ETIOPATHOGENESIS OF TYPE I AND TYPE II DIABETES:

RECLASSIFICATIONS AND INTERVENTIONS?

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INTRODUCTION

The standard classification of overt diabetes mellitus (Table 1) into insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) types is, of course, based on obvious and unmistakable clinical distinctions that have been appreciated ever since Hippocratean times: the juvenile-onset or ketoacidosis-prone type and the adult or maturity-onset ketoacidosis resistant form. In April, 1978, an NIH sponsored international workshop, subsequently called the National Diabetes Data Group, gave this distinction official status by offering a new terminology for these two categories of diabetes, IDDM or Type I and NIDDM or Type II, respectively, a nomenclatural system with built-in therapeutic guidelines based solely on whether or not there is sufficient insulin secretion to prevent ketoacidosis (1). While separation of diabetes on such quantitative pathophysiologic grounds is conceptually important and serves as a valuable guide in evaluating the therapeutic options available to a given patient, it provides virtually no information concerning the etiology of the condition, that is to say its pathogenetic mechanism, information that may be essential for choosing patients for appropriate prophylactic interventions now undergoing clinical trial in several institutions throughout the world. Because all currently employed interventions are merely pathophysiologic, i.e., are intended to prevent or correct the pathophysiologic abnormalities that form the basis of the standard classification, they may not be appropriate guides for interventions that are designed to interrupt the pathogenic process that produce these syndromes. With the current system of classification there is a blurring of the clinical and pathophysiological distinction between the syndromes, which could confuse the proper choice of prophylactic or corrective interventions, interventions such as interruption of the autoimmune insulopathy in a Type I prediabetic for example. In this Grand Rounds we will review the two major diabetic syndromes from both the pathophysiologic and etiologic aspects in an effort to provide a framework for ultimate interruption of etiopathogenic mechanisms.

THE PATHOPHYSIOLOGY OF IDDM

IDDM is defined clinically as a diabetic state in which deprivation of exogenous insulin initiates a catabolic cascade culminating in diabetic ketoacidosis and death. The massive overproduction of glucose and ketones that by definition makes diabetes IDDM rather than NIDDM can only exist if insulin levels are too low to accomplish: 1) restraint of lipolysis in adipocytes so as excessive delivery of FFA, the substrate for ketogenesis, to the liver; and, 2) opposition to the hepatic actions of glucagon which otherwise converts the liver from a nonketogenic to a ketogenic organ. Indeed, it must be emphasized that a diabetic cannot become ketoacidotic, or even have fasting hyperglycemia above 180 mg/dl range, unless glucagon is present, i.e., in the absence of glucagon IDDM cannot exist (2). IDDM must, therefore, be defined pathophysiologically as a state in which the ratio of insulin to glucagon is sufficiently low to permit uninhibited effects of glucagon on the liver.

How unopposed glucagon produces IDDM (for review see reference 3): Glucagon acts by increasing hepatic cyclic AMP. This raises the concentration of cyclic-AMP-dependent kinase which promotes a variety of phosphorylation reactions that cause: 1) activation of the enzyme phosphorylase (which enhances the

conversion of glucose-1-phosphate to glucose-6-phosphate) and inactivation of glycogen synthetase (the key enzyme in glycogen formation); 2) activation of the enzyme that enhances the degradation of the factor fructose-2,6-bisphosphate the allosteric inhibitor of gluconeogenesis and promoter of glycolysis (4). The first actions break down glycogen and block new glycogen formation. The second action, reduction in F-2,6-P_2 blocks glycolysis and promotes gluconeogenesis. The result is increased hepatic glucose production (Figure 1).

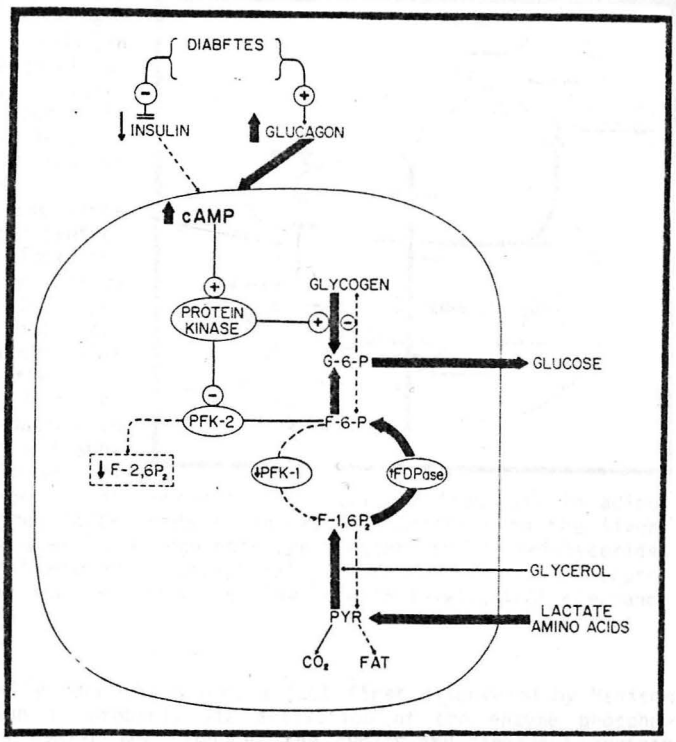


FIG. 1: The biochemistry of the action of glucagon on glucose metabolism. Glucagon reacts with a receptor initiating a complex series of reactions [Rodbell M. Reactions of glucagon at its receptor: Regulation of adenylate cyclase. In Glucagon I, PJ Lefebvre (ed), Berlin: Springer-Verlag, pp. 263-90, 1983] that result in increase in hepatic cyclic-AMP. The increased cyclic-AMP-dependent protein kinase 1) stimulates glycogenolysis and inhibits glycogenesis; and 2) stimulates gluconeogenesis and also blocks glycolysis by inhibiting phosphofructokinase-2, thus reducing fructose-2,6-P_2 (F-2,6-P_2), the activator of the glycolytic enzyme phosphofructokinase-1 (PFK-1) and inhibitor of fructose diphosphatase (FDPase), a key enzyme in the gluconeogenic pathway. These effects increase hepatic glucose production from glycogenolysis and gluconeogenesis. The block in glycolysis profoundly limits the flow of 3-carbon fragments (PYR) towards fat, which has important consequences for fatty acid synthesis and ketogenesis, as depicted in Figure 2.

At the same time, the glycolytic block caused by the low F-2,6-P_2 reduces the flow of three carbon fragments available for fatty acid synthesis to a trickle, i.e., it blocks lipogenesis. McGarry and Foster (5) discovered that malonyl-CoA, the first committed intermediate in fatty acid synthesis, is a potent inhibitor of ketogenesis, and that a block in fatty acid synthesis and the resulting fall in malonyl-CoA concentration releases from inhibition the

enzyme carnitine palmitoyl transferase-1 (CPT-1). CPT-1 is the enzyme which converts the fatty acyl CoA to fatty acyl carnitine, thereby permitting it to cross the mitochondrial membrane into the mitochondrium where it would undergo β-oxidation to ketones. The reduction of malonyl-CoA thus permits unfettered CPT-1 activity and ketone production (Figure 2).

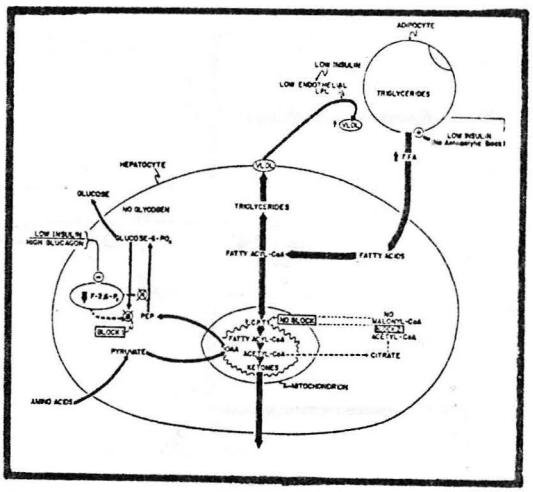


FIG. 2: The biochemistry of low insulin-glucagon ratio on fat and ketone metabolism: The fall in F-2,6-P_2 caused by the high glucagon-low insulin mixture blocks glycolysis and thereby reduces the flow of glucose-derived 3-carbon fragments for fatty acid synthesis as depicted in Figure 4. Consequently, the levels of the first intermediate in fatty acid synthesis, malonyl-CoA, which blocks the enzyme carnitine parmitoyl transferase-1 (CPT-1), fall. Increased CPT-1 activity converts fatty acyl CoA to fatty acyl acylcarnitine in which form it can cross the inner mitochrondrial membrane into the mitochondrion for β-oxidation to ketones. The fatty acyl CoA substrate for CPT-1 is present in abundance because the low insulin levels permit increased lipolysis in adipocytes and delivery of free fatty acids in increased quantities to the liver. Fatty acids that are not used for ketogenesis are reesterified to triglycerides and packaged as VLDL for transport to peripheral tissues. However, if lipoprotein lipase is reduced as the consequence of low insulin levels, VLDL clearance will be low.

Insulin acts directly upon the liver, a fact first discovered by Madison et al. (6). Its action is probably via activation of the enzyme phosphodiesterase which reduces cyclic AMP, reduces the cyclic-AMP-dependent protein kinase, thus opposing these glucagon-mediated effects. This deactivates phosphorylase thus reducing glycogenolysis, and reestablishes high levels of F-2,6-P_2, which stimulates glycolysis and inhibits gluconeogenesis (Figure 3). The flow of three carbon fragments, the substrate for fatty acid synthesis is thereby reestablished. Resumption of fatty acid synthesis restores malonyl CoA levels which inhibits ketogenesis (Figure 4). These effects of insulin oppose glucagon, but if glucagon is not present and cyclic AMP is not increased then insulin would have no detectable effect on the hepatocyte, at least not on glucose and ketone production (7). Thus, the absence of glucagon during insulin lack would convert IDDM into very mild NIDDM since the major metabolic lesion resulting from a bihormonal deficiency would be impaired glucose tolerance (Figure 5).

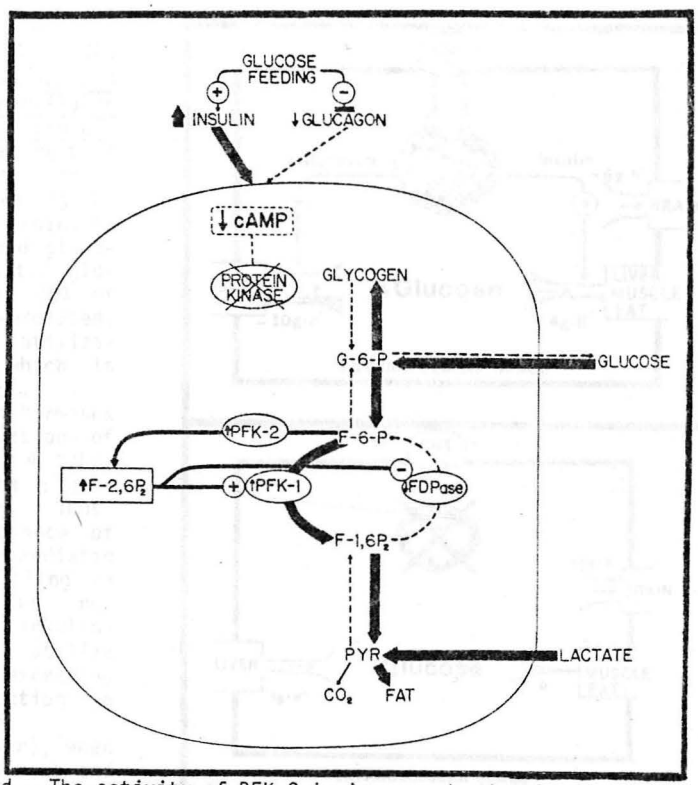


FIG. 3: The biochemistry of insulin-mediated opposition to the actions of glucagon on the liver. When insulin levels are high relative to glucagon, as during glucose feeding in a nondiabetic or in a well-insulinized diabetic, circulating glucagon levels are suppressed by the insulin but at the hepatic level glucagon action is opposed by insulin. Insulin lowers cyclic-AMP levels, probably by promoting the activity of phosphodiesterase, the enzyme that destroys cyclic-AMP. As a result, cyclic-AMP-dependent protein kinase is reduced. Glycogenolysis is thereby inhibited and glycogen formation increased. The activity of PFK-2 is increased, thereby increasing the levels of the key activator substance, F-2,6-P_2 which promotes glycolysis by stimulating PFK-1 activity and inhibits gluconeogenesis by suppressing FDPase activity. The result is more flow down the glycolytic pathway and increased generation of 3-carbon fragments (PYR), the substrate for fatty acid synthesis (see Figure 4).

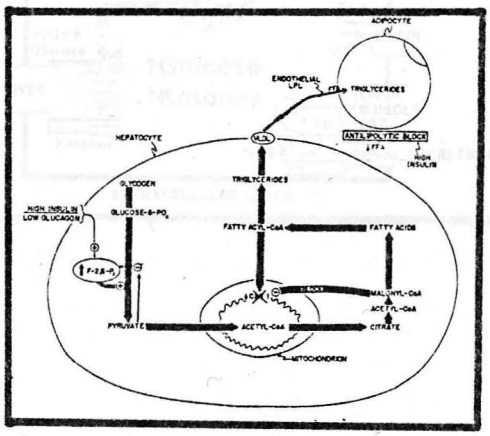
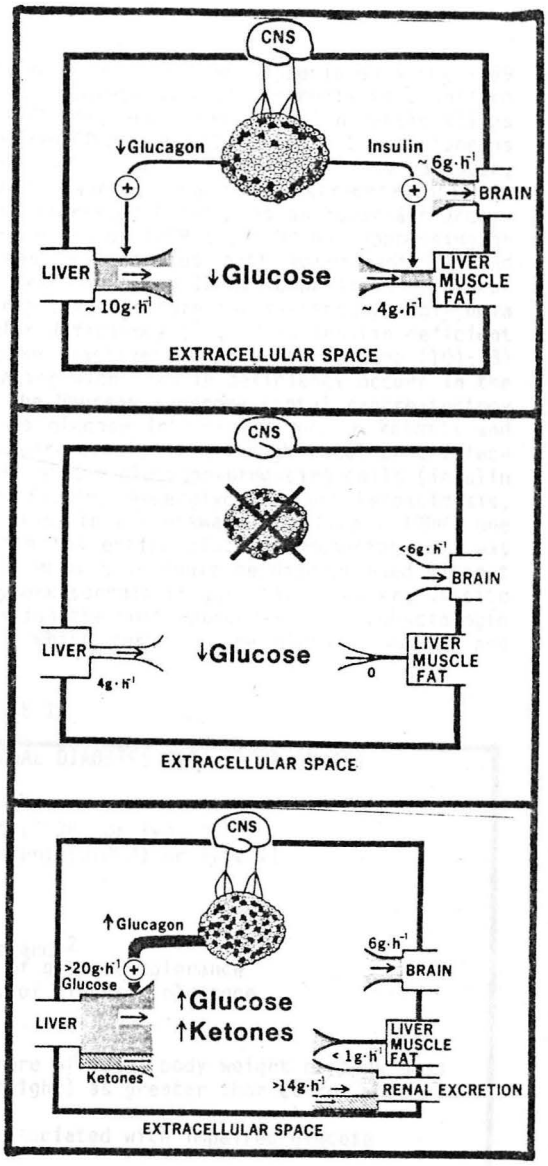


FIG. 4: The effect of a high insulin-low glucagon mixture on fatty acid synthesis and ketogenesis. As shown in Figure 3, the increased F-2,6-P_2 restores glycolysis, thereby furnishing 3-carbon fragments for fatty acid synthesis. Malonyl-CoA, the first committed intermediate in fatty acid synthesis, blocks CPT-1 activity, which prevents fatty acyl CoA from crossing the inner mitochondrial leaflet to enter the mitochondrium, the site of β-oxidation to ketones. Instead, the newly synthesized fatty acyl CoA is esterified to form triglycerides, which are packaged as VLDL and secreted. VLDL reaches adipocytes where in the presence of normal LPL activity free fatty acids are removed and stored within the adipocyte as fat. The high insulin also reduces lipolysis and limits the flow of free fatty acids to the liver.

FIG. 5: Schemes depicting the contributions of insulin and glucagon to glucose influx and efflux from the extracellular space and upon glucose concentration. In the normal resting state (upper), efflux and influx are maintained at equality by the appropriate coordinated secretion of insulin and glucagon so that total hepatic glucose production, about 70% of which is glucagon-mediated, equals total glucose utilization, about 40% of which is insulin-mediated at rest.
In the absence of both hormones (center), liver production of glucose drops to about 4 g/hr, which is less than the 6 g/hr required by the brain. Thus, even in the total absence of insulin, with insulin-mediated glucose utilization falling to zero, hyperglycemia will not develop because the insulin-independent brain would utilize glucose at a rate exceeding hepatic glucose production in the absence of glucagon.
In untreated IDDM (lower), when insulin levels fall to zero and glucagon secretion is not restrained by the presence of insulin, the effects of the high levels of glucagon upon the liver are unopposed by insulin. Hepatic glucose and ketone production rise inexorably and glycosuria becomes the major avenue of glucose efflux.



The key role of the glucagon in diabetes has been appreciated since 1969 when it was discovered that relative or absolute hyperglucagonemia is a uniform finding in insulin-dependent diabetes mellitus and indeed in all diabetic states (8). Also in all diabetic states, human IDDM and NIDDM (Table 1) spontaneous IDDM-like syndromes of rodents such as the NOD or bb Wistar rat or db/db mouse, virally induced diabetes in mice, and diabetes induced by streptozotocin in rodents and by alloxan in dogs exhibit increased A-cells as an invariant accompaniment of the loss of β-cells. Conversion of IDDM to NIDDM by suppressing or blocking glucagon has frequently been demonstrated both experimentally and clinically: 1) in total insulin deficiency in human IDDM, suppression of glucagon secretion by somatostatin completely prevents both the fasting hyperglycemia and the ketoacidosis of complete insulin deficiency (9); 2) in insulin deficient rats blockade of glucagon action with an inactive analog does the same (10); 3) chronic glucagon deficiency in association with insulin deficiency occurs in the somatostatinoma syndrome (11) and in the Houssay syndrome (total pancreatectomy together with hypophysectomy); there is glucose intolerance but no ketosis and fasting glucose levels are normal or near-normal; 4) although total pancreatectomy in man usually fails to remove all of the glucagon-producing cells (insulin deprivation in such patients causes fasting hyperglycemia and ketoacidosis, although at a slower rate than after insulin withdrawal in a Type I IDDM) one patient has been reported (12) in which the entire glucagon-producing mass was apparently removed surgically and in whom insulin could be discontinued without the development of hyperglycemia or hyperketonemia (Figure 6). However, despite the useful effects of glucagon suppression the most appropriate pathophysiologic intervention remains insulin delivery which corrects the glucagon excess and restores the actions of insulin.

TABLE 1

CLASSIFICATION OF THE NATIONAL DIABETES DATA GROUP (NDDG)

I. Idiopathic diabetes mellitus
   1. Insulin-dependent (IDDM) or Type I
   2. Non-insulin-dependent (NIDDM) or Type II
      a. Non-obese
      b. Obese[1]

II. Gestational diabetes

III. Impaired glucose tolerance[2]

IV. Previous abnormality of glucose tolerance

V. Potential abnormality of glucose tolerance

VI. Secondary diabetes

[1]Obesity is defined as 120% or more of ideal body weight or body mass index (kg of body weight/m^2 of height) as greater than 25 for women or 27 for men.

[2]A complete list of conditions associated with impaired glucose tolerance is given in Table 7.

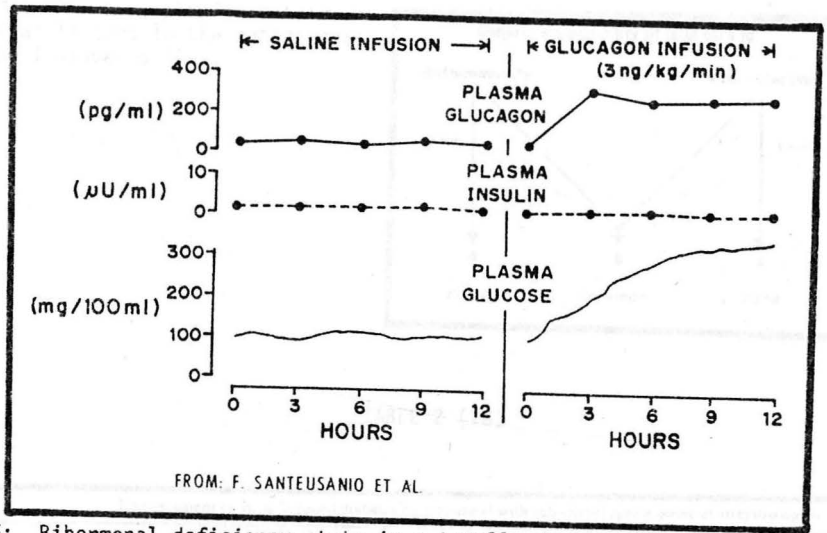


FIG. 6: Bihormonal deficiency state in a totally depancreatized patient. Note lack of hypoglycemia (left) and effect of glucagon (right).

ETIOPATHOGENESIS OF TYPE I IDDM (see 13 and 14 for reviews)

Primary β-cell destruction of sufficient magnitude to produce IDDM is believed to be initiated by viral and/or nonviral environmental insults of varying magnitude and completed by a secondary autoimmunity of varying magnitude (Figure 7). There are rare recorded instances of β-cell destruction that would appear to be solely the result of a massive dose of an environmental agent and those that appear to be unprovoked primary autoimmunity (if this truly exists). In the first category are the reported cases of Vacor poisoning (15). Nitroso compounds found in cured mutton are also said to produce β-cell injury (16); in Germany two HLA non-identical siblings developed diabetes within a one-month period after mumps infection (17). In animals subdiabetogenic doses of a beta-cytotoxin such as streptozotocin increases diabetogenecity of EMC, Coxsackie B3 and B5 viruses in normally resistant mice (Table 2), raising the possibility of heterogeneous environmental insults to β-cells causing permanent damage (18).

FIG. 7: The interplay of autoimmune and viral factors in the pathogenesis of Type I diabetes (13).

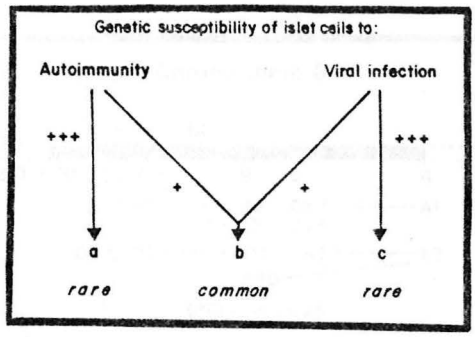


TABLE 2 (18)

Enhancement of virus-induced diabetes by treatment with sub-diabetogenic doses of streptozotocin

Mouse strain	Streptozotocin		EMC virus		Streptozotocin and EMC virus	
	Glucose index*	Diabetic (%)†	Glucose index	Diabetic (%)	Glucose index	Diabetic (%)
Diabetes-prone						
NIH/Swiss	142±29	0	223±89	28	442±153	92
SJL/J	166±16	0	333±113	76	466±126	89
NFS/N	172±15	0	358±47	100	448±80	100
Diabetes-resistant						
C3H/HeJ	186±18	0	151±23	0	202±30	18
C57BL/6J	126±24	0	152±33	6	203±89	30
CBA/J	185±17	0	183±24	0	234±38	53
AKR/J	189±39	13	172±29	0	345±95	100

Each mouse was given 1 mg of streptozotocin and 12 days later infected with 1.0×10^4 plaque-forming units (PFU) of the D variant of EMC virus.
* Approximately 20 mice were tested in each group (mean ±s.d.).
† Percentage of mice with a glucose index 3 s.d. above the mean of uninfected controls.

However, 90% of patients with β-cell destruction are DR3 or DR4 and 55% have a D3-D4 (19); in the rare non-Caucasian IDDM, D8 seems to substitute for DR3. This clearcut association of susceptibility to IDDM with the immune response genes on the sixth chromosome (Figure 8) strongly suggests that immune response plays a role in the β-destruction with autoimmunity either acting alone as a primary seemingly unprovoked initiating factor or as a secondary response to some initial toxic and/or infectious β-cell injury. The array of evidence implicating the immune system in the pathogenesis of this form of diabetes is now overwhelming, both in human IDDM and in animals with experimentally induced or naturally occurring autoimmune insulopathy [Table 3 summarizes evidence that has been reviewed elsewhere (13,14)]. Despite controversies, the evidence favors the existence of an immunoregulatory disorder at the outset of this form of diabetes.

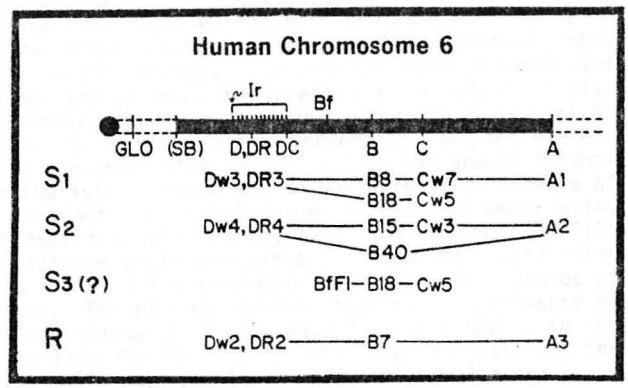


FIG. 8: The Cudworth concept of two independent susceptibility axes (S) for Type I diabetes in Caucasian populations with a substantial Caucasian gene pool. DR8, B18 may substitute for DR3 in non-Caucasian Type I diabetes. The third susceptibility axis is still in dispute. The existence of a resistance axis (R) is also uncertain.

TABLE 3

EVIDENCE FOR A ROLE OF AUTOIMMUNITY IN TYPE I IDDM

1. Linkage of Type I IDDM to specific Class II antigens associated with autoimmune disease.
2. Coexistence of Type I IDDM with autoimmune endocrinopathy (thyrotoxicosis, Hashimoto's thyroiditis and Addison's disease).
3. Familial aggregation of Type I diabetes and other autoimmune conditions, such as pernicious anemia, vitiligo, myasthenia gravis, rheumatoid arthritis and collagen diseases.
4. Lymphocytic insulitis in the islets of Langerhans of Type I diabetics who die soon after diagnosis.
5. Human survivors of poisoning by the β-cytotoxic rodenticide Vacor exhibit islet cell surface antibodies.
6. Increased leukocyte migration inhibition by extracts or homogenates of pancreas in Type I diabetics (Nerup, Diab. 29:424, 1971).
7. 50-60% of newly diagnosed diabetic children have significantly raised levels of killer lymphocytes which correlate strongly with antibody-dependent cytotoxicity.
8. The presence of circulating islet cell antibodies in a high proportion of Type I diabetics at the time of diagnosis.

Here I will mention only very recent information that provides the best view of the experimental and natural development of Type I diabetes in a perfectly normal pancreas. Dr. David Sutherland, Department of Surgery, University of Minnesota, has submitted for presentation at the spring clinical meetings in Washington (20) the account of experience with four segmental grafts of distal hemipancreas transplanted from nondiabetic donors to long-term diabetic twin recipients. The donors were monozygotic twins of a Type I diabetic and the donors had been discordant for diabetes for more than 15 years after the

appearance of diabetes in their twin. The donors were islet-cell antibody negative. Since they were monozygotic twins, no immunosuppression was required to prevent graft rejection, but one twin received immunosuppression anyway. Each graft was followed by immediate restoration of normal insulin secretion, normoglycemia and independence of insulin therapy. However, all three unsuppressed patients exhibited a gradual decline in insulin secretion and a return of glucose intolerance and mild hyperglycemia four to eight weeks after transplantation. The one patient who had been given immunosuppression, did not exhibit this. Serial graft biopsies in the three with recurrent diabetes showed lymphocytic infiltration limited to the islets; there was no vasculitis or evidence of rejection. Typing of the inflammatory cells in the biopsy specimens using monoclonal antibodies showed that the infiltrating cells were largely T8-T11. In later biopsies insulin-containing cells diminished. Islet cell antibodies appeared in these patients two months after transplantation. Viral cultures of the graft biopsies were negative. The authors conclude that this is evidence of an anamnestic reenactment of the course of spontaneous Type I diabetes in the grafts with T-cell memory persisting for 15 to 26 years. They suggest that the β-cells share a specific antigen with some putative historical viral agonist.

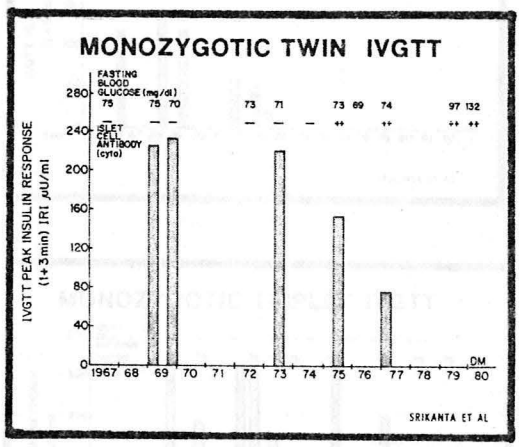


FIG. 9: The progression of fasting blood glucose, ICA-cyto and insulin response to IV glucose in a monozygotic twin of a Type I diabetic for 13 years of discordance until the appearance of diabetes mellitus (DM) in 1980.

The spontaneous natural history of the immunopathy of Type I diabetes is detailed in Figures 9, 10 and 11 (21). Figure 9 shows the islet cell antibody (cyto) titer, fasting glucose levels and insulin response to IV glucose in an initially discordant monozygotic twin whose index twin developed diabetes in 1944 at age 12. Between 1967 and 1974 the discordant twin was repeatedly negative for anti-islet antibodies and had a normal insulin response to IV glucose. In 1975 ICI-cyt were first detected in association with a decrement in peak insulin response to IV glucose. Two years later this decrement became greater. Finally in 1980 diabetes was diagnosed and insulin begun at age 48. Figures 10 and 11 show the course of two monozygotic triplets initially discordant for diabetes with an index triplet who developed Type I diabetes in 1965 at age 13. One of the discordant triplets (Figure 10) was ICA-cyt positive from the first

observation in 1966 and continues to be positive at each subsequent follow-up through the year 1978, the last time he was studied. In December, 1973, he developed polyuria, polydypsia and polyphagia and lost 25 pounds over eight weeks. In March, 1974, his blood glucose ranged between 220 and 280 and he had marked glycosuria and was started on insulin treatment. The other triplet (Figure 11) has been ICA-cyt negative with perfectly normal glucose tolerance and insulin response through all tests up until April, 1982.

FIG. 10: The course of islet cell antibodies fasting blood glucose and insulin response to IV glucose in an initially discordant monozygotic triplet of a patient with Type I diabetes. Diabetes mellitus (DM) developed after 8 years of ICA-positivity.

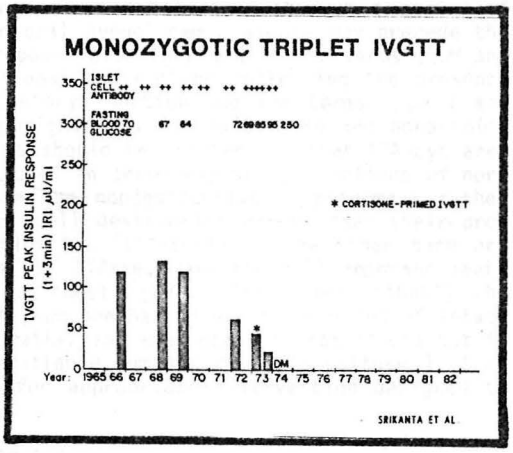
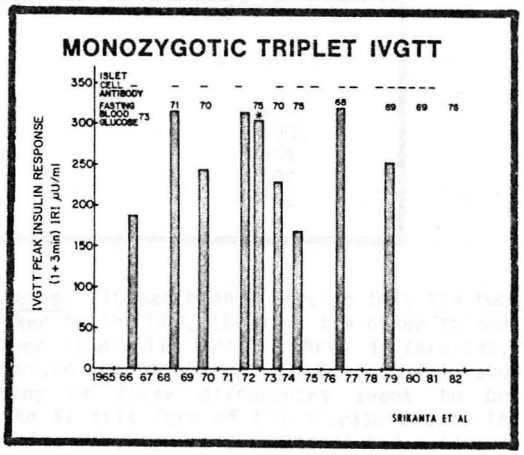


FIG. 11: In the other still discordant triplet of the patient in Figure 10 ICA has been persistently negative and neither the fasting blood glucose levels nor the insulin response to IV glucose has been impaired.



These two groups of findings appear to establish an immunopathic basis for the waning of islet cell function in a most dramatic way. They also reveal that

Type I diabetes may be an insidious process that develops silently over a period of years, rather than a disease of explosive onset, as it seems to be when the first clinical contact with the patient is at the time of the appearance of symptomatic diabetes. In other words this form of diabetes goes through a non-insulin-dependent form, which means that the standard classification in which the terms IDDM and Type I diabetes are used synonymously is incorrect. Table 4 substantiates this, showing that 0.5% of the general population are ICA-cyt positive, 3% of first-degree relatives of Type I patients, 10% of gestational diabetics and 20% of new onset nonobese so-called NIDDM patients (22). Progression of ICA-cyt positive individuals from a period of normal glucose tolerance through a period of impaired glucose tolerance through a period of overt diabetes treatable with diet or oral hypoglycemic agents may precede the period of insulin dependence. (We propose below that use of the terms IDDM and NIDDM be restricted to clinical-functional description reflecting the presence or absence of endogenous insulin secretory function and the terms Type I and Type II be used as etiopathogenetic designations for autoimmune and nonautoimmune diabetes respectively. [NOTE: It should be pointed out that ICA-cyt are, of course, cytoplasmic antibodies detected in serum exposed to sections of normal human pancreas and may, therefore, be nondestructive epiphenomena rather than cytotoxic, i.e., markers of islet cell destruction rather than their probable cause. Islet cell surface antibodies (ICA-surf) on the other hand are known to be destructive and impair Na^+,K^+ ATPase, make the cell membrane leaky and impair insulin secretion and biosynthesis (23). These are probably the destructive antibodies, but to measure them one has to use suspensions of intact islets. The percent of positivity is rather low when one uses rat islets but is very high (over 90%) if one uses unavailable human β-cells in culture.] Such distinctions are obviously essential for appropriate intervention designed to interrupt the pathogenetic mechanisms.

TABLE 4

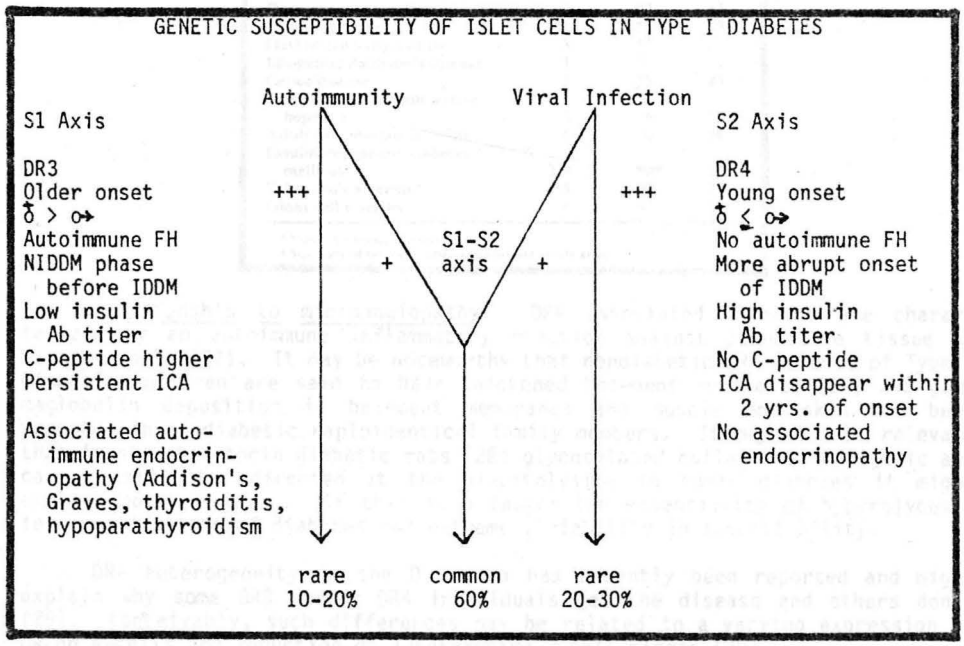
PREVALENCE OF ICA-CYTO IN VARIOUS POPULATIONS

POPULATION	% POSITIVE
Nondiabetics	0.5%
New onset Type I IDDM	60-90%
New onset non-obese NIDDM	20%
Gestational diabetics	10%
1° relatives of Type I IDDM	3%

Subclassification of Type I diabetes: It has been suggested that the two distinct susceptibility genes, one linked to the DR3, B8 axis, the other to the DR4, B15 axis, differ from one another clinically (24). These differences, outlined in Table 5, have been observed in Edinburgh, London, Vienna and elsewhere although increasing blurring of these differences seems to be emerging. It does seem likely that the S1 axis form of the disease occurs in that approximately 10% of Type I diabetics in whom there is associated evidence of autoimmune endocrine deficiency involving thyroid, adrenals, parietal cells and sometimes associated with vitelligo. In contrast to other forms of Type I IDDM, these patients exhibit persistence of islet cell antibodies and are said

to have low titers of antibodies to insulin. Since they also tend to have higher C-peptide levels, one wonders if the persistence of ICA-cyt may not simply be the consequence of persistance of β-cells undergoing slow destruction. By contrast, DR4 patients have a younger age at onset of IDDM, no female preponderance, higher insulin antibody titers and no association with other autoimmune manifestations. C-peptide levels are usually zero and ICA are usually negative within two years of onset, possibly because there are no longer any β-cells left to undergo destruction.

TABLE 5



D3 is, of course, the antigen most closely associated with production of autoantibodies and other autoimmune conditions (Table 6) (25). DR4 is the antigen associated with rheumatoid arthritis but there is no known association between IDDM and rheumatoid arthritis (25). More than half of IDDM Caucasians are DR3/DR4 heterozygotes and such individuals carry an increased risk of the disease, whereas homozygotes for DR3 or DR4 do not have an increased risk (26). In racial groups where DR8 substitutes for DR3, DR4/DR8 heterozygotes have a similarly increased risk, suggesting the conflux of two independent susceptibility mechanisms. Such patients have the earliest age of onset and are said to be less apt to have microvascular complications.

TABLE 6

Association Between HLA-D, DR, and Human Diseases

Diseases	HLA-D,DR Association	Frequency	
		Patients	Controls
		%	
Goodpasture's syndrome	2	88	32
Multiple sclerosis	2	58	28
Optic neuritis	2	45	24
Buerger's disease	2	59	22
Primary Sjögren's syndrome	3	64	31
Dermatitis herpetiformis	3	97	25
Graves' disease	3	53	19
Hashimoto's thyroiditis	3	55	26
Idiopathic Addison's disease	3	70	21
Celiac disease	3	88	25
Autoimmune chronic active hepatitis	3	78	19
Adult rheumatoid arthritis	4	70	28
Insulin-dependent diabetes mellitus	3,4	50†	20†
Takayasu's arteritis*	4	70	27
Giant cell arteritis	4	40	19

* North American patients only.
† Summary of several studies; approximate values given.

Relationship to microangiopathy: DR4 associated diseases are characterized by an autoimmune inflammatory reaction against connective tissue or blood vessels (27). It may be noteworthy that nondiabetic DR4 parents of Type I diabetic children are said to have thickened basement membranes (27) and gammaglobulin deposition in basement membranes and muscle and skin has been reported in nondiabetic haploidentical family members. It may also be relevant that in streptozotocin diabetic rats (28) glycosylated collagen is antigenic and causes antibodies directed at the glucitolysine in human diabetes it might explain both residues. If this is a factor the essentiality of hyperglycemia for complications of diabetes and extreme variability in susceptibility.

DNA heterogeneity in the D region has recently been reported and might explain why some DR3 and/or DR4 individuals get the disease and others don't (29). Conceivably, such differences may be related to a varying expression of DR on β-cells and reduction of autoreactive T-cell clones (30).

RECLASSIFICATION OF DIABETES

Since Type I patients with autoimmune insulopathy may not be or ever become IDDM patients as defined, the standard classification of diabetes (Table 7) must be revised to accommodate non-insulin-dependent autoimmune insulopathy, i.e., Type I NIDDM. This is accomplished with minimal readjustment by simply ending the current synonymity of IDDM and Type I, which is based on a probable misconception, and redefining Type I as an autoimmune insulopathy which may produce NIDDM as well as IDDM. The differences between Type I IDDM and Type II NIDDM are shown in Table 8.

TABLE 7

MODIFIED SUBCLASSIFICATION OF IDDM

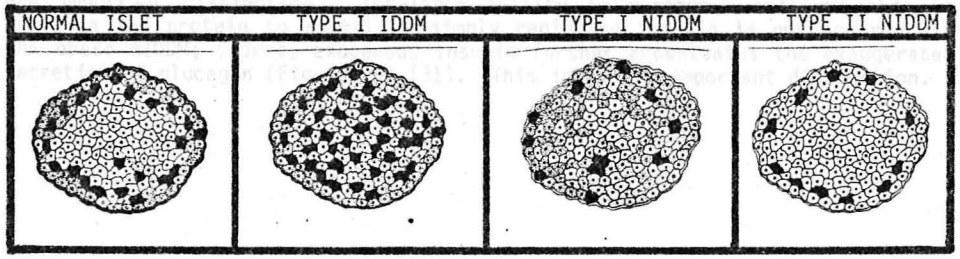
A. Insulin-dependent diabetes mellitus (IDDM)

1. Type I diabetes (see Table 6 for subclassification of Type I)
2. Polyendocrine deficiency [Type I diabetes plus other autoimmune endocrinopathies (Schmidt's syndrome)]
3. Poisons (Vacor[1], N-nitroso compounds[2])
4. Congenital absence of the pancreas
5. Congenital absence of the islets
6. Hereditary relapsing pancreatitis (may also be NIDDM at least transiently)
7. IgA deficiency-malabsorption syndrome
8. Thiamine-responsive megaloblastic anemia
9. Wolfram Syndrome [Diabetes insipidus and diabetes mellitus, optic atrophy and deafness (DIDMOAD)]

B. Non-insulin dependent diabetes mellitus (NIDDM)

1. Type II
   a. Obese
   b. Nonobese
2. Type I (incomplete) (Ib of Cudworth)
3. MODY
4. Pancreatic diseases (pancreatitis, hemochromatosis, cystic fibrosis)
5. Hormone excess syndromes (Cushing's, acromegaly, glucagonoma, somatostatinoma)
6. Abnormal insulin biosynthesis
   a. Mutant insulinemia
   b. Proinsulinemia
   c. J-type diabetes
7. Non-autoimmune diabetes of Southern black children (McLaren)
8. Rare genetic insulin resistant syndromes

[1]A rodenticide
[2]In cured mutton (Rossini, AA., NEJM 308:333-335, 1983)



β-cells Δ-cells α-cells

TABLE 8

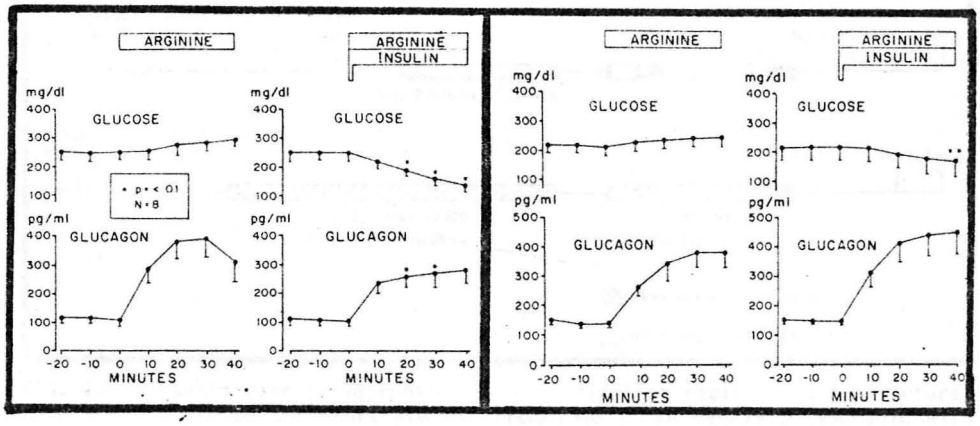
	TYPE I NIDDM	vs.	TYPE II NIDDM
Weight:	Normal		Obese
Onset:	Younger age; usually <40		Usually >40
HLA:	DR3 and/or DR4		No HLA pattern
Family history:	Usually negative for diabetes; May be positive for autoimmune disease		Usually positive for diabetes
Other autoimmune disease:	May be present		Absent
C-peptide:	Low		Not low
Insulin antibodies if on insulin rx:	Low		Normal
Arginine or protein-induced hyperglucagonemia:	Corrected by insulin		Not corrected (worsened) by insulin
Loss of glucagon response to hyperglycemia:	After 2 yrs. probably (not certain)		Not unless autonomic neuropathy is present (not certain)

NIDDM

NIDDM, as now redefined, must include: 1) Type I diabetics in whom residual β-cell function is capable of preventing ketoacidosis; 2) disorders of varying etiology, most of them rare, in which ketoacidosis does not occur (alcoholic pancreatitis, mutant insulin, cystic fibrosis, MODY genetic syndromes of insulin resistance, etc.); and, 3) the largest category of NIDDM, Type II NIDDM.

Their clinical characteristics and differences from Type I NIDDM are outlined in Table 8. Obesity is the rule. Insulin and C-peptide levels will be normal or high, whereas in Type I NIDDM they will be low. Functional abnormalities of glucagon secretion observed in IDDM are also present in NIDDM, with one important distinction. Insulin's ability to restore α-cell response to arginine and protein to normal by simply repleting insulin is not apparent in the obese NIDDM; indeed, exogenous insulin further accentuates the exaggerated secretion of glucagon (Figure 12) (31). This is a very important distinction.

FIG. 12: Left-hand panel: The glucagon response of Type I diabetics to arginine alone or to arginine plus insulin. The addition of insulin lowers the exaggerated arginine response to well within the normal range.
Right-hand panel: The same experiment in obese Type II diabetics in an equally poor state of control. The addition of insulin does not correct the abnormally high glucagon response to arginine and may, in fact, make it a bit worse.



There will be a strong family history of Type II diabetes in the family, whereas in patients with Type I this is unusual. There is no HLA-linked susceptibility gene, in contrast to the high prevalence of DR3 and/or DR4 in Type I NIDDM. Islet cell antibodies will be absent in obese Type II and present in Type I NIDDM. The report (32) that NIDDM patients have a higher frequency of a large insert in the polymorphic region flanking the human insulin gene (Figure 13) on the short arm of chromosome 11 is probably incorrect; rather there may be a higher frequency of small alleles in IDDM (33). There is a normal glucagon response to hypoglycemia, whereas the glucagon response to hypoglycemia tends to wane in longstanding Type I diabetes.

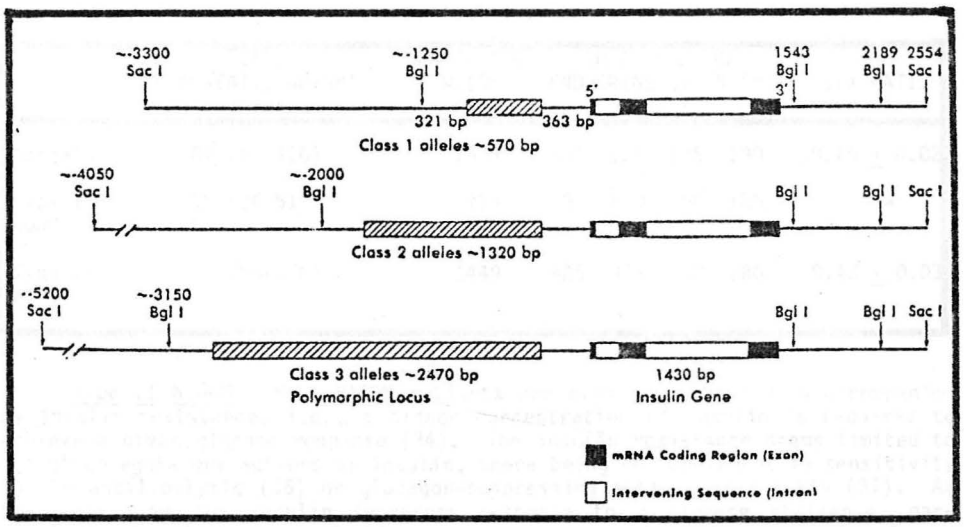


FIG. 13: Insulin gene polymorphism. The 5' flanking region of the structural gene for insulin on the short arm of chromosome 11 in man is polymorphic with respect to the number and arrangements of members of a family of tandemly repeated nucleotides beginning 363 based pairs upstream from the transcription site. Homozygosity for a long (>1500 based pair) fragment was initially reported to be associated with susceptibility to Type II NIDDM. However, another larger study failed to confirm this and found the 570 based pair fragment to be present in higher frequency in Caucasians with Type I IDDM, often with homozygosity. They concluded, therefore, that the polymorphic cycles associated with Type I and not Type II diabetes. It is possible that this is linked to a gene that confers a modest increase in susceptibility to diabetes (33).

PATHOPHYSIOLOGY OF NIDDM

NIDDM is defined clinically as a diabetic state in which deprivation of exogenous insulin will not precipitate diabetic ketoacidosis. Pathophysiologically this is explained by the secretion of insulin at rates that are sufficient to prevent the full metabolic consequences of unopposed glucagon action. There may be in obesity a type of glucagon resistance. Despite hyperglucagonemia the levels of F-2,6-P_2 remain high and may permit sufficient three carbon flow for malonyl-CoA synthesis to restrain ketogenesis. (The fact that adipocytes are sensitive to the antilipolytic action of insulin in obese NIDDM patients also limits the flow of free fatty acids to the liver and thereby reduces ketogenic substrate.) Pathologically the islets of Langerhans reveal only a modest reduction in β-cells in some patients while in others β-cells are normal and α-cells increased (33) (Table 9).

TABLE 9

	TOTAL PANCREATIC WEIGHT (mean and range) (g)	ENDOCRINE WEIGHT (ng)	TOTAL MASS OF ENDOCRINE CELLS (mg) β	α	Δ	PP	α/β RATIO
Normals	82 (67-110)	1395	850	225	125	190	0.26 ± 0.02
Type I IDDM	39 (26-51)	413	0	150	90	185	∞
Type II NIDDM	73 (55-100)	1449	825	375	100	180	0.43 ± 0.03

Type II NIDDM: Most NIDDM patients are obese and obesity is accompanied by insulin resistance, i.e., a higher concentration of insulin is required to achieve a given glucose response (34). The insulin resistance seems limited to the glucoregulatory actions of insulin, there being no impairment in sensitivity to the antilipolytic (36) or glucagon-suppressing actions of insulin (37). At the same time the insulin secretory response to a glucose challenge, particularly the first phase of this response, is markedly reduced, ranging from a delayed and shortened upstroke in the mildest NIDDM (impaired GTT) (38) to a virtual absence of glucose response in severe cases (39) (Figure 14). Despite

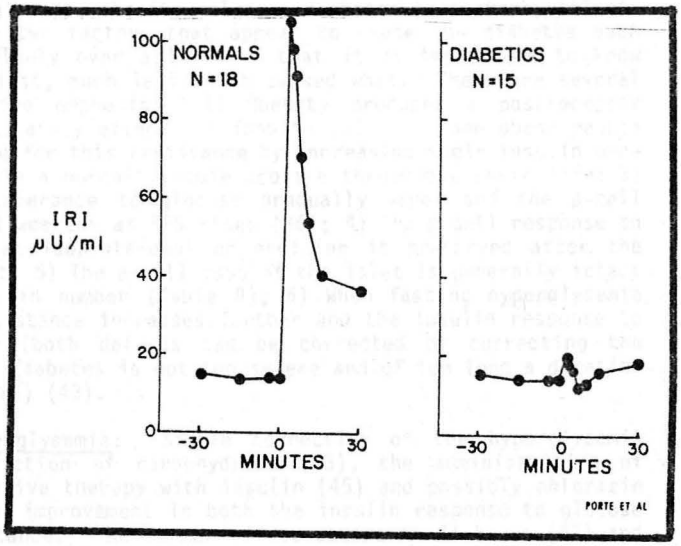


FIG. 14: A comparison of the acute insulin response to 20 g of glucose given as an IV bolus in normals and Type II NIDDM patients (39). The diabetics had an FPG >120 mg/dl.

this there is relative integrity of the insulin secretory response to nonglucose secretagogues such as arginine or isoproteronol (Figure 15). The key point to

be introduced here and again referred to subsequently is that the defective insulin response to glucose can in mild and moderately severe NIDDM be corrected by imposing a brief (>20 hours) period of normoglycemia -- irrespective of whether the normoglycemia is produced by dietary restriction, sulfonylurea treatment, aggressive insulinization, or other means (40). The insulin resistance can also be improved by normoglycemia of >3 weeks duration (41).

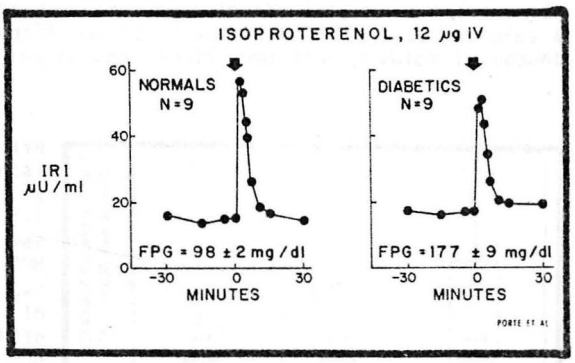


FIG. 15: The response of Type II NIDDM subjects with FPG >120 mg/dl to 12 mg of isoproteronol IV. Very little difference between normal and diabetic patients is observed. Yet, as shown in Figure 14, there is a marked lessening of the acute insulin response to IV glucose. Thus, in mild Type II NIDDM there appears to be a defect in the insulin response to glucose rather than a non-specific defect in insulin secretion.

ETIOPATHOGENESIS OF OBESITY-ASSOCIATED[1] TYPE II NIDDM

Type II, or non-autoimmune, obesity related, diabetes is pathophysiologically complex because the two factors that appear to cause the diabetes each progress in parallel so slowly over a lifetime that it is impossible to know which, if either, comes first, much less which caused what. There are several relevant facts that require emphasis: 1) Obesity produces a postreceptor resistance to the glucoregulatory effects of insulin (42); 2) Some obese people are capable of compensating for this resistance by increasing their insulin production and thereby maintain a normal glucose profile throughout their life; 3) In other obese people, tolerance to glucose gradually wanes and the β-cell response to a glucose load weakens as FPS rises (36); 4) The β-cell response to non-glucose stimuli such as isoproteronol or arginine is preserved after the response to glucose is lost; 5) The β-cell mass of the islet is generally intact but α-cells are increased in number (Table 9); 6) When fasting hyperglycemia supervenes and insulin resistance increases further and the insulin response to glucose decreases further (both defects can be corrected by correcting the hyperglycemia provided the diabetes is not too severe and of too long a duration (FPS >250; duration >5 years) (43).

Correcting the hyperglycemia: Simple correction of the hyperglycemia whether by dietary restriction of carbohydrate (43), the administration of sulfonylureas (44), aggressive therapy with insulin (45) and possibly phlorizin (46) will result in marked improvement in both the insulin response to glucose loading and insulin resistance. The former effect occurs in 24 hours (47) and its mechanism is unknown; the latter effect requires approximately three weeks of normoglycemia and its mechanism is unknown (Figure 16). Correction of the obesity will also diminish the resistance. The inescapable conclusion from the

above is that the total insulin resistance in an obese Type II diabetic is the sum of obesity-induced insulin resistance and hyperglycemia-associated insulin resistance. We believe that these are two independent causes of insulin resistance because in the nondiabetic obese individual have insulin resistance (which can be corrected by weight reduction) and non-obese IDDM patients also have insulin resistance. In obese Type II diabetes correction of the hyperglycemia without reduction of the obesity will result in the substantial reduction in insulin resistance coupled with an improvement in the insulin responsiveness which persists long after the regime has terminated (45). It also restores a relationship between degree of obesity and insulin resistance which is absent during hyperglycemia.

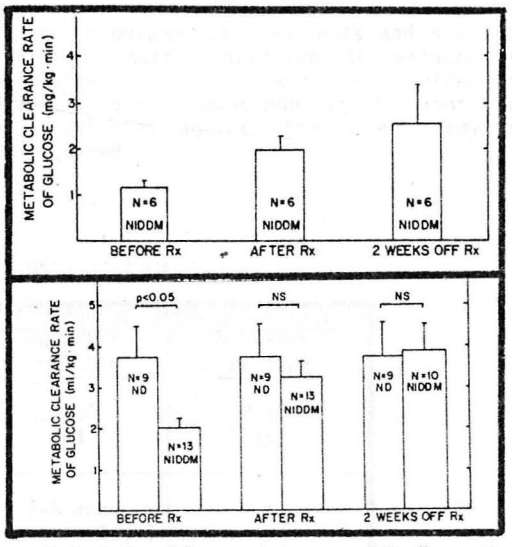


FIG. 16: The effect of intensive insulin treatment on the mean metabolic clearance rate of glucose at a clamped insulin level of 100 μU/ml (upper panel) and 250 μU/ml (lower panel) in obese Type II NIDDM before, immediately after and two weeks after the insulin regime. In the lower panel the values for obese nondiabetics (ND) are shown. The relationship between the degree of obesity, body mass index (BMI), and insulin resistance, metabolic clearance rate of glucose (MCR_g) in obese Type II NIDDM patients in poor control with fasting hyperglycemia, during normalization of glycemia by intensive insulin treatment and two weeks after stopping the above regime. Note the lack of relationship between BMI and MCR_g before therapy and the excellent correlation during and after therapy. This suggests elimination of hyperglycemia-related insulin resistance with "unmasking" of the residual obesity-related insulin resistance.

It is obviously impossible to determine whether the β-cell failure is purely secondary exhaustion, a "high output failure" consequent to the peripheral insulin resistance or whether it represents the concurrence of an impairment in the ability of the islet to compensate and meet the increased demands in the way that nondiabetic obese individuals are able to do. My own view that we are dealing with a polygenic disorder in which the various contributing factors may vary in magnitude relative to one another but in which there is an intrinsic defect in islet cell function which is unmasked only when insulin need is increased by the presence of obesity. When hyperglycemia develops, it in itself is an aggravating factor because it diminishes β-cell function and it enhances the glucagon secretion. When hyperglycemia is corrected in a totally insulin deficient dog, not with insulin, which would directly suppress glucagon, but rather by giving phloridzin, which causes massive renal glyco-

suria, as the glucose levels reach normal and despite the lack of any measurable insulin, α-cells regain their responsiveness to glucose. Thus, there is reason to believe that hyperglycemia may be detrimental to the entire glucoregulatory system impeding both insulin action in tissues and islet cell functions.

INTERVENTIONS IN TYPE I DIABETES

Remission induction: Thus far, neither plasmaphoresis, polyclonal anti-lymphocyte globulin or cyclosporin have reversed established Type I diabetes (48). The consensus is that once the islet cell destruction has exceeded a certain level, intervention is too late. Better results are obtained if intervention takes place within the first six weeks after the onset of clinical diabetes. A clinical trial of cyclosporin being carried out by Drs. Stiller and Dupre in London, Ontario, suggests that the remissions occur twice as frequently in immunosuppressed patients as they do in unsuppressed patients and may last longer, although the experience is still not sufficiently long to evaluate the results (Table 10). Moreover, it would appear from the experience of Sutherland in transplanted pancreases from nondiabetic to a diabetic monozygotic twins that risk of recrudescent of autoimmunity directed against the β-cells may be constant and that retreatment will be required.

TABLE 10

REMISSIONS* OF IDDM

	NO THERAPY	CYCLOSPORINE IMMUNOSUPPRESSION	
		<6 WEEKS OF IDDM	>6 WEEKS OF IDDM
REMISSIONS	25-30%	20/30 60%	2/13 15%
DURATION OF REMISSION	6-9 mos.	7-8 mos. (longest 1 yr)	?

* FPS <140 mg/dl
Normal basal and glucagon-stimulated C-peptide

Prophylaxis: A wealth of experimental evidence in animals suggests that destruction of β-cells following sub-massive doses of a β-cytotoxin can be prevented by immunosuppression. The risk of immunosuppression have thus far inhibited clinical trials of prophylactic interventions in Type I prediabetics. Prophylaxis might be entertained in monozygotic twins of Type I diabetics whose risk of developing diabetes is approximately 50%. If, as in Figure 13, they develop ICA and exhibit impairment in the insulin response to glucose, the risk of diabetes would exceed 50%. Obviously, such a study would be most difficult to control. The advent of lower risk immunosuppression therapy will justify studies on larger populations with a lower risk of developing diabetes, such as haploidentical siblings of Type I diabetics who have approximately a 30% risk of

developing the disease. Clearly, prophylactic interventions in Type I prediabetes are still in the future, but remission induction immediately after onset of the disease, while not yet justifiable, may become so shortly. If so, the appropriate laboratory capabilities required to diagnose autoimmune insulopathy and to follow the immunologic response to intervention will become mandatory.

INTERVENTION IN TYPE II DISEASE

Prophylaxis: Prophylaxis of obesity-related Type II disease obviously is best be achieved by preventing or correcting obesity, although bona fide Type II disease probably occurs in the absence of obesity in certain families with very high prevalence of NIDDM (49). According to one carefully controlled Scandinavian study it can be prevented in patients with abnormal glucose tolerance by the administration of sulfonylureas (50).

Remission-induction: Once established, many patients with obesity-related NIDDM can be improved, both with respect to glucose-mediated insulin secretion and with respect to insulin resistance by three weeks of normoglycemia. It does not seem to matter how the normoglycemia is achieved. The beneficial effects on insulin secretion and insulin sensitivity persist for at least two weeks after the period of gluconormalization has ended. While the duration of such remissions is not known, a study of their potential usefulness of this approach may be worthwhile. For example, patients who cannot reduce their weight and who are no longer responsive to sulfonylureas might regain drug responsiveness after a 3-week course of intensive glucoregulation with insulin, which they might be loathe to accept as a permanent form of treatment; such patients are very common and constitute a substantial segment of the poorly controlled diabetic population.

A more recent development is a drug that specifically diminishes obesity-related (but not hyperglycemia related) insulin resistance via post-receptor mechanisms, ciglitizone, which has thus far been tested only in obese hyperglycemic rodents (51).

APPENDIX I

Type II diabetics retain the normal glucagon response to hypoglycemia while Type I diabetics ultimately lose this. We now have reason to believe that loss of this response may be related to a destructive change in islet anatomy, perhaps reflecting loss of islet mass. The glucagon response to hypoglycemia is normally the consequence of several simultaneous events: 1) a drop in endogenous insulin produced in the medulla of the islet and flowing directly to the glucagon-containing cells in the cortex which are disinhibited by a drop in the local insulin concentration (Figure 17). Thus, the glucagon response to change in glucose concentration is reduced when insulin is neutralized during its passage through the islets as in the experiments in Figure 18. 2) Release of norepinephrine from adrenergic nerve endings which form abundant contacts with α-cells within the cortex of the islet and thus control approximately 70% of the glucagon response to hypoglycemia. After the β-cells have been destroyed in Type I diabetes the glucagon response to hypoglycemia remains relatively normal for a year despite their loss, presumably because of local release of catecholamines, norepinephrine being a powerful stimulus of glucagon secretion. But after 18 months or more from the onset of IDDM the glucagon response to hypoglycemia wanes, not because of peripheral neuropathy because every functional test for the autonomic nervous system is normal and catecholamine responses to hypoglycemia are normal. We have suspected that the explanation is a local disorder of the adrenergic innervation of the α-cells resulting from inflammation and/or contraction of the islet with respect to its autonomic connections as depicted in Figure 19. The evidence in support of a local adrenergically mediated glucagon response to hypoglycemia is based on the finding that in the isolated perfused rat pancreas adrenergic blockade knocks out about 70% of the glucagon response even though the pancreas is totally separated from the central nervous system (Figure 20). Consequently, we would propose that insulitis might be reflected by a loss of the glucagon response to hypoglycemia. This could be clinically helpful in distinguishing between Type I and Type II NIDDM.

FIG. 17: Depiction of current concept of insulin as a release-inhibiting factor for glucagon. Normally insulin is carried from the central B-cell region of the islets to the A-cell region. Insulin thus influences the final proportion of insulin to glucagon that leaves the islets. When the B-cells are destroyed, as in Type I diabetes, glucagon secretion is devoid of insulin inhibition and without insulin treatment will remain high.

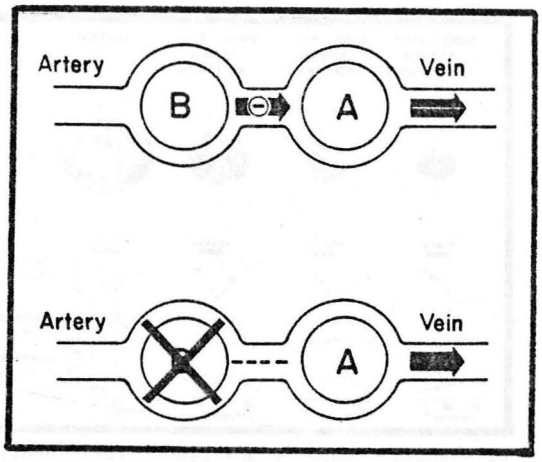
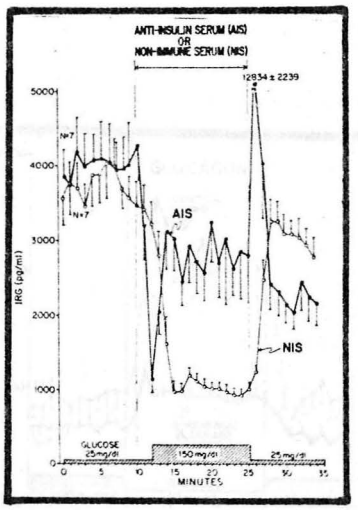


FIG. 18: The effect of antiinsulin serum on glucagon response to changes in glucose concentration in an isolated perfused pancreas. This is a nonrecirculating system so the effects of the antiserum, which are compared to nonimmune serum, reflect neutralization in the vasculature of the islets during a single pass.



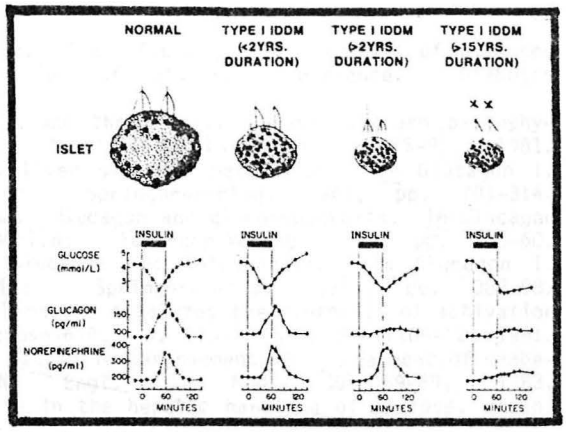


FIG. 19: An hypothesis to reconcile the waning of the glucagon response to hypoglycemia at or after two years of Type I IDDM and in the absence of any evidence of peripheral neuropathy. According to this scheme, loss of β-cells does not result in loss of the glucagon response because a sufficient number of α-cells maintain contact with adrenergic nerve endings, which are believed to stimulate about 70% of the glucagon response to hypoglycemia. At or after two years of Type I IDDM, however, these relationships are diminished, perhaps because of anatomical distortion resulting from the insulitis. Thus, the glucagon response to hypoglycemia is lost even though the sympathetic nervous system is otherwise intact, as evidenced by the rise in norepinephrine during hypoglycemia. Late in the disease a generalized loss of norepinephrine response provides evidence of generalized sympathetic neuropathy. Experimental evidence to support this hypothesis appears in Figure 20.

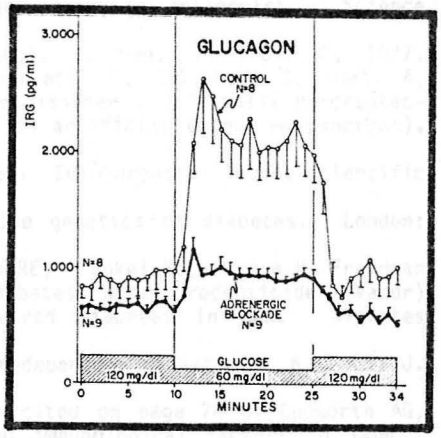


FIG. 20: Evidence of local adrenergic mediation of the glucagon response to hypoglycemia in the isolated perfused rat pancreas. Since the pancreas has been removed from the rat for more than 30 minutes the fact that adrenergic blockade reduces the glucagon response to hypoglycemia by about 70% suggests that a local system near the islets senses the glycopenia and causes the release of norepinephrine in the vicinity of α-cells. The existence of a local system of this type might explain why after two years of destructive insulopathy the glucagon response to hypoglycemia is lost while its response to other stimuli is intact and sympathetic function elsewhere is normal.

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