

ABSTRACT SERVICE MALNUTRITION-RELATED DIABETES MELLITUS

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REVIEW ARTICLES & MONOGRAPHS:

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2. Viswanathan M. Pancreatic Diabetes in India An overview. In: Secondary Diabetes : The spectrum of the diabetic syndromes. Podolsky S, Viswanathan M (Eds), Raven Press, New York; (1980) 105-116.
3. Mohan V, Ramachandran A, Viswanathan M Tropical Diabetes. In: Diabetes Annual/1. Alberti KGMM & Krall LP (eds), Elsevier Science Publishers B.V., Amsterdam; (1985) 82-92.
4. Geevarghese PJ Calcific pancreatitis. Varghese Publishing House, Bombay (1986).
5. Balakrishnan V Tropical Pancreatitis (Pancreatite tropicale). In: Maladies du pancreas exocrine. Bernades P & Hugier M (eds), Doin; Paris; (1987) 1-33.
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7. Mohan V, Ramachandran A, Viswanathan M Diabetes in the tropics. In: Diabetes Annual/4. Alberti KGMM & Krall L (eds), Elsevier, Amsterdam; (1988) 46-55.
8. Mohan V, Ramachandran A, Viswanathan M Diabetes secondary to pancreatopathy in the tropics. In: Diabetes Secondary to pancreatopathy. Tiengo A, Alberti KGMM, Del Prato S & Vranic M (eds), Elsevier, Amsterdam; (1988) 215-226
9. Mohan V, Ramachandran A, Viswanathan M Other malnutrition-related-diabetes-meliitus. In: World Book of Diabetes in Practice, 3. Krall LP & Alberti KGMM (eds), Elsevier, Amsterdam; (1988) 31-36.
10. Rao RH Diabetes in the undernourished: coincidence or consequence?. *Endocrine Rev* (1988) 9:67-87.
11. Proceedings of WHO Workshop on Malnutrition Related Diabetes, London, Alberti KGMM, Keen H & Parry E (eds.): Oxford University Press (1988) .
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15. Mohan V, Alberti KGMM. Diabetes in Tropics. In: International Textbook of Diabetes. Alberti KGMM, DeFronzo RA, Keen H & Zimmet P (eds.), John Wiley & Sons, Chichester; (1992) 177-196.

"CLASSIC" EARLY PAPERS

Diabetes in Jamaica

Hugh-Jones P., The Lancet 1955; 2; 891-97

An analysis of 215 diabetic patients consecutively attending hospital in Jamaica showed that they could be divided clinically into the two main types seen elsewhere: Type 1, of early-age onset, insulin sensitive and ketotic (26 cases); and Type 2 of middle-age onset, insulin resistant, with a tendency to be obese but not to have ketosis, if without insulin, unless they have an infection (172 cases, nearly three quarters in women). A third variety, not previously described, also occurred (type J, 13 cases). It was peculiar in its onset in young thin people who were, however, relatively insulin resistant and lacking in ketosis. The significance of type J as well as of some sporadic cases of temporary diabetes seen in Jamaica is discussed in relation to the pathogenesis of diabetes in man. Liver biopsy in 3 cases of type J diabetes showed them to resemble type 1 diabetes in that the liver was normal in contrast to the fatty change common in type 2 diabetes. Preliminary trials with local plants, reputed to cure diabetes, were unconvincing, though periwinkle (*Vinca rosea*) and mistletoe (*Phthirusa pauciflora*) may raise the renal threshold for sugar. Clinical trials with ackee (*Blighia sapida*), which is known to cause hypoglycaemia could not, it was felt, be undertaken without more information. Complications of diabetes were common and may reflect the results of "free diets". Hypertension was particularly associated with type 2 diabetes independently of the effects of age, sex and

obesity. Points about the local management of diabetes are presented in relation to diets, social conditions, prevalence of insulin resistance without ketosis, and the value of using insulin-zinc suspensions.

Aetiology of chronic pancreatic fibrosis with calcification seen in Uganda

Shaper A. G., Br Med. Jr. 1964; 1 : 1601-09.

The main clinical features present in 36 African subjects with pancreatic calcification are described and the possible aetiological factors discussed. The natural history of this disorder resembles that of alcoholic pancreatitis seen in other countries, and, while episodic heavy drinking (but not necessarily alcoholism) was noted in about half the subjects, it is emphasised that it took place against a background of low-protein high-carbohydrate nutrition. It is suggested that this tropical syndrome and alcoholic pancreatitis may have a similar pathogenesis, and that, in a pancreas rendered susceptible to injury by nutritional imbalance, alcohol and/or other factors may initiate progressive and irreversible pancreatic damage. It must be emphasised that this is not regarded as alcoholic pancreatitis, nor is it thought that the problem is purely one of protein malnutrition.

Observations on Clinical Patterns of Diabetes Mellitus in India

Tripathy B. B., Kar B. C. Diabetes 1965; 14:404-12.

Several points of difference can be made between features of diabetics of the Western world and the tropical countries. In addition to a lower incidence of juvenile diabetes and diabetic coma in the tropics there is a high incidence of marked underweight among diabetics of the older age group as well as the young. Observations on ninety-six patients at Cuttack, India, reveal that apart from a few cases of juvenile diabetes and a moderate number of elderly-obese patients there is a high incidence of atypical cases. Some of these are young and very lean but require large doses of insulin for control and are not prone to ketosis ("J") type. Others are middle-aged and generally responsive to sulphonylurea compounds but are very lean even at onset of disease (elderly-lean type). Division of the patients into two groups - one seen in the hospital wards and the other in the private clinics (domiciliary), makes it apparent that the unusual types of diabetics are for the most part the poorer hospital (ward) patients. Of these 39.8 per cent are "J" type and 43.7 per cent are elderly - lean types compared with zero and 4.9 per cent, respectively, in the domiciliary group.

The hospital patients have been subject to chronic undernutrition and most of them take large carbohydrate meals at long intervals, often only one a day. It is postulated that imposition of this dual stress of intermittent starvation and overload on carbohydrate metabolism may be related to the atypical patterns of clinical diabetes.

"J" Type Diabetes

Tulloch J.A. & Macintosh D., Lancet 1961; 2:119-21.

The course of 24 "J" -type diabetics attending the University College Hospital of the West Indies was reviewed. The "J" -type is not a separate subgroup, so called "J" -type cases are type II cases in which the diabetes has been badly treated.

CLINICAL DESCRIPTIONS

A short review of pancreatic diabetes in Uganda

Kajubi S. K. E. African Med. J. 1976; 56: 625-30

Twenty-two patients with pancreatic diabetes investigated personally between 1968 and 1971 are reviewed. Nineteen presented with frank diabetic symptoms while three presented with steatorrhoea initially. Six were females aged 16-49 years (mean 27) and sixteen were males aged 10-69 years (mean 35). Common findings were significant abdominal pain, weight loss, calcifications on abdominal X-rays, parotid gland enlargement, steatorrhoea, soft uncurled hair and reduced duodenal trypsin. Uncommon were retinopathy, neuropathy, albuminuria and anaemia. Management was by means of tolbutamide (8 cases), lente insulin (13 cases) and lente insulin + tolbutamide (1 case). Hypoglycaemia was seen in six cases (2 on tolbutamide and 4 on lente insulin).

Before insulin therapy was commenced plasma insulin was measured during a glucose tolerance test and after intensive beta-cell stimulation. The latter showed compromised insulin producing capacity indicating a reduced beta cell mass. HGH was measured during insulin induced hypoglycaemia in some cases and it was found to be deficient compared to controls. In the light of these findings the pathophysiology of pancreatic diabetes is discussed and a plea is made to physicians in the tropics to look for this disease with vigour as this may help to elucidate its epidemiology and aetiology which are currently incompletely understood.

A Search for Malnutrition Diabetes in an Ethiopian Diabetic Clinic

Lester F. T. IDF Bulletin XXIX 1984; 29:14-16

A search for patients fitting the published criteria for "Malnutrition diabetes" was made among 773 patients of a Diabetic Clinic in Addis Ababa. Ethiopia a country where poverty and malnutrition are common. Only 4 patients who fit the criteria were found, and none were convincing cases. It is concluded that, although many young patients are thin and undernourished, the Ethiopian diabetics seen in this clinic can generally be classified into IDDM (Type 1) and NIDDM (Type II), the latter usually non-obese, with no need to invoke a 'third syndrome'.

Nutritional status of young adult Ethiopians before onset and after treatment of diabetes mellitus

Lester F. T. Ethiop. Med. J. 1990; 28: 1-7

Young diabetics in tropical countries are often undernourished, insulin-requiring and ketosis-resistant, and are sometimes considered to have a distinct type of diabetes. Therefore, a survey of young adult diabetics attending Yekatit Hospital, Addis Ababa, was made to determine clinical features and the relation between their diabetes and their nutritional state. In May, 1988, 894 of 1490 registered diabetic patients were attending regularly, of whom 248 became diabetic between the ages of 15 and 35 years. Many had been followed for 6 years or more. Of the 248, 69 males and 29 females (39.5%) had body mass index (BMI) of less than 18 kg/m² at diagnosis of diabetes. However, only 3.5% of the 199 who knew their pre-diabetic weight had been less than 18 kg/m²; 13.8% of males and 48.5% of females had been obese. At their last attendance, 50% of those whose BMI at diagnosis was less than 18 were of normal weight and only 13% had gained no weight. Of the 98 with BMI less than 18 at diagnosis, and the further 18 less than 18 kg/m² by the time insulin was started, ketosis occurred at some time in 22%. Only 1 patient takes more than 1.5 units of insulin per kg per day, and 30% of those needing 1.0 to 1.5 U/kg have had tuberculosis. Only 15 of the 116 patients who had BMI less than 18 failed to gain weight on treatment. It is concluded that, in most, the malnutrition at presentation was due to the diabetic state and did not precede the diabetes. The observed clinical features do not suggest that these young Ethiopians have a distinct type of diabetes.

Insulin-dependent ketosis-resistant diabetes in Ethiopia

Abdulkadir J., Mengesha B., Gebriel Z. W., et al Trans, Royal Society Tropical Med. & Hygiene 1987; 81:539-43

Anthropometric, clinical and biochemical findings

were compared in 30 rural (group A), 18 urban insulin requiring (group B) and 45 urban oral agent responsive (group C) newly diagnosed diabetics. Mean ages at onset were 28.3 ± 12.0, 25.6 ± 14.5 and 42.1 ± 10.5 years respectively. The differences between A and C and between B and C were significant. Group A were poor and malnourished, with body mass index (BMI) 15.9 ± 1.9 and 17.2 ± 3.7 kg/mt2t for males and females respectively, presented with a long history of classical diabetes without ketoacidosis and required insulin in modest doses. 3 of 10 cases had excess stool fat but none of 13 unselected cases had pancreatic calcification. Group C were better nourished, with BMI 22.6 ± 2.8 and 22.4 ± 4.5 kg/mt2t and responded to oral agents. Group B with BMI 17.2 ± 2.6 and 18.6 ± 3.1 kg/mt2t, required insulin for control but had C-peptide levels above 0.02 nmol/l in 10 of 15 cases. Anthropometric indices for males, but not for females, were significantly lower in group A than in group B or C. There were significant differences in levels of glucose between A and B and A and C, free fatty acids between A and C and B and C, insulin between A and B and A and C and C-peptide between A and C and B and C. Of the 3 groups the rural type most closely resembled the tropical variants.

Diabetes Mellitus with Onset Under 40 Years In North India

Vaishnava H., Bhasin R.C., Gulati P.D., et al Jr Asso. Phys. Ind. 1974; 22:880-87

1. Onset of diabetes mellitus, starting below 40 years of age, was observed in 3705 (32.6%) out of 11359 patients; 265 (2.3%) were juvenile diabetics, onset starting below the age of 15 years, 24 of which were ketosis-resistant. 2. Oral hypoglycaemic agents could control the disease in 37.2% of diabetics with onset below age of 40 years. These had features simulating those of the maturity onset type. 3. Ketosis-resistant, growth-onset diabetes, mostly seen in tropics, constituted 24.3% in the present series. It has marked predilection for males (M:F : 5.1:1) Other acknowledged predisposing factors such as heredity, rich diet, hyperasthenic body-build and high socio-economic status were remarkable by their absence. 4. The most frequently encountered complications in order of their prevalence were (i) peripheral neuropathy-60.4%, (ii) pyogenic infections-28.3%, (iii) urinary tract infection-22.8%, (iv) diabetic retinopathy-21.5% and (v) pulmonary tuberculosis-13.9% 5. Plasma FFA was markedly raised in the ketosis-prone diabetics as compared to the ketosis-resistant ones, in the uncontrolled state of the disease; in both groups, in vitro studies on subcutaneous adipose cells showed insignificant lipolytic reaction to epinephrine in the uncontrolled state. However,

after the control, lipolysis was significant in ketosis-prone patients but the resistance to lipolysis was noticed in the ketosis-resistant subject. In vivo, mobilisation of FFA from the adipose tissue in the ketosis-resistant diabetics was inadequate. This may be attributed to the relative insensitivity of the adrenergic receptors and/or unresponsiveness of the adenyl cyclase-cyclic AMP-lipase system in the adipose tissue of these young diabetics.

Tropical pancreatic diabetes in South India : heterogeneity in clinical and biochemical profile

Mohan V., Mohan R., Susheela L. et al Diabetologia 1985; 28:229- 32

Clinical and biochemical studies were carried out in 33 patients with diabetes secondary to chronic calcific, non-alcoholic pancreatitis (tropical pancreatic diabetes) and in 35 Type 2 (non-insulin-dependent) diabetic patients and 35 non diabetic subjects. Despite lower body mass indices, only 25% of patients with tropical pancreatic diabetes had clinical evidence of malnutrition. There was no history of cassava ingestion. Mean serum cholesterol concentration was significantly lower in the tropical pancreatic diabetic patients ($p < 0.01$) in comparison with the Type 2 diabetic patients or non-diabetic subjects, due to a significantly decreased concentration of LDL cholesterol ($p < 0.01$) and VLDL cholesterol ($p < 0.05$). Basal and post-glucose stimulated concentrations of serum C-peptide were highest in those pancreatic diabetic patients ($n=11$) who responded to oral hypoglycaemic drugs, intermediate in the majority ($n=17$), who were insulin dependent and ketosis resistant and negligible in a small sub-group ($n=5$) who were ketosis prone. The occurrence of microangiopathy in pancreatic diabetic patients was common and similar to that in Type 2 diabetic patients. Thus, tropical pancreatic diabetes in South India appears to be heterogeneous with respect to level of nutrition, severity of glucose intolerance, B-cell function, response to therapy and the occurrence of microvascular complications.

Clinical features of diabetes in the young as seen at a diabetes centre in South India

Ramachandran A., Mohan V., Snehalatha C., et al DRCP 1988; 4:117- 25

This study reports on the clinical pattern of 545 consecutive young diabetic patients with age at onset below 30 years attending a diabetes centre in Southern India. Three hundred and fourteen patients (57.7%) were classified as having non-insulin dependent diabetes of the young

(NIDDM), 119 (22%) as insulin-dependent diabetes (IDDM) and 28 (5%) as malnutrition-related diabetes (MRDM) : 4% fibrocalculous Pancreatic diabetes and 1 % protein-deficient pancreatic diabetes. The remaining 84 patients could not be classified into any of the above categories. A positive family history of diabetes was more common in NIDDM compared to the other groups ($p < 0.001$). While 40.3% of patients with IDDM had age at onset below 15 years, the other types of diabetes was rarely seen in patients younger than this. Body mass index (BMI) did not reliably indicate the MRDM forms of diabetes as 70% of patients with IDDM also had a BMI of less than 18, one of the criteria recommended for the diagnosis of MRDM. C-peptide levels in MRDM were intermediate between the IDDM and NIDDM groups. Microvascular complications were present in all the groups of young diabetics. The frequency was higher in NIDDM patients who also had a longer duration of diabetes. There was an increasing prevalence of complications with increasing duration of diabetes.

“AETIOLOGY” - CLINICAL STUDIES

Absence of diabetes in a rural West African population with a high carbohydrate/cassava diet

Teuscher T., Baillod P., Rosman J.B. and Teuscher A. Lancet 1987; 1: 765-68

1028 (99%) of the 1038 inhabitants of the West African village of Agbave and a random sample of 353 (12.4%) of the population of 2850 in Kati, another West African village, were screened for diabetes. Also recorded were their anthropometric data, dietary habits, possession of antibodies to malaria, and serum IgG concentrations. About 85% of the study population consumed cassava root at least once a day. The mean (SD) capillary random blood glucose concentration was 5.1 (1.1) mmol/l in men and 5.1 (0.6) in women. The mean (SD) body mass index was 20.2 (1.8) in men and 20.7 (2.3) in women. The mean blood glucose was similar whether cassava was consumed once daily, more than once daily or less than once daily. None of the 1381 subjects examined had diabetes. This finding suggests that a high carbohydrate/cassava intake (84% of a mean daily supply of 1916 calories) combined with a low protein consumption (8% of caloric supply) does not cause diabetes. This does not support the World Health Organisation hypothesis that malnutrition-related diabetes exists, at least not in this West African rural population.

Familial aggregation in fibrocalculous pancreatic diabetes

Mohan V., Chari S.T., Hitman G.A., et al
Pancreas 1989; 4:690-93

There is very little information on the genetic factors associated with fibrocalculous pancreatic diabetes (FCPD). 98 first degree relatives of FCPD patients are subjected to detailed studies which included glucose tolerance tests, X-ray films of the abdomen, ultrasonography and studies of exocrine pancreatic function. The study shows that there is a familial aggregation of FCPD with evidence of vertical transmission of the disease from parent to offspring in some families. Routine screening of families of FCPD probands helped to pickup cases in the stage of impaired glucose tolerance. There is heterogeneity in FCPD with respect to familial factors. Some families show marked familial aggregation of FCPD while in others the disease occurs either sporadically or in association with other family members who have abnormal glucose handling.

The genetic predisposition to fibrocalculous pancreatic diabetes

Kambo P. K., Hitman G.A., Mohan V., et al
Diabetologia 1989; 32:45-51

Fibrocalculous pancreatic disease (previously known as tropical pancreatic diabetes) is a rare cause of diabetes confined to countries within the tropical belt. The aetiology of fibrocalculous pancreatic disease is thought to be environmental although the agent(s) is unknown. We have investigated a possible genetic basis of this disease by looking for restriction fragment length polymorphisms of genes implicated in the aetiology of diabetes mellitus. Seventy-six Dravidian patients with fibrocalculous pancreatic disease were studied and the restriction fragment length polymorphisms obtained compared to racially matched control subjects (n = 94), patients with type 2 (non- insulin-dependent) diabetes (n = 87) and type 1 (insulin- dependent) diabetes (n = 58). No association of fibrocalculous pancreatic disease was found with restriction fragment length polymorphisms of the insulin receptor gene. Although no association of fibrocalculous pancreatic disease was found with polymorphism of the HLA DRa/DQa/DXa genes an association was found with the Taq 1 restriction fragment length polymorphisms of the DQB gene (DQB T2/T6 present in 39% of patients with fibrocalculous pancreatic disease compared to 19% in control subjects; p = 0.01; corrected p value = 0.04) which is similar to that found in type 1 but not type 2 diabetes. An association of fibrocalculous pancreatic disease was also found with the hypervariable region in the 5-prime flanking region of the insulin gene; 40% of patients possessed the class 3 allele compared to

9.5% of controls (p = 0.0001; corrected p value = 0.0008). In type 2 diabetes similar results were obtained with 33% subjects possessing the class 3 allele (p value compared to control subjects = 0.0005; corrected p value 0.004. This study suggests that fibrocalculous pancreatic disease has a genetic component in its aetiology. Furthermore its origin might be related to an individual with part of the genetic predisposition to diabetes (type 1 or type 2 diabetes) who additionally has evidence of chronic calcific pancreatitis.

Xenobiotics and Tropical Chronic Pancreatitis

Bragania J.M., John S., Padmalayam I., et al
Intn. J. Pancreatol 1990; 231-45

The prevalence of chronic pancreatitis in tropical zones is far higher than in temperate zones, but there is no explanation for this difference. Detailed social, occupational, and dietary histories were taken from 79 patients attending two hospitals in Madras, South India. There were 53 apparently sporadic cases with both pancreatic calculi and diabetes; six apparently sporadic cases with noncalcific disease, usually with diabetes; four pairs of first-degree relatives with either calcific or noncalcific disease, with or without diabetes; and two families in which several members had one or another variant of the disease. Three trends emerged from these histories; 1. Regular exposure to a xenobiotic inducer of cytochromes P4501 (smoke from cigarettes, burning firewood, or vehicle emissions; a cooking oil composed of C 18:2 fatty acids); 2. Concurrent exposure to a chemical that undergoes metabolic activation (petroleum products, notably kerosene fumes; cyanogenic glycosides; solvents; paint); and 3. low intakes of micronutrients required to synthesis/refurbish glutathione. These trends, similar to those noted at Manchester, North West England, suggest a unifying template for tissue damage in chronic pancreatitis, namely, heightened but unmitigated oxidative detoxification reactions mediated by cytochromes P450. The higher prevalence of the disease in underprivileged communities of the tropics may reflect poorer availability of micronutrient antioxidants.

The clinical and hormonal (C-peptide and glucagon profile and liability to ketoacidosis during nutritional rehabilitation in Ethiopian patients with malnutrition-related diabetes mellitus

Abdulkadir J., Mangesha B., Welde, Gebriel Z., et al
Diabetologia 1993; 33:222-27

Cases of malnutrition-related diabetes mellitus conforming to the description of the protein defi-

cient pancreatic diabetes type in Ethiopian patients were compared with Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetic. 14 of 39 MRDM patients had fat malabsorption compared with only two of ten Type 1 diabetic patients and one of nine control subjects. Xylose absorption was normal favouring a pancreatic cause for the malabsorption. Plasma C-peptide during oral glucose tolerance test was significantly lower than that in Type 2 diabetic patients and normal control subject ($p < 0.01$ to 0.001) and was also consistently but not significantly higher than in Type 1 diabetic patients. Glucagon secretion patterns were similar in malnutrition-related and Type 1 diabetic patients. Of 23 new malnutrition-related diabetic patients treated with glibenclamide after nutritional rehabilitation and insulin treatment, only three responded, 14 were unresponsive but remained ketosis free for over eight days while another six developed ketoacidosis or significant ketonuria within two to six days during the trial. Sixteen unselected Type 1 diabetic patients who discontinued their insulin therapy all developed frank ketoacidosis after a mean of 5.5 days. The similarity of the malnutrition-related and Type 1 diabetes mellitus in age of onset, insulin requirement for diabetic control and appearance of ketosis-proneness in some cases, together with the similarity of C-peptide and glucagon secretion patterns suggest that the protein deficient pancreatic diabetes variant of malnutrition-related diabetes mellitus may be Type 1 diabetes mellitus modified by background of malnutrition rather than an aetiologically separate entity. Community based studies are required to ascertain frequency and types of diabetes mellitus in malnourished populations and the role of genetics and environment in their aetiology.

HLA-DR and -DQ antigens in malnutrition-related diabetes mellitus in Ethiopians: a clue to its etiology?

Abdulkadir J., Worku Y., Schreuder G.M.T.D., et al Tissue Antigens 1989; 34:285-89

Thirty Ethiopian malnutrition-related diabetes mellitus (MRDM) patients were HLA typed and their HLA antigen frequencies were compared to diabetes mellitus (IDDM) patients and to 98 controls from the same ethnic background. In comparison to controls, a striking association between MRDM and HLA-DR3 ($\chi^2 = 15.15$, $p = 0.0001$) was observed whereas the frequency of HLA-DR4 was non-significantly increased ($RR = 1.72$). The frequency of DR2, DQw1, and DQw6 was decreased among MRDM. In comparison to IDDM that is associated with both DR3 and DR4 in this population, MRDM showed no significant

differences in HLA class II antigens frequencies. Therefore, the genetic basis of susceptibility to MRDM and IDDM in Ethiopia is at least partially identical.

"AETIOLOGY" - EXPERIMENTAL STUDIES

Effects of severe protein-calorie deficiency on the endocrine control of carbohydrate metabolism.

Heard CRC Diabetes 1966; 15:78-79

Severe protein-calorie deficiency resembling human syndromes (e.g; marasmus and kwashiorkor) has been produced in young pigs by manipulations of dietary protein and carbohydrate levels. These animals show impaired glucose tolerance; increased insulin sensitivity, including hypoglycaemia nonresponsiveness; accumulation of glycogen in the liver and deficiency of hepatic glucose-6-phosphatase; normal or raised excretion of urinary corticosteroids. Tissue water content is elevated but fat accumulates only in animals receiving extra carbohydrate. It is suggested that a deficiency of insulin and of thyroid and growth hormones and a consequent relative excess of adrenocortical hormones is characteristic of severe protein-calorie deficiency in humans and experimental animals and explains many of the biochemical changes.

Insulin secretion and carbohydrate metabolism in experimental protein malnutrition

Khardori R., Bajaj J.S., Deo M.G. and Bansal D.D.J. Endocrinol. Invest 1980; 3:273-78

In order to study the evolution to endocrine and metabolic changes in protein malnutrition, we created a replica of this human syndrome in a primate model. This model was free from stress factors like infestations and infections and provided an opportunity to study the details more closely. Our results showed that definite endocrine and metabolic changes are established by six weeks of protein deprivation. The study demonstrated that protein deprivation results in decreased fasting blood glucose levels associated with diminution in fasting and total insulin output when presented with a glucose load. There is also deterioration of carbohydrate tolerance. It is suggested that decreased fasting blood glucose is a consequence of impaired breakdown and/or depletion of glycogen stores, and hepatic dysfunction secondary to fatty infiltration. The exact cause of decrease in insulin output remains to be clearly elucidated. The carbohydrate intolerance is attributed to insulin lack, hepatic dysfunction and decreased glucose disposal consequent to protein deprivation.

Intermittent protein-calorie malnutrition in the young rat causes long-term impairment of the insulin secretory response to glucose in vitro

Swenne I., Crace C.J. and Jansson L. J. Endocr 1988; 118:295-302

The effect of a limited period of protein-calorie malnutrition in young rats on insulin secretion in the adult has been studied. Three-week-old rats were weaned onto diets containing 5% protein (low protein; LP) or 15% protein (control; C) and maintained for 3 weeks on their respective diets. A third experimental group was weaned onto standard rat chow {18% protein; normal diet; N). From 6 weeks of age onwards all rats were fed the standard rat chow. Pancreatic islets were isolated from rats aged 3, 6 and 12 weeks and their insulin secretory response to glucose or arginine was tested. At 12 weeks the effects of the secretagogues were also tested using perfusion of isolated pancreatic glands. In islets from 6-week-old LP rats the glucose-stimulated insulin release was only 25% of that of C and N rats of the same age. Islets from C and N rats responded to arginine in the presence of a low glucose concentration with a small increase in insulin secretion, whereas no such response could be demonstrated in islets from 6-week-old LP rats. Islets from 6- and 12-week old N rats responded to glucose and arginine. Islets from 12-week-old C rats had a similar response to glucose but did not respond to arginine in the presence of a low glucose concentration. In islets from 12-week-old LP rats the secretory response to glucose remained only 40% that of C and N rats and there was no response to arginine in the presence of a low glucose concentration. The observations on the secretory response of isolated islets from 12-week-old rats were paralleled by similar findings with the perfused, isolated pancreas. It is concluded that protein-calorie malnutrition early in life persistently impairs the insulin secretory response of the B-cell: The individual may, as a consequence, have a lowered ability to respond to nutritional and diabetogenic challenges and it is thus possible that early protein-calorie malnutrition predisposes for diabetes.

Effect of a low protein diet during pregnancy on the foetal rat endocrine pancreas

Snoeck A., Remacle C., Reusens B. and Hoet J. J. Biol Neonate 1990; 57:107-18

The administration of a low protein (LP, 8% protein/dry matter) but isocaloric diet to gestating rats did not affect their fertility, but slightly reduced the quantity of food intake as well as body weight gain. The LP diet also did not affect the placental weight, but the weight of the off-

spring was decreased. Accordingly the foetal endocrine pancreas was altered by the LP diet. Two different morphometric analyses showed that in the LP neonate B-cell proliferation and islet size were reduced in the head of the pancreas. In the pancreatic tail, these parameters were also decreased but to a lesser extent. Islet vascularization in the neonate was dramatically reduced in both parts of the pancreas when the mothers were fed with the LP diet.

PATHOLOGY

Pathology of pancreas in pancreatic calcification with diabetes

Nagalotimath S. J., Darbar R. D., Jogalekar M. D. and Desai S. G. Jr. Asso. Phys. Ind. 1979; 27:1318

Autopsy specimens of four cases of pancreatic calcification with diabetes mellitus were studied by gross and histological methods. The salient findings were severe fibrosis, dilated and distended ducts, with viscous, calcium rich acidic ductal secretions, degeneration of the epithelium of intercalated ducts and moderate hyperplasia of islets of Langerhans. The workers have suggested a new postulation to explain the probable pathogenesis of this disorder with the background of present observations, and recent physiological researches.

BIOCHEMISTRY

Differential mobilisation of non-esterified fatty acids and insulin reserve in various clinical types of diabetes mellitus in India

Ahuja M.M.S. and Viswanathan K. Ind: Jour. Med. Res. 1967; 55:870-83

1. The observed variations in clinical characterization of diabetes in the tropics, especially those resistant to development of ketoacidosis in some young diabetics are inadequately explained by variations in climate, diet or by a primary pancreatic involvement or endocrinal imbalance.
2. Variation in biochemical parameters as response of non-esterified fatty acids and plasma insulin-like activity to glucose, insulin, growth hormone, epinephrine and starvation in this study indicated two distinct patterns, one in which the mobilization of non-esterified fatty acids was quantitatively more and the insulin reserve inadequately low for the metabolic demands made. The ketosis-prone young diabetics belonged to this category. Ketosis-resistant young diabetics and those with maturity-onset disease behave alike and the differential non-esterified fatty acid mobilization to stimuli, such as epinephrine and growth hormone, was delayed and the insulin

reserve reduced. The body built, age of onset and response to oral sulphonylurea drugs in these two latter groups remain as the distinction. The metabolic variations are probably due to the difference in the available insulin reserve, presence of antagonists or to the degree in which labile free fatty acids are utilized for energy.

Observations on Lipolysis in Ketosis-resistant, Growth-onset Diabetes

Hagroo A.A., Verma N. P. S., Datta P., et al Diabetes 1974; 23:268-75

This study was undertaken to determine the mechanism of ketosis resistance, which is often observed among patients with growth-onset diabetes in the tropics. Lipolysis was tested in vivo in the ketosis-resistant patients with growth-onset diabetes by determining: (1) Plasma immunoreactive insulin (IRI), blood glucose, and serum free fatty acid (FFA) concentrations during tests with epinephrine, phentolamine and epinephrine, and propranolol and epinephrine in twenty-five patients; and (2) blood ketone bodies during epinephrine and propranolol and epinephrine tests in fifteen patients. The findings were compared with results obtained in a similar number of ketosis-prone subjects with growth-onset diabetes and twenty-two normal controls. The mean fasting plasma IRI levels were significantly lower in the ketosis-resistant diabetics than in the normal subjects, although the fasting blood glucose levels were three and one-half times greater in these diabetics than in the controls. There was no significant change in the glucose and IRI levels during the three tests. Fasting serum FFA levels were significantly lower in the ketosis-resistant than those in the ketosis-prone diabetics. No detectable serum FFA response was observed in the ketosis-resistant patients during any of the three tests. Blood ketone levels were comparable with the values obtained in the normal controls, but were significantly lower than those in the ketosis-prone patients. Blood ketones also did not change significantly during epinephrine and propranolol with epinephrine tests in the ketosis-resistant patients. These results are interpreted to indicate that the mobilisation of FFA from the adipose tissue is inadequate in the growth-onset diabetics who are ketosis resistant. The failure is attributed to insensitivity of the adrenergic receptor sites and/or unresponsiveness of the adenyl cyclase cyclic AMP-lipase system in the adipose tissue of these young diabetics. The absence of ketonaemia in these diabetics is attributable to an insufficient delivery of the substrate (FFA) from the adipose tissue to the liver.

Suppressible glucagon secretion in young, ketosis-resistant, type "J" diabetic patients in India

Harsha Rao R., Vigg B. L. and Jaya Rao K. S. Diabetes 1983; 32:1168-71

Plasma glucagon levels were measured in young individuals with severe, insulin-dependent, juvenile-onset diabetes mellitus to study whether differences in glucagon secretion were related to ketosis proneness and resistance. Fasting glucagon levels were similarly elevated in both classical, ketosis-prone, type 1 diabetic subjects and ketosis-resistant, type "J" subjects [70 ± 7 pmol/L (mean \pm SEM) and 81 ± 10 pmol/L, respectively] compared with nonobese, nondiabetic controls (36 ± 3 pmol/L, $p < 0.01$). After oral glucose administration, however, glucagon responses were strikingly dissimilar in the two groups. In type 1 diabetic individuals, glucagon rose paradoxically during OGTT by 21 ± 4 pmol/L, an increase of $33 \pm 10\%$; on the other hand, glucagon levels in type "J" diabetic individuals fell by 28 ± 7 pmol/L, a decrease of $33 \pm 5\%$. 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.

Plasma glucagon response in tropical fibrocalculus pancreatic diabetes

Mohan V., Snehalatha C., Ramachandran A., et al Diab. Res. Clin. Prac. 1990; 9: 97-101

Plasma insulin and glucagon responses to a glucose load were measured in a group of patients with fibrocalculus pancreatic diabetes (FCPD) and compared with patients with noninsulin-dependent diabetes mellitus (NIDDM) and control subjects. Both diabetic groups had markedly diminished insulin responses but the differences between FCPD and NIDDM groups were not significant. In control subjects, in response to the glucose load, plasma glucagon levels decreased while they increased in NIDDM patients. In FCPD patients there was no significant change in glucagon levels in response to the glucose load. The study shows that FCPD patients lack pancreatic alpha-cell responses to a glucose load. This may play a role in protecting these patients against ketosis.

A study of intermediary metabolism in different clinical types of diabetes mellitus in India (with reference to pyruvate, lactate, glycerol and plasma insulin)

Krishna, Ram B. and Ahuja M.M.S. Ind. Jr. Med. Res. 1970; 58:456- 67

The intermediary metabolism in control and different clinical types of Diabetes mellitus in India was studied. Blood glucose, pyruvate, lactate and glycerol in fasting state and following a glucose load and insulin were studied over a four hour period. Plasma immunoreactive insulin in fasting state and following stimulation with sulphonylurea was also determined. The responses of different metabolites suggest : (a) The young ketosis prone diabetics (insulin-dependent) have an insulinoprivic state. Insulin secretory response to sulphonylurea is limited. Sensitivity to exogenous insulin is intact. The blood glucose, glycerol and acetone levels are maximally raised and following glucose insulins, maximal alterations in pyruvate, lactate and glycerol are seen in this group indicating reversibility of metabolic aberrations. (b) The young ketosis resistant and the maturity onset diabetics have raised fasting plasma immunoreactive insulin values. Following sulphonylurea stimulation, immunoreactive insulin levels further rise. Both the diabetic groups had moderate hyperglycaemia and no significant acetonemia. The fasting pyruvate and lactate values were of the highest order in the young ketosis resistant diabetics. Following glucose insulin the changes in glycerol in the young ketosis resistant diabetics are lower than the other groups while the changes in pyruvate and lactate are similar to the maturity-onset diabetes. The effectivity to immunoreactive insulin in this group is modified as hypoglycaemic effect is even less than that seen in maturity-onset diabetics. Intermediary metabolic alterations in this group of diabetics are unique and seem related to a subdued and retarded lipolysis or to difference in biological effectivity of endogenous insulin.

Insulin secretion in pancreatic diabetes mellitus

Kannan V. Jr. Asso. Phys. Ind. 1981; 29:321-31

The insulin secretory reserve of 36 patients (31 males and 5 females) with pancreatic diabetes has been determined after oral glucose and intravenous tolbutamide tests and compared with the response of 25 healthy subjects. All the pancreatic diabetic patients had radiological evidences of pancreatic calculi and the mean duration of abdominal pain in them was 5.9 years. Blood glucose, plasma immunoreactive insulin and free fatty acid levels were determined during oral glucose (50 g) tolerance test and intravenous tolbutamide (1.0 g) test. In the control group, plasma insulin levels increased from a basal level of 16.1 ± 1.2 uU/ml to a peak of 62.1 ± 7.0 uU/ml

(at 30 minutes) during the GTT and a peak of 79.1 ± 4.7 uU/ml (at 10 minutes) during tolbutamide tests. In the pancreatic diabetes group, mean fasting plasma insulin level (7.6 ± 2.5 uU/ml) was significantly less than that of the control groups ($p < 0.001$). The maximum insulin rise during the glucose tolerance test was 25.5 ± 7.9 (at 30 minutes) and 23.9 ± 3.2 during tolbutamide test (20 minutes) revealing a significant reduction of insulin secretion in pancreatic diabetes in response to both oral glucose and intravenous tolbutamide stimuli. The degree of impairment was related to the duration of pain as, well as degree of glucose tolerance. Three groups of pancreatic lithiasis subjects could be identified, based on glucose, insulin responses and clinical picture. Group I had mild hyperglycaemia (FBG < 130 mg/dl) with relatively well preserved insulin responses to oral glucose but impaired insulin responses to intravenous tolbutamide, short duration of abdominal pain and late age of onset. Group II (FBG 131-200 mg/dl) had impaired insulin responses to both oral glucose and intravenous tolbutamide. Group III with severe hyperglycaemia (FBG > 201 mg/dl) had total loss of insulin reserve at young age and long duration of abdominal pain: The basal free fatty acid concentrations were higher in pancreatic diabetes subjects (888 ± 34 uEq/l) than controls (621 ± 42 uEq/l) ($p < 0.001$). The mean FFA decrements after oral glucose were 525, 594, 750, 730 and after intravenous tolbutamide 444, 597, 730, 763 in control I, II and III groups respectively. The insulinogenic index in the three groups of pancreatic diabetes were 18, 9.7 and 1.4 compared to 45 in controls during oral glucose tolerance tests and 35.8, 18 and 1.8 compared to 102 in control during intravenous tolbutamide tests. The acquired beta cell deficiency in pancreatic diabetes was seen even when the fasting blood glucose levels were mildly elevated (Group I) and seemed to worsen with further deterioration of glucose tolerance. The impairment of tolbutamide induced insulin secretion was observed to occur earlier than that of glucose. The relationship of the insulin responses to body weight and responsiveness to drug therapy for diabetes has been discussed.

Pancreatic B-cell function in tropical pancreatic diabetes

Mohan V., Snehathatha C., Ramachandran A., Metabolism 1983; 32: 1091-92

Individuals with tropical pancreatic diabetes (TPD) have features of malnutrition and insulin-dependent diabetes but do not exhibit ketosis on withdrawal of insulin. Fasting and postglucose C-peptide responses were assessed in TPD and compared with noninsulin-dependent (NIDDM),

insulin-dependent (IDDM), and control groups, matched for body weight. The C-peptide concentrations were lower in TPD in comparison with the controls and NIDDM patients but were significantly higher than in classical IDDM. It is likely that the higher C-peptide is responsible for the ketosis resistance in these patients.

C-peptide response to glycaemic stimuli

Samal K.C., Das S., Parija C.R. and Tripathy B.B. Jr. Asso. Phys. Ind. 1987; 35:362-64

Total C-peptide immunoreactivity (CPR), serum insulin and blood glucose was estimated in 10 healthy controls, 10 freshly detected patients with fibrocalculous pancreatic diabetes (FCPD) and 8 with insulin dependent diabetes mellitus (IDDM), all aged below 25 years. Basal levels of total CPR were similar in controls (0.82 ± 0.1 ng/ml) and patients of FCPD (0.86 ± 0.2) but much lower in IDDM (0.39 ± 0.04). The CPR response after a mixed meal was significantly higher ($p < 0.01$) in FCPD than in IDDM. There was further rise of CPR in patients with FCPD in response to oral glucose but not in cases with IDDM. Patients with IDDM have both low basal B-cell activity and low reserve. Those with FCPD have near normal basal levels and low reserve compared to controls but higher than that of IDDM.

C-Peptide secretion in calcific tropical pancreatic diabetes

Vannasaeng S., Nitiyanant W., Vichayanrat A., Metabolism 1986; 35:814-17

Serum C-peptide levels were measured during a glucagon stimulation test in ten normal nonobese controls and 54 diabetic patients with recent onset of diabetes under 30 years of age. Diabetic patients were comprised of 13 CTPD, 23 IDDM and 18 NIDDM. As similar to IDDM patients, serum C-peptide concentrations did not rise significantly ($p > 0.05$) in response to glucagon administration in CTPD-patients. Mean baseline and peak serum C-peptide concentration in CTPD-patients were significantly lower ($p < 0.001$) than the values in normal controls and NIDDM patients, but were significantly higher ($p < 0.05$) than those in IDDM patients. We conclude that CTPD patients have partial C-peptide reserve, which may protect against ketosis and contribute to ketosis resistance in CTPD. Our results also suggest that CTPD patients require insulin treatment. Neither baseline nor peak C-peptide levels after glucagon could discriminate CTPD from IDDM and CTPD from NIDDM.

Pancreatic C-peptide response to oral glucose in fibrocalculous pancreatic diabetes

Yajnik C.S., Kanitkar S.V., Shelgikar K.M., et al Diabetes Care 1990; 13:525-27

B-cell function (plasma C-peptide) in 17 fibrocalculous pancreatic diabetic (FCPD) subjects (14 newly diagnosed) was not different at presentation from that in 14 matched insulin-dependent diabetic subjects. After insulin treatment and improvement in the patients' nutritional and metabolic status, fasting and post glucose plasma C-peptide concentrations showed a significant increase (fasting 0.06 ± 0.01 to 0.17 ± 0.03 nM; peak 0.11 ± 0.02 to 0.29 ± 0.06 nM, mean \pm SE; $P < 0.01$ both). Thus, severely diminished B-cell function in FCPD is partially reversible after treatment. This could contribute to the clinical metabolic peculiarities of this group of patients.

The spectrum of pancreatic endocrine and exocrine (Beta-cell) function in tropical calcific pancreatitis

Yajnik C.S., Shelgikar K.M., Sahasrabudde R.A., et al Diabetologia 1990; 33; 417-21

Exocrine pancreatic marker (Immunoreactive-trypsin) and endocrine Beta-cell function (plasma insulin and C-peptide during an oral glucose tolerance test) were studied in 40 subjects with tropical-calcific-pancreatitis [7 non-diabetic, 7 with impaired glucose tolerance and 26 diabetic (Fibro-calculous-pancreatic-diabetes)]. In non-diabetic and impaired-glucose-tolerance subjects there was evidence of active pancreatitis in some and exocrine function was partially preserved. Fibro-calculous-pancreatic-diabetic subjects showed severely diminished pancreatic function; none showed 'pancreatic' elevation of immunoreactive trypsin. Beta-cell function was preserved in non-diabetic and impaired glucose tolerance subjects; diabetic subjects variable Beta-cell function but it was severely diminished in more than 75% Immunoreactive trypsin and C-peptide were directly correlated ($rs=0.55$, $p < 0.01$). This study demonstrates, for the first time, that the Beta cell loss in tropical-calcific-pancreatitis is related to the exocrine loss. It suggests that diabetes in tropical-calcific-pancreatitis is either secondary to pancreatitis or that a common factor(s) acts simultaneously on both the components.

Exocrine pancreatic function in tropical fibrocalculous pancreatic diabetes.

Mohan V., Snehathatha C., Ahmed M.R., et al Diabetes Care 1989; 12:145-47

Exocrine pancreatic function was studied by faecal chymotrypsin test in three groups of diabetic patients seen in Southern India. Exocrine

pancreatic insufficiency, as shown by low faecal chymotrypsin levels, was seen in 87.5% of patients with fibrocalculous pancreatic diabetes (FCPD), in 23.5% of insulin-dependent diabetes mellitus patients, and in 4.5% of non-insulin-dependent diabetes mellitus patients. There was no correlation between faecal chymotrypsin levels and serum amylase, serum lipase, age, body mass index, duration of diabetes, fasting plasma glucose, or glycosylated haemoglobin levels. The faecal chymotrypsin test is a useful additional investigation for the diagnosis of FCPD found in tropical countries.

Exocrine pancreatic function (Serum immunoreactive trypsin, faecal chymotrypsin, and pancreatic isoamylase) in Indian Diabetics

Yajnik C.S., Sahasrabudhe R.A., Naik S.S., et al Pancreas 1990; 5: 631-38

Forty-nine patients with tropical calcific pancreatitis (TCP), 51 insulin-dependent diabetics (IDDMs), 87 non-insulin dependent diabetics (NIDDMs), and 66 nondiabetic controls were studied to evaluate their exocrine pancreatic function by measurement of serum immunoreactive trypsin (IRT, normal for white Caucasians from the U.K. of 140 - 414 ug/L), pancreatic isoamylase (PIA, normal of 35 - 125 U/L) and faecal chymotrypsin (FCT, normal of 76.6 u/g). The majority of patients were studied within 1 year of diagnosis. TCP subjects included seven nondiabetics, 6 with impaired glucose tolerance (IGTTCP), and 36 diabetics [fibrocalculous pancreatic diabetes-(FCPD)]. There was evidence of active pancreatitis (IRT > 800 ug/L) and partial preservation of function in nondiabetic TCP subjects [median IRT of 220 ug/L (range of 102-1360 ug/L, FCT of 2.2 u/g (range 0.7-12.8 u/g)] and also in IGT TCP subjects [IRT of 370 ug/L (range of 301360 ug/L), FCT of 4.2 u/g (range of 1-38 u/g)]. FCPDs showed severely diminished exocrine function [IRT of 50 ug/L (range of 0-184 ug/L), FCT of 0.23 u/g (range of 0-10.4 u/g)]; none showed IRT > 800 ug/L. IDDMs and NIDDMs also showed diminished exocrine pancreatic function in ~30% and ~10% respectively. Controls showed a wide range of IRT and FCT concentrations; IRT concentrations tended to be higher than those reported in white Caucasians from the U.K. Three controls, one IDDM and two NIDDMs showed 'pancreatic' IRT concentrations in absence of symptoms. PIA

concentrations were diminished in FCPD but were similar in IDL7M and NIDDM subjects compared to controls. Simultaneous measurements showed that IRT concentrations were reduced when PIA concentrations were still normal. Our results suggest that TCP and FCPD (diagnosed by radiographically demonstrable pancreatic calculi) represent advanced disease and that a subclinical 'pancreatopathy' appears to be common in tropical subjects (diabetic as well as non-diabetic). Endocrine impairment (hyperglycaemia) in TCP parallels exocrine damage.

The ketosis-resistance in fibro-calculous-pancreatic-diabetes. 1. Clinical observations and endocrine metabolic measurements during oral glucose tolerance test

Yajnik C.S., Shelgikar K.M., Naik S.S., et al DRCP 1992; 15:149- 56

We measured circulating levels of C-peptide, pancreatic glucagon, cortisol, growth hormone and metabolites (glucose, non-esterified fatty acids, glycerol and 3-hydroxybutyrate) in fibro-calculous- pancreatic diabetic (FCPD, n = 28), insulin-dependent diabetic (IDDM, n = 28) and non-diabetic control (n = 27) subjects during an oral glucose tolerance test. There was no difference in the two diabetic groups in age (FCPD 24 ± 2 , IDDM 21 ± 2 years, mean \pm SEM, BMI (FCPD 16.0 ± 0.6 , IDDM 15.7 ± 0.4 kg/m²), triceps skinfold thickness (FCPD 8 ± 1 , IDDM 7 ± 1 mm), glycaemic status (fasting plasma glucose, FCPD 12.5 ± 1.5 , IDDM 14.5 ± 1.2 mmol/l), fasting plasma C-peptide (FCPD 0.13 ± 0.03 , IDDM 0.08 ± 0.01 nmol/l), peak plasma C-peptide during OGTT (FCPD 0.36 ± 0.10 , IDDM 0.18 ± 0.03 nmol/l) and fasting plasma glucagon (FCPD 35 ± 4 , IDDM 37 ± 4 ng/l). FCPD patients however, showed lower circulating concentrations of non-esterified fatty acids (0.73 ± 0.11 mmol/l), glycerol (0.11 ± 0.02 mmol/l) and 3-hydroxybutyrate (0.15 ± 0.03 mmol/l) compared to IDDM patients (1.13 ± 0.14 , 0.25 ± 0.05 and 0.29 ± 0.08 mmol/l, respectively). This could be due to enhanced sensitivity of adipose tissue lipolysis to the suppressive action of circulating insulin and possibly also to insensitivity of hepatic ketogenesis to glucagon. Our results also demonstrate preservation of α -cell function in FCPD patients when B-cell function is severely diminished, suggesting a more selective B-cell dysfunction or destruction than hitherto believed.