Protein Deficient Diabetes Mellitus (PDDM) in India

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INTRODUCTION

Of the two sub-classes of MRDM spelt out by WHO Study Group the entity protein-deficient pancreatic diabetes (PDPD) has remained more contentious [1,2]. Controversy was mooted in the very name coined by the learned members of the Study Group. Having stated that in this category "pancreatic calcification and fibrosis are absent" [1] and laying emphasis on the "absence of radiographic or other evidences of intraductal pancreatic calcification or dilatation of the ducts and absence of demonstrable malabsorption of nutrients caused by exocrine pancreatic insufficiency [1] there does not appear any justification for naming it protein-deficient *PANCREATIC* diabetes. This was pointed out by one of us to Prof. J.S. Bajaj, vice –chairman of the Study Group who realised the discrepancy and agreed upon the currently used term protein-deficient diabetes mellitus (PDDM), originally adopted at the VI-National Congress of the Diabetic Association of India, Cuttack, 1987 and the 13th Congress of International Diabetes Federation, Sydney. 1988.

HISTORY, PROGRESS AND CONTROVERSIES

In 1955, Hugh-Jones reviewed 215 patients of diabetes attending University College Hospital, Jamaica, West Indies over a period of 18 months [3]. Thirteen (6 per cent) subjects could not be classified as either type-1 (IDDM) or type-2 (NIDDM). These patients were young and thin, thus superficially resembling type-1 but were insulin insensitive, 'persistently' requiring large doses of insulin (above 80 U/day) for control of glycosuria. They did not become ketotic if insulin was withheld. Similar cases were reported from Malaya and Ibadan (Nigeria) in the past and from many other tropical countries during the next 5 years. Contraversies on the special status of 'J' type were raised from the same place where it was first mooted [4]. Follow up of 13 patients originally described by Hugh-Jones and 11 subsequent cases revealed that 3 cases had developed ketoacidosis, 8 required less insulin and many gained weight. Based on these data the authors concluded that 'J' type behaviour is a phase in the natural history of badly treated type-2 diabetes. Other atypical forms of diabetes continued to be published from East Pakistan [5], India [6-9] and other tropical and developing countries. Investigations on metabolic characterisitics were carried out in late '60s [10-13] and immunoreactive insulin (IRI) assay by the early '70s [14-16]. The first direct suggestions implicating the role of malnutrition in the pathogenesis of so call 'J' –type diabetes were offered from our center in 1963 [7,17,18]. During the same period glucose intolerance was reported in patients of Kwashiorkor [19, 20], experimentally malnourished dogs and pigs [21] as well as in adults with chronic malnutrition [22, 23]. In addition to low insulin response to glucose, low sensitivity to insulin action has been demonstrated in the above situations [21, 24]. Clinical observations during the following years [25-33] and presentation of data at the 9th Congress of International Diabetes Federation 1976, New Delhi [34, 35] created international awareness which led to recognition of protein deprivation as a plausible predisposing factor for 'J' type diabetes [36-37]. This was subsequently designated protein deficient pancreatic diabetes mellitus [1].

Controversies on the status of type 'J' diabetes raised by Campbell [38] and Tulloch and Macintosh [4] who considered it as a stage in type-2 diabetes continued as Vishwanathan and colleagues [9, 39] considered the condition secondary to pancreatic disease. McMillan and Geevarghese presumed J-type to be associated with milder grades of malnutirition while tropical pancreatic diabetes a more severe form [40]. Ahuja, for a period (1979-88), believed J-type (ketosis resistant young diabetes) to be an early state of FCPD [41] but currently considers it as a variant of IDDM [42]. Lester [43,44] had difficulty in finding PDDM in undernourished population of Ethiopia while Abdulkadir [45] believes that cases who present as PDDM are modified forms of IDDM. Keen [46] suggested the term 'phasic insulin dependent diabetes' (PIDDM) and Seshiah [47] 'insulin requiring diabetes' (IRDM) to circumvent the controversial 'J' type or PDPD. Oli Commented: "Indeed it is a precalcific stage of FCPD or the IDDM of the tropics" [48]. Mohan and co-workers, [49] reporting in World Book of Diabetes in Practice and Yajnik in Diabetes Annual [50] have expressed grave doubts about the existence of a clinical entity such as PDDM in the absence of a definite marker for its diagnosis. In spite of the heavy cloud of doubts

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a plethora of data in our possession and those generated more recently from Bangladesh, Indonesia, Korea and Jamaica, presented below may hopefully be helpful in clearing some of the misgivings particularly from the mind of those who do not have the opportunity to see these cases for geographical and other reasons.

CLINICAL FEATURES

During the latter half of 1950's we described young patients of diabetes who did not manifest some of the cardinal features of type-I diabetes described by Lawrence [51]. Search of literature revealed that the characteristics of these patients fitted perfectly to the characteristics for type "J" described by Hugh-Jones from Jamica [3]. Having observed a substantial number (~2000) of PDDM patients over last several years we have listed their clinical features (Table 1), which is an improvisation over Ahuja's criteria [52]. The last feature differentiates them from FCPD. We are perhaps the only centre to have described both PDDM and FCPD patients in large number over last 2 decades [53]. It is believed that features other than those of exocrine pancreatic deficiency also apply to tropical calcific pancreatic diabetes [54]. This is not entirely true (Table 2).

Table – 1
Clinical Criteria of PDDM

1. Severe diabetes – fasting blood glucose more than 200 mg/dl.
2. Onset of diabetes before the age of 30 years.
3. Leanness body-mass index < 18 kg/m^2
4. Absence of ketosis on withdrawal of insulin.
5. Poor socio-economic status, history of childhood malnutrition.
6. Insulin requirement more than 60 U/day or more than 1.5 to 2 U/kg/day.
7. Of rural origin (as per our experience).
8. Absence of radiographic or sonographic findings of pancreatic calculi, ductal dilatation and fibrosis; laboratory evidences of exocrine pancreatic dysfunctions.

Patients of PDDM almost exclusively attend charitable public hospitals because of poverty. Hence, it may be difficult for physicians practicing in other institutes to appreciate the extent of the problem.

The following is an overview of clinical picture observed in 545 cases diagnosed and adequately documented during last 13 years.

Table – 2
Comparative Data on PDDM and FCPD as observed at Cuttack

	PDDM	FCPD
Incidence among Diabetics		
All ages	5.2%	2.2%
Upto 30 years	52.5%	22.4%
Age at onset (yrs)	10-30	10-40
M : F	2.7 : 1	3 : 1
Rural	All	83%
Very poor	95%	60%
Middle income	Nil	15%
Childhood malnutrition	90%	54%
Stigmata of severe malnutrition	More common	Less common
Gross underweight	95%	54%
Standard weight	Nil	18%
Mean BMI (kg/m^2)	14	15.2
Abdominal pain	Unusual	40%
Diabetes		
Severe (Fasting blood) glucose > 250 mg/dl)	92%	63%
Mild (Fasting blood glucose upto 150 mg/dl)	Nil	13%
Ketonuria	Nil	16%
Neuropathy	77%	40%
Faecal fat (mean/day)	6.2 g	29.5 g
Plasma C-peptide	present (low)	present (low)
Pancreatic enzymes	Normal	Serum↑(40%) Duodenal ↓↓ (all)
X'ray abdomen:	Nil	present
Pancreatic Calculi		
Sonography		
Pancreatic size	Normal	Often shrunken
Duct	Normal (2mm)	Dilated (3-11mm)
Gall bladder disease	Nil	8%
Mean insulin requirement	88 U/day	56 U/day
Response to oral hypoglycaemic agents	Nil	12%
Hypoglycaemia	Rare	Not uncommon
Macroangiopathy	Rare	Rare
Microangiopathy	20-27%	12-17%

Large majority of the patients present in the diabetes clinic in a very miserable state of health, with emaciation, asthenia, weakness bordering on prostration, body pain muscle cramps, often with paraesthesias, skin infections and dehydration. Polyuria, polydipsia and polyphagia are often evident. Abdominal pain is unusual. Onset of symptoms is usually rapid (6 months to 2 yrs). Some try local remedies, but most neglect their symptoms till they are severely ill. Most patients present between 12 and 25 yrs of age, though occasionally younger [55]. Recently, 3 preschool children with PDDM have been

reported from The School of Tropical Medicine, Calcutta [56, Chatterjee, personal communication]. One has to be very careful to diagnose PDDM above 35 yrs of age, though some are reported from Agra [57] and Jamaica [58]. Males usually outnumber females.

During last 35 yrs we have never seen patients with PDDM of urban origin; though few are described in other centres [32].

Over 90 per cent of our patients with PDDM are very poor [59]. Similar experience has been reported from Delhi and Bangladesh [30,60].

Detailed dietary evaluation in our patients suggests inadequate intake from very early age. Rural patients consume ~1500 calories/day (~ 20 g protein and very little fat).

Family history of diabetes was present in upto 8% of our patients. It was less common in other centres [30,32] but 20 per cent in patients reported from Bangladesh.

All our patients with PDDM are lean, many are emaciated. Body weight ranged from 30 to 52 per cent of desirable (ideal) weight for height [6,7], BMI: mean 14 kg/m^2 (range 12-16) [59]. On history , patients appear to be lean even before onset of symptoms of diabetes. Similar degree of malnutrition is reported from other centers [30,32,56].

Linear growth and sexual maturity are retarded in children and adolescents with PDDM [61].

Around 20 per cent of our patients manifest overt signs of nutritional deficiency (hair, mucous membrance, skin and nail changes). Parotid enlargement is a feature of FCPD.

Severity of diabetes: There is severe glycosuria without ketonuria. Most of the patients have very severe diabetes (FPG> 250 mg/dl, 14.0 mmol/L). Ketosis is absent at diagnosis or during later follow up even insulin is stopped and despite systemic infections. Corticosteroids, epinephrine and salbutamol do not produce the degree of ketosis seen in IDDM [28,62,63].

Over 70 per cent of our patients suspected to have MRDM do not show pancreatic calculi on X-ray of the abdomen. Similar observations are reported in North India [8, 28, 30, 32] but pancreatic calculi are quite common in South India [26].

Treatment

During the first several months high caloric diet rich in carbohydrates (cereals) is desirable in view of emaciation and undependable digestive system. Following treatment these patients develop ravenous appetite.

Sulphonylureas are ineffective in controlling hyperglycaemia in these patients [4, 6, 7, 28, 30, 32, 63, 64, 65] perhaps because of the low endogenous insulin reserve [14, 16, 62, 67].

Insulin is essential for control of diabetes . Unlike patients with IDDM who are insulin sensitive and can be stabilised with 30-60 U/day [51], PDDM patients require higher doses. Long term requirement ranges from 60-150 U/day (upto 230 U in Jamaica) [3,4] with a mean of 88-90 U at our center [59].

We performed glucose-insulin sensitivity test in these patients [22,66]. We observed impaired insulin sensitivity in PDDM while Ahuja and co-workers found either no significant difference from IDDM [28] or a greatly diminished hypolglycaemic response to exogenous insulin [12].

Long term management of these patients is problematic as the vast majority cannot afford insulin treatment. Hence they discontinue insulin and are obliged to visit hospital from time to time. Most are lost to follow up. When treatment is continued for over a year gain in weight occurs but is painfully slow. We are yet to see any patient who has attained desirable weight or BMI of 22. Irregular treatment may not be the sole cause for failure to gain adequate weight.

Biochemical parameters (Table 3): Hyperlipidaemia is not remarkable inspite of severe hyperglycaemia. HDL concentrations are relatively high particularly after institution of insulin therapy . FFA and ketone values are substantially lower than those in IDDM. Normal values of faecal fate after high fat diet suggest normal exocrine pancreatic function.

Table – 3
Mean values obtained from routine biochemical tests in patients with PDDM

Serum proteins	3.23 ± 1.28 g/dl
Serum cholesterol	190 ± 28 mg/dl
Serum triglycerides	175 ± 35 mg/dl
Serum free fatty acids (NEFA)	721 ± 53 mEq/l
Plasma ketones (basal)	1.8 ± 1 mg/dl
After epinephrine	3.1 ± 1.9 mg/dl
Faecal fat	6.2 g/day

Complications

Acute metabolic complications are rare. Ketosis does not occur, when it occurs it is usually mild. Hypoglycaemia is uncommon. Despite severe hyperglycaemia and dehydration hyperosmolar nonketotic coma has not been observed in PDDM.

Scabies, fungal skin infection and pyoderma are seen in ~40 per cent of cases. Pulmonary tuberculosis is relatively common (10 per cent). Symptoms of peripheral neuropathy are most common (77 per cent). It is of the acute, reversible, predominantly sensory type of symmetrical polyneuropathy. Retinopathy (21 per cent) is more than nephropathy (10 per cent). Microalbuminuria is common but not frank proteinuria. Hypertension, coronary artery disease and cerebrovascular disease are not encountered. Peripheral vascular disease can be detected in 10 per cent, but foot problems are more due to trauma and infection. Only 6 per cent of those who could take insulin regularly developed retinopathy compared to 13 per cent in patients with IDDM observed over 10 yrs.

Diagnosis

In our situation diagnosis of PDDM offers no problems. However, classification of clinical disorders is often artificial and may be arbitrary [7]. Overlap of certain features between clinical types may be the rule rather than exception. A large group of patients resembling PDDM in all respects but not requiring high doses of insulin were reported by Moses [26]. It may be difficult to elicit history of malnutrition in infancy and early childhood. Bajaj [68] introduced a score system for diagnosis of MRDM. Unfortunately the two subclasses are lumped together in this system when the crux of the problem is to identify individuals with PDDM more accurately [69]. The practical difficulties in this system are discussed [70]. As rightly suggested, past and present malnutrition are essential for diagnosis of PDDM; diagnosis of FCPD depends more on demonstration of pancreatic calculi and exclusion of alcohol indulgence and biliary disease than the rest of the clauses in the system. We have suggested a modified score system to diagnose PDDM, based on our experience of both PDDM and FCPD patients. It may be seen that higher weightage has been given to history of childhood malnutrition than stigmata at presentation. Lack of proneness to ketosis and absence of evidence of typical pancreatic pathology for exclusion of IDDM and FCPD respectively have the maximal weightage.

Table – 4
Modified score system for the clinical diagnosis of PDDM

Clinic Profile		Score
Age at onset	10-30 years	1
Poor economic status (Rural origin		1
Leanness, BMI < 16 kg/m2		2
	< 18 kg/m2	1
History of malnutrition in childhood		2
Stigmata of malnutrition (clinical) (past or present)		1
Severe hyperglycaemia (fasting blood glucose > 200 mg/dl)		1
Lack of proneness to ketosis:		
(Absence of Ketonuria on withdrawal of insulin for long periods)		3
Insulin requiring:		
Over 60 U/day (2U/day body wt.) unresponsive to Sulphonylurea compounds		2
Absence of X'ray/Ultrasound evidence of pancreatic calculi and ductal dilatation		3
TOTAL SCORE :		16

Diagnostic score - 13

Suggestive score - 12

PDDM has to be differentiated mainly from 3 other types of diabetes occurring in the young, viz. FCPD, IDDM, NIDDY. FCPD can readily be excluded by radiology. Some have anticipated development of pancreatic calculi in course of time, although such phenomena have scarcely been reported. Improper first investigation may account for discovery of calculi at a later date as in one case originally described by Hugh Jones [3,4]. Misra and Samal followed up 34 cases over 10 yrs. Findings are given in Table 5. None has evidence of pancreatic pathology. Preservation of residual B-cell function (Figure 2) over long years refutes the possibility of smouldering IDDM. Absence of ketoneuria and inspite of very severe hyperglycaemia and heavy glycosuria after long periods of insulin withdrawal provides strong evidence against diagnosis of IDDM.

Table - 5
Clinical and radiographic findings on 34 patients of PDDM followed for 10 years or longer

	(M – 27, F – 7)	
	First visit	10 yrs follow up
Age (yrs)	23.4 ± 2.6	37 ± 5 yrs
BMI (kg/m^2)	14.8 ± 1.1	15.8 ± 1.8
Fasting blood glucose mg/dl	335 ± 62	371 ± 104
Insulin dose (units/day)	75 ± 15	70 ± 18
Plasma C-peptide (Fasting)	0.6 ng/ml	0.7 ng/ml
Plain X'ray abd.	--	No calculi
	--	No calcification
Pancreatic Ultrasonography	--	Head – 18 mm
		Body – 15 mm
		Tail – 11 mm
		Duct – 2 mm
		Normal echogenecity
Abdominal C-T Scan (n-11) No evidence of Shrinkage of pancreas	--	Normal

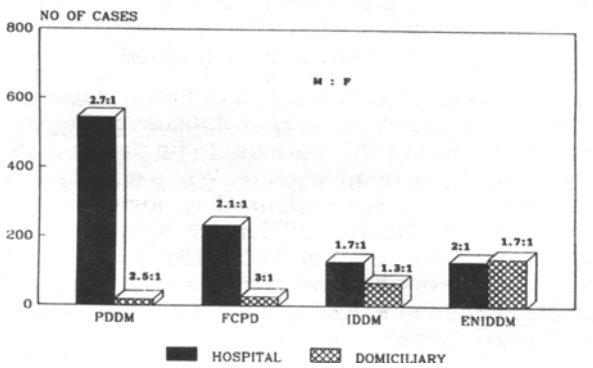

Fig. 1 Distribution of young onset diabetes; hospital and domiciliary data (1980-93)

In our experience large majority of patients with NIDDY have a family history of diabetes and belong to better socioeconomic class and are not underweight. They are controlled on diet or oral hypoglycaemic agents.

Not withstanding the above, some of our recent findings call for caution in arriving at the final diagnosis. Out of 108 patients provisionally diagnosed PDDM on clinical and radiological basis, sonography revealed pancreatic fibrosis and increased echogenicity in the absence of intraductal calculi in 23 [71]. It is suggested that the WHO nomenclature PDPD [1] may be most suitable for these subjects.

Hospital prevalence of PDDM among patients with onset of diabetes before the age of 30 yrs in some centres from India is shown in Table 6. Prevalence of the other types is provided for comparison. Data from 2 centres in Orissa and 1 from Bangladesh are graphically presented in Figure 3.

Table – 6
Reported incidence of PDDM and other clinical types among youth onset patients of Diabetes (onset by 30 yrs) in India

Hospital	No.			PER CENT	
	PDDM	FCPD	IDDM	NIDDM	
Madras (a)	300	58	18	10	3
(b)	539	50	5	13.5	24
Cuttack	790	58.3	24.2	10.3	6.2
Delhi	1783	73.5	--	22.5	4.3
Jabalpur	210	75.5	--	23.5	1.0
Jhansi	105	84	--	16	--
Private					
Madras	545	1.3	4	22	57.7
Cuttack	150	7.4	12	36	44.6

* Rest unclassified.
(a) S.G.P. Moses (1970)
(b) V. Seshiah (1985)

PDDM is obviously the commonest type of diabetes that affects the poorest sections of the population. We believe it occurs in all parts of India and can be detected wherever there is awareness. At the AIIMS, New Delhi, around 30 patients are observed annually [72], incidence is fairly high in Uttar Pradesh as reported from Jhansi, Agra, Lucknow and Varanasi. Cases are encountered at Bombay, Nagpur, Indore and Jaipur. High incidence of PDDM has been reported from Jabalpur (Madhya Pradesh). PDDM was seldom reported from Hyderabad apart from a few cases observed at the National Institute of Nutrition. Within last 1 yr, 11 cases of PDDM and 15 cases of FCPD were documented at Osmania Hospital in a group of 63 young diabetic patients [73].

Special investigations

Hormones: Patients with PDDM are partially insulinopenic. Basal plasma insulin levels are 5-8 mU/l compared to > 10 mU/l in controls. Following glucose load, peak values (18-24 mU/l) are less than half of those in the controls. Fasting plasma C-peptide levels are between 0.4-0.8 ng/ml. Post glucagon values are upto 30% of those observed in controls. Thus, in contrast to IDDM, residual B-cell function is retained above a critical level and remains

preserved over long periods of time (Fig 3) although, the insulinogenic reserve is low.

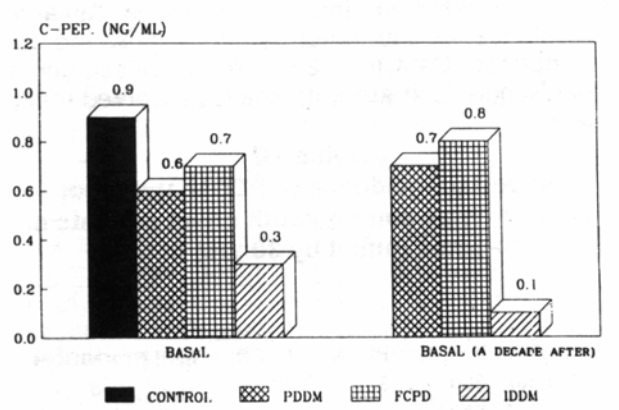

Fig. 2 Serum C – peptide levels in different clinical types of young diabetics over a decade

Basal serum hGH levels are high. Following glucose load, the levels rise (Fig 4) [74]. These findings are similar to observations on patients of chronic malnutrition [24]. Fasting serum glucagon levels are high and showed a fall by 28 per cent after oral glucose in contrast to paradoxical rise of over 20 per cent in IDDM [75].

Pancreatic function: Faecal fat estimation and secretin - pancreozymin test revealed normal exo-

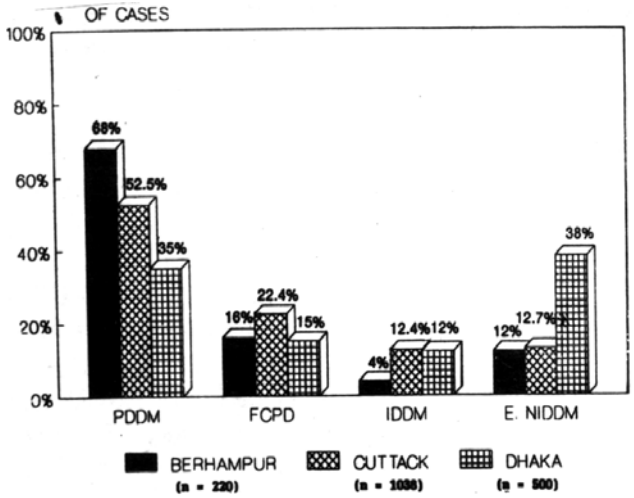

Fig. 3 Clinical types among young diabetics; hospital data

crine function [76]. Faecal chymotrypsin estimation revealed normal values in PDDM and IDDM while it was grossly reduced in FCPD [77]. AIthough PABA excretion was found to be lower in PDDM than in controls, it was much higher than in FCPD (43 per cent vs 29 per cent) and endoscopic retrograde pancreatography revealed normal ducts in PDDM patients [60].

Study of circulating islet cell antibodies (ICA) reveal variable results. Positive results have been reported from Agra (38 per cent) [57] and 10-20 per cent of cases clinically diagnosed as ketosis resistant young diabetes (PDDM). These are categorised as type 1B in view of persistent character of lCAs and its association with other autoantibodies. While these may ultimately develop type 1 diabetes the rest 80-90 per cent have undisputed PDDM.

HLA association: HLA typing has been carried out particularly in patients from Ethopia, Korea and Madras. Abdulkadir et al. [79] found strong association of DR3 with PDDM. They concluded that MRDM and IDDM were at least 'partially identical' [79]. On the other had Hub et al. report DR4 to be related to PDDM. They infer that MRDM is another expression of IDDM caused by shortage of some nutrients for the functional maintenance of pancreatic B- cells [78]. In contrast the genetic background of patients with MRDM (PDDM) has been found to be different from that of IDDM in Madras [80].

Pathogenesis: PDDM seems to evolve from the combined effect of substantial loss of B-cell function and high grade insulin resistance. Clinical and laboratory evidence for both these phenomena has already been discussed.

PDDM is idiopathic in the sense that it develops independent of any other known disease. Genetic factors, if any, in PDDM are yet to be determined. Family history is relatively rare. While obesity and sedentary habits are supposed to foster insulin resistance in NIDDM, clinical & epidemiologic evidence points to poor socio-economic status and deficient nutrition as possible environmental factors in case of PDDM. Can these factors foster insulin resistance?

Clinically insulin resistance has been documented in patients with chronic malnutrition [23, 66, 81]. Experimental evidence for the same has been elucidated by Rao [82]. It has been shown that insulin resistance in PDDM is not mediated by insulin antibodies. Low levels of insulin receptors have been reported in PDDM [58] as well as in matnutrition. Indeed these are the only situations where insulinopenia is associated with low receptor binding [82].

Conflicting reports on presence [78, 79] and absence [72] of ICA and HLA association [78, 79, 80, 83] in

PDDM makes it doubtful if immune mechanisms are involved in islet destruction.

Can malnutrition in any way impair B-cell function? The topic has been exhaustively reviewed by Rao [84, 85]. The morals from these have been spelt out as follows: "lt must be recognised that undernutrition, no less than obesity, plays an important role in the aetiopathogenesis of diabetes."

Is there a special role for protein deficiency as compared to calories? Clinically it is documented that glucose intolerance, insulinopenia and insulin resistance occur more often in kwashiorkor rather than marasmus [83]. Alteration in carbohydrate metabolism has been induced in dogs especially by protein deprivation [21]. These abnormalities have been induced in young rhesus monkeys by feeding isocaloric low protein diet [86]. Further demonstration of persistent impairment of insulin secretory response after limited period of low protein diet [87] and intermittent low protein diet [88] in 3 wks old rats are most convincing. More recently Hoet demonstrated impairment of islet function in offsprings of rats fed on protein diet. When the offspring were also fed low protein diet, insulin levels remained low. Feeding normal diet after birth does not restore insulin response to normal in adult life [89, 90]. Hoet infers that children of developing countries, where protein deficiency is endemic, may have IGT and insulin resistance in early life. These observations suggest that protein deficiency while in the womb and in early infancy may be a key factor in the diabetogenic potential of MRDM.

There is a striking clinical and epidemiological association of PDDM with malnutrition [83]. The condition occurs only in developing countries of the tropics and among the poorer sections of society in these countries [7, 59, 60]. Detailed analysis of diet at presentation revealed sustenance on diet of low protein and calorie value [78]. Enquiry reveals poor nutritional availability to the mother during pregnancy and low protein diet since weaning. Insulin levels are low, counter regulatory hormones such as hGH and glucagon are high in subjects with protein calorie malnutrition [91] as well as in patients with PDDM under circumstances.

It thus appears that protein malnutrition in mother during pregnancy, and the offspring during early infancy could play an important role in pathogenesis of the type of diabetes designated as PDDM.

Associated micronutrient deficiency could cause free radical damage to sensitive B-cells.

A mathematical model has suggested that insulin deficiency in PDDM is not due to reduction in number but to impairment of the function of B-cells [83]. This runs counter to the idea that PDDM may be nutritionally modified form of IDDM. Experimental corroboration is provided by morphometric analysis of islet cells in protein deficient rats [91, 92].

Thus reduced B-cell reserve from neonatal life in the face of coexisting insulin resistance could lead to decompensation and clinical diabetes at an early age. Other factors (genetic, toxic, infective) could also operate.

Resistance to ketosis is a cardinal feature of PDDM. Several explanations have been offered to explain this metabolic enigma. Absence of depot fat, resistance of adipose tissue to lipolysis, altered mobilisation of FFA, dietary deficiency of lysine leading to hepatic carnitine deficiency, suppressibility of glucagon by mounting hyperglycaemia and presence of insulin levels above critical limit have a11 been examined and discussed. Persistence of subnormal level of insulin appears to be the most plausible explanation. Low levels of basal insulin (5 mU/L) may be adequate to stall excessive lipolysis but much higher levels are required to regulate hepatic glucose output and to increase glucose uptake by muscles. Severe hyperglycaemia in PDDM is maintained by excessive gluconeogenesis. This is evident from heavy deposit of glycogen leading to ballooning of nuclei of the hepatocytes [6, 7].

DISCUSSION

A strong opinion has built during last few years challenging the position of MRDM in the WHO classification of diabetes. Antagonism to PDDM is mainly based on 2 scores: (1) Does it have well defined borders to justify its recognition as a definite clinico-pathological type? (2) Are there sufficient data to specify its name 'protein deficient'?

Doubts based on the first are possibly due to (a) Lack of scope for personal observation or (b) Improper selection of cases at first diagnosis with apparent changes of character on follow up.

Objection to PDDM on the first account comes from workers such as Lester from Ethiopia [43, 44]. She looked for PDDM in her own field and did not find typical cases in situations when they are likely to be seen. To question the existence of a type because it is rare in any geographic area does not appear

justifiable, because the presentation of disease depends on many factors.

Critics of the second type consider PDDM as poorly treated type 2, as modified type 1 and still others as a forme fruste of FCPD (Figure 4).

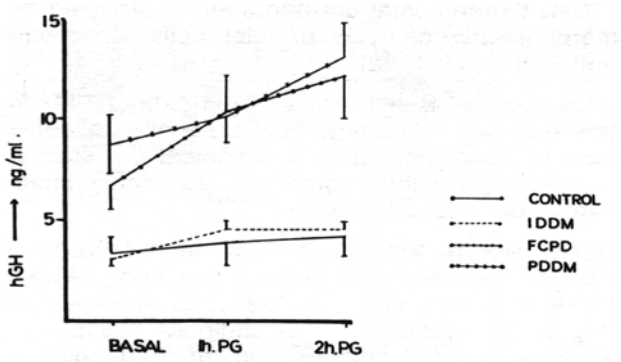

Fig. 4 Serum hGH response of three clinical types of diabetes

Analysis of data of Tulloch [4], the main proposer of type 2, shows that out of 24 cases, 3 developed ketoacidosis and another 6 required less than 60 units insulin/day for control, needing reclassification. His claim about 3 patients aged 20, 15 and 14 years, weighing 45, 44 and 36 kg and requiring 270, 220 and 240 U of insulin/day to be 'passing through a phase in the natural history of badly treated type 2 diabetes' may not appeal to many.

In 1987 Abdulkadir et al described 30 rural, poor, undernourished or cachectic patients who fitted the description of PDDM except for moderate insulin requirement [93]. Subsequently in a follow up of 23 hospitalised cases of MRDM in Ethiopia it was found that 3 could be managed with glibenclamide and 6 became ketotic on withdrawal of insulin [93]. Rest 14 cases who apparently belonged to PDDM are not discussed. Although only 3 of the patients responded to Sulfonyl Urea drugs, all the cases diagnosed as MRDM have been considered as variants of type 1 modified by malnutrition. Obviously the group consisted of admixture of different types. Residual endogenous insulin secretion and the mathematical model [83] negates the type-I hypothesis. However whether they are 'partially identical' to IDDM [79] needs to be further studied.

Presumption that all atypical young diabetics of the tropics have pancreatic disease [39] was discarded by the same group of workers by 1988. Those who consider PDDM as an early stage of FCPD [41, 48] may revise their impression after our follow up study.

Abu-Bakare et al [54] while accepting that mal nutrition may be a plausible factor have suggested that until more information on clinical and biochemical features and aetiology is available, MRDM may be continued to be known as tropical diabetes. As if in answer to this, Bajaj [94] states 'Thus there is sufficient clinical, epidemiological endocrinal, biochemical, experimental and mathematical evidence to support the assignment of a separate descriptive type to PDDM'.

In contradiction to Oli [48], Johnson [95] favours retaining the term 'protein deficient' and hopes that J type diabetes will enjoy increasing status as a subclass.

To look for an 'infallible marker' for a disease more so for any particular type is probably asking for too much, asking nature to behave itself. There does not appear to be any particular marker for NIDDM, although ketosis proneness (IDDM) and pancreatic calculi (FCPD) are specific in some ways. If one asks for definition ketosis resistance (49) one should have answers to define ketosis proneness in order to diagnose IDDM clinically. Only a few clinical criteria may be pathognomonic for a few disorders and score systems have been proposed for several diseases, if NIDDM patient becomes ketosis prone at a later date, he should be reclassified as IDDM.

CONCLUSION

No wonder 'does malnutrition related diabetes exist?' [44] has been matched by a similar question for NIDDM by Zimmet [96] who concludes that NIDDM does exist. We hope we have presented data which will lead to acceptance of PDDM as an entity. Barnot's comment `for the present the case for preceding malnutrition being important in development of this type of diabetes is good, but other factors are also likely to be involved' [97] appears most appropriate.

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