerance alone, and 124 when all three conditions were present. The prevalence of concentrations (milliequivalents per liter) of erythrocyte $Na + \geq 7.0$ $K+ < 92.5$, and plasma $K+>4.5$ in a subsample of 59 individuals with all combinations of abnormal tolerance obesity and hypertension was compared with those in 30 individuals free of these conditions. Altogether, 88.1% of the former vs. 40.0% of the latter group presented at least one of these three markers of internal cation imbalance ($P <0.001$). It is concluded that insulin resistance and/or hyperinsulinemia (a) are present in the majority of hypertensives, (b) constitute a common pathophysiologic feature of obesity, glucose intolerance, and hypertension, possibly explaining their ubiquitous association, and (c) may be linked to the increased peripheral vascular resistance of hypertension, which is putatively related to elevated intracellular sodium concentration.

Hughes LO, Cruickshank JK.
Hypothesis: excess insulin secretion contributes to established ischaemic heart disease in British Asians and Whites
Diab Med 1989; 6 Suppl 2:8A. (From: Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex).

Authors have tested the hypothesis that serum insulin and C-peptide concentrations might be associated with established ischaemic heart disease (IHD) which is epidemic in migrants of Indian subcontinent origins ("Asians"). A consecutive series of 74 Asian and 76 white men surviving first myocardial infarction were compared with 58 and 57 respective controls without IHD, randomly sampled from the community, by 2h 75g glucose tolerance tests.

Significantly more Asian patients and controls had impaired glucose tolerance and overt diabetes than respective whites (32% v 15% [$p < 0.001$]; 28% v 6% [$p<0.001$]). Two hour serum insulin, C-peptide and triglyceride values were greater in both patient groups than in respective controls ($p<0.001$) and were higher in Asian than in whites ($p<0.001$) irrespective of glucose tolerance status. Total and HDL cholesterol concentrations were lower in both Asian groups than in respective whites ($p<0.005$); the total: HDL cholesterol ratio was more closely associated with IHD. Raised insulin, C-peptide and triglyceride concentrations are found in survivors of MI and may be important in the pathogenesis of the disease and could explain the high incidence of IHD in Asian Indians.

Association between obesity (trunkal much more than generalised) and increased mortality from coronary events is well known. Insulin is known to increase sodium reabsorption from the renal tubules, ultimately causing a high intra-cellular sodium (hyperinsulinemia leading to volume expansion and increased peripheral resistance); hyperglycemia itself contributes to the volume expansion. In fact Jarett et al (Glucose tolerance and blood pressure. Int J Epidemiol 1978; 7:15) found stepwise increase in systemic blood pressure from normoglycemic individuals through those with borderline

diabetes to newly diagnosed diabetes. The syndrome of "hyperinsulinemia-obesity- hypertension-glucose intolerance" is acquiring epidemic proportions in developing societies (as mentioned earlier). This has been shown in South Asians in the form of an increased basal and stimulated insulin levels, raised triglycerides, and a high waist to hip ratio (trunkal obesity).

Iwase M, Kikuchi M, Nunoi K, Maki Y, Wakisaka M, Wada M, Fujishima.
Residual B cell function in patients with long standing NIDDM and its relation to metabolic control and diabetic complications.
Endocrinol Jpn 1988; 35:803-8. (From: Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan).

The authors have evaluated the residual pancreatic B-cell function by glycogen load test in 28 patients with non insulin dependent diabetes mellitus (NIDDM) of a duration of 20. The increase in serum C-peptide at 6 minutes after glycogen administration (Dalta C-peptide) was used as an index of residual B-cell function. There was much less Delta C-peptide in patients treated with insulin than in those treated with sulfonylurea (P), and it was significantly correlated with the body mass index (r=0.40, P). Long term metabolic control assessed by the average annual mean fasting blood glucose for the observation period (mean, 21 years) was not correlated with Dalta C-peptide (r=10.13). The prevalence of retinopathy which needed photocoagulation therapy and of neuropathy in patients with poor residual B-cell function (Delta C-peptide + 0.3 ng/ml) was the same as that in those with good residual B-cell function (Delta C-peptide 1.0 ng/ml). The present study shows that the residual B-cell function is not correlated with long-term glycemic control and the prevalence of diabetic complications in long-standing NIDDM patients.

Nelson RG, Bennett PH.
Diabetic renal disease in Pima Indian
Transplant Proc. 1989; 1:3913-5. (From: National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix).

Diabetic renal disease is a major source of morbidity and mortality in Pima Indians. Excess mortality in NIDDM occurs principally in those with proteinuria regardless of whether death is due to cardiovascular or renal disease. Diabetes duration is a strong predictor of diabetic renal disease. Additional predictors include blood pressure, severity of diabetes, and, most likely, genetic or shared environmental determinants. The incidence rate of diabetic renal disease in Pima Indians with NIDDM is similar to that reported for subjects with IDDM with equivalent durations of diabetes. These observations suggest that clinical proteinuria and renal failure may occur in patients with NIDDM just as frequently as in those with IDDM. This finding has important implications and suggests that the variations in the frequency and age of onset of NIDDM among different populations and ethnic groups may be primarily responsible for the apparent variations in the frequency of ESRD associated with diabetes in different populations. Furthermore, diabetic renal disease appears to account for virtually all of the excess mortality associate with diabetes among Pima Indian and may perhaps do so in other populations. Improved survival of persons with NIDDM, an increasing incidence of this disease, and a relatively early age of onset in many populations could lead to a dramatic increase in the incidence of ESRD in the future. On the other hand, if diabetic renal disease and its consequences could be prevented, a profound improvement in the longevity and quality of life of those afflicted with diabetes might be possible.

Walker JD, Bending JJ, Dodds RA, Mattock MB, Keen H, Viberti GC.
Restriction of dietary protein and progression of renal failure in diabetic nephropathy
Lancet 1989; 11:1411-5. (From: Guy's Hospital, London).

In a study of the effect of a low-protein diet on the progression of renal disease 19 insulin-dependent diabetic patients with persistent clinical proteinuria were observed for 12-39 (mean 29) months while they were on a normal-protein diet (1.13 [O.06] g/kg per day), then for 12-49 (mean 33) months on a low-protein diet (0.67 [O.03] g/kg per day). The low-protein diet had no adverse effect on nutrition or glycosylated haemoglobin concentration. Mean supine blood pressure (BP) fell slightly on the low-protein diet and was probably due to the start or modification of antihypertensive medication in 9 patients. The mean rate of decline in glomerular filtration rate fell from 0.61 (SEM 0.14) ml/min. per month with the normal protein diet to 0.14 (0.08) with the low-protein diet, and this effect remained highly significant after adjustment for blood pressure, energy intake, and glycosylated haemolobin. The rise in the fractional clearance of albumin during a normal protein diet stopped with the low-protein diet, and there was a significant fall in albumin excretion from 467 (95% CI 234-895) Hg/24 h on the normal protein to 340 (138-719) on the low-protein diet. Thus, a low-protein diet, with its reduction in protein and possibly other dietary components such as phosphate or fat, seems to retard the rate of decline of glomerular filtration rate in diabetic nephropathy independently of blood pressure changes and glycemic control.

Samanta A, Burden AC, Feehally J, Walls J.
Diabetic Renal Disease: differences between Asian and White patients
Br Med. J 1986; 293:366-7.

Authors studied 370 consecutive Asian and 368 consecutive white patients who had attended the diabetic clinic for at least one year. Proteinuria was found in 53 (14%) of the Asian and 23 (6%) of the white patients ($p<0.001$). There was no difference in the sex distributions of patients with proteinuria. Proteinuria in the Asian tended to occur with diabetes of shorter duration (< 10 years) ($p<0.01$) and in the absence of clinical retinopathy ($p<0.001$). No significant differences were noted in glycemic control or the prevalence of hypertension between the two groups. Twenty five of the 228 Asian men had a serum creatinine concentration above normal (> 120 mmol/1 (> 1.4 mg/100 ml), compared with 11 of the 223 white men (P=0.02). No such difference was found in the women. Results indicate that proteinuria is more common in Asian than white diabetics attending the diabetic clinic at Leicester. We believe that this is due to small vessel disease of diabetes as we excluded other causes of renal disease both clinically and radiologically. A larger proportion of Asian patients had proteinuria with diabetes mellitus of less than 10 years duration and in the absence of clinical retinopathy. The shorter duration of diabetes may partly be because many of the Asians had non insulin dependent diabetes mellitus. It is also possible that differences in immunogenetic influences in populations from different cultures determine the development of diabetic nephropathy.

Mangili R, Bending JJ, Scott G, Li LK, Gupta A, Viberti GC.
Increased sodium-lithium counter-transport activity in red cells of patients with insulin-dependent diabetes and nephropathy
N Engl J Med 1988; 318:146-50.

Susceptibility to diabetic nephropathy may be related to a predisposition to arterial hypertension. We have studied the activity of sodium-lithium counter transport in red cells, a marker of risk for essential hypertension, in white European adults with insulin dependent diabetes and diabetic nephropathy, a matched group of patients with diabetes without renal disease, and non-diabetic patients with renal disease. Measures of metabolic control and concentrations of plasma free insulin and growth hormone were similar in the two diabetic groups. The degree of impairment in renal function was similar in the diabetic and non-diabetic patients with renal disease. Body-mass index and plasma potassium

concentrations were similar in all three groups. Diastolic blood pressure was elevated to a similar degree in the two groups with renal disease, as compared with that in the diabetic patients without renal disease.

The rates of sodium lithium counter-transport in red cells were significantly higher in the diabetic patients with renal disease (mean + SD, 0.55+0.19 mmol of lithium per liter of red cells per hour) than in the diabetic patients without renal disease (0.33+0.16; $P<0.005$) and in the non-diabetic patients with renal disease (0.31+0.14; $P<0.001$).

Predisposition to hypertension, as indicated by elevated sodium lithium counter-transport activity in red cells, may serve as a marker for the risk of renal disease in patients with insulin-dependent diabetes.

The problem of increasing incidence of NIDDM in developing populations is compounded by increase in risk for nephropathy and coronary event (the main causes of morbidity and mortality amongst such populations). What predisposes an NIDDM to develop these complications? Though initial reports from diabetes control and complication trial (DCCT, USA) show that the rate development of complications can be altered with a better control of diabetes, all practitioners have experienced patients with very poor control but no complications. Iwase et al shows that residual beta cell function cannot be correlated with diabetic complications.

Two factors turn out to be important determinants of development of nephropathy. The genetic component is relating propensity to develop hypertension as evidenced by a positive family history of hypertension and presence of a marker of future development of hypertension (high Na-Li counter transport in RBCs).

The environmental factors also seem to be important. A higher dietary protein, associated with a relatively rapid progression of nephropathy is slowed down with a reduction in dietary proteins (0.67 g/kg body weight) (Walker et al).

An earlier onset of type II diabetes, a higher waist to hip ratio with a higher degree of insulin resistance, a higher triglyceride level and higher incidence of proteinuria, all seem to predispose the developing populations to a higher coronary risk and nephropathy. It is thus imperative to act fast and effectively to prevent diabetes and its complications in populations which otherwise also lack good medicare.