AMYLIN
A New Beta-Cell Hormone
And Its Potential Role
In Diabetes

Internal Medicine Grand Rounds

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Kenneth L. Luskey, M.D.

The clinical manifestations of noninsulin-dependent diabetes (NIDDM) are well known among clinicians. Hyperglycemia and the associated "polys" are the hallmarks of the disease and complications such as retinopathy, neuropathy, vascular and renal disease are common accompaniments. However, despite our familiarity with NIDDM once it is clinically established, our understanding of the events leading to this disease are largely unknown. Over the last several decades work has focused on understanding insulin secretion and action, however this has not solved the mystery of NIDDM. One area that holds potential promise is the finding of another secretory product of the pancreatic β-cell, known as amylin. This peptide was initially identified in pancreatic amyloid deposits of patients with NIDDM. Current studies have suggested mechanisms by which amylin might play a role in the early pathogenesis of NIDDM.

GENETICS OF NIDDM

Recent studies have provided a better estimate of the frequency of NIDDM in the U.S. population. In the National Health and Nutrition Examination Survey (NHANES II) that was conducted from 1976-1980 participants were initially screened by means of a questionnaire and examination (1). In addition oral glucose tolerance tests were administered to almost 4,000 individuals. Based on these studies it was found that in the U.S. population age 20-74 years physician-diagnosed diabetes was present in 3.4% of the individuals. In addition undiagnosed diabetes by the National Diabetes Data Group criteria was present in an additional 3.2% of the population. Thus, the combination of diagnosed and undiagnosed diabetes was present in 6.6% of the population. As shown in Figure 1, the prevalence of diabetes increased with the age of the participants. In the 20-44 year group the prevalence of total diabetes was 2% whereas in the 65-74 year group the prevalence rose to 17.7%.

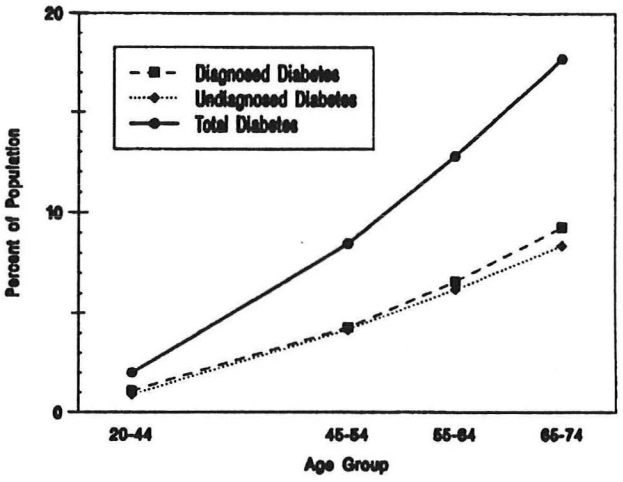

Figure 1 Prevalence of diabetes in the NHANES II study (1).

In this large population study it was found that the parental diabetes status as well as the presence of obesity in the subject played a significant role in determining the rate of diabetes in the individual. As shown in Table I, obesity approximately doubled the rate

of diabetes whether the subject had no diabetic parents or had a diabetic parent. Similarly in both non-obese and obese subjects the presence of a diabetic parent roughly doubled the rate of diabetes (1).

TABLE I. Prevalence of diabetes in NHANES II Subjects age 45-74 yr (1).

	No diabetic parent nonobese	Diabetic parent nonobese	No diabetic parent obese	Diabetic parent obese
Diagnosed diabetes	3.5	10.6	6.2	13.9
Undiagnosed diabetes	3.9	3.5	8.6	14.3
Total diabetes	7.4	14.1	14.8	28.2

Despite such studies that suggest that diabetes in a parent plays a significant role in determining if a child will develop diabetes, the genetics of NIDDM are not clear cut. If NIDDM were due to a single gene inherited in an autosomal recessive fashion, then diabetes should occur in all (l00%) of the children of two parents with diabetes. However, this is not the case. Different studies have estimated that diabetes occurs in the offspring of such marriages in anywhere from l0-67% of the children (2). Such variation is no doubt due in part to the different methods by which investigators have defined the presence of NIDDM, however it is clear that at least one-third of the offspring of two diabetic parents do not develop NIDDM in their lifetime.

One other piece of evidence strongly suggests that genetics plays a major role in the development of NIDDM. This comes from twin studies that have been done in the United Kingdom, the United States and Japan (3-6). In such studies an extremely high rate of concordance for diabetes is found in identical twins in which one twin initially develops NIDDM. This is indicated in Table 2 from the studies of Pike and his co-workers in England. Two hundred pairs of identical twins in which l twin had diabetes were studied. In insulin-dependent diabetes approximately 60% of the twins were concordant for diabetes. However, among those twins with non-insulin dependent diabetes more than 90% were concordant for NIDDM (3). Of note, when these studies were published diabetes had been diagnosed within three years in all the discordant pairs. Further follow up has indicated that essentially all of the twins with NIDDM are concordant for their diabetes within l0 years (4).

Table II. Diabetes in 200 pairs of identical twins in Great Britain (3).

Type of diabetes	Concordant	Discordant	Total
Insulin dependent	80	67	147
Non-insulin dependent	48	5	53
	128	72	200

Newman, et al, reported on diabetes in monozygotic and dizygotic white male twin pairs who were born between 1917 and 1927 and identified from military records (5). The incidence of NIDDM in twin pairs that were studied between 1969-1973 (ages 42-55) and ten years later between 1981-1982 (ages 52-65) is shown in Table III. At the first examination there were only 3 monozygotic twin pairs in which both twins were affected. However, at the later follow-up period there were 14 monozygotic twin pairs in which both were affected and 20 with only one affected twin, resulting in a concordance rate of .58. Of note, only one of the 15 NIDDM discordant monozygotic twin pairs at first examination remained discordant for diabetes ten years later. Among the dizygotic twin pairs the concordance rate for NIDDM was only .17, substantially less than the monozygotic twins

Table III. NIDDM among monozygotic and dizygotic twin pairs in the United States (5).

	No. pairs	Both affected	One twin affected	Concordance
Status at first examination				
Monozygotic	176	3	15	.286
Dizygotic	186	1	12	.143
Status at second examination				
Monozygotic	176	14	20	.583
Dizygotic	186	4	38	.174

twin pairs between 52 and 65 years old. Studies in Japan have also found a high rate of concordance for NIDDM in monozygotic twins (83%) versus 40% in dizygotic twins (6).

The incidence of NIDDM is quite variable in different populations of the world. The lowest prevalence rates of <2% occur in Eskimos, certain Alaskan Indians, the Indian subcontinent and the Far East (7). In contrast, the highest prevalence rates are in the american Pima Indians (8) and the Micronesian population of Nauru (9) where NIDDM occurs in about 35% of the population. This high frequency of diabetes appears to be a relatively recent observation, probably brought about by the change in diet in these populations. Other ethnic groups such as the Yemenites in Israel have manifested an increase in the frequency of diabetes when exposed to a Western diet. Although these populations may represent very unique examples of diabetes that are not exactly like all NIDDM throughout the world they have served as unique situations in which to study the development of diabetes. As shown in figure 2, in the Pima Indians either fasting glucose levels or two hour glucose levels during an oral glucose tolerance test show the present of two distinct populations. In the Pimas the incidence of diabetes is influenced by the presence of obesity (figure 3) as well as the presence of diabetes in one or both of the parents (figure 4) (10). Compared to an individual with no diabetic parents, the incidence of diabetes was 2.3 times greater with one diabetic parent and 3.9 times greater with two diabetic parents.

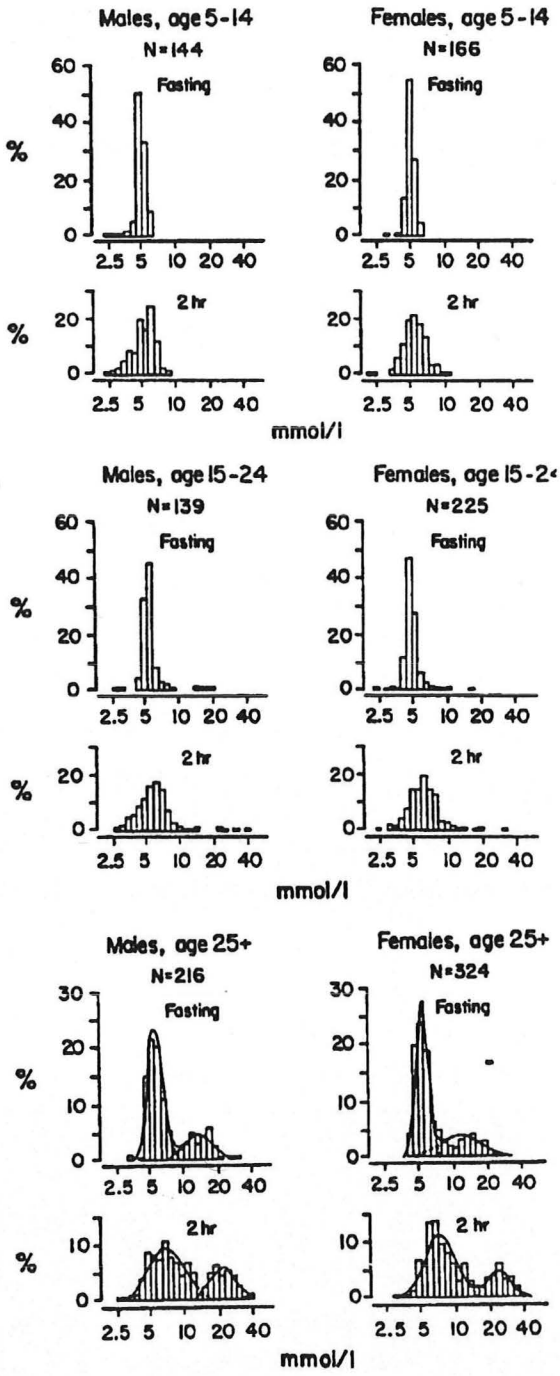

Figure 2 Fasting and 2 hour glucose levels in Pima Indians (8).

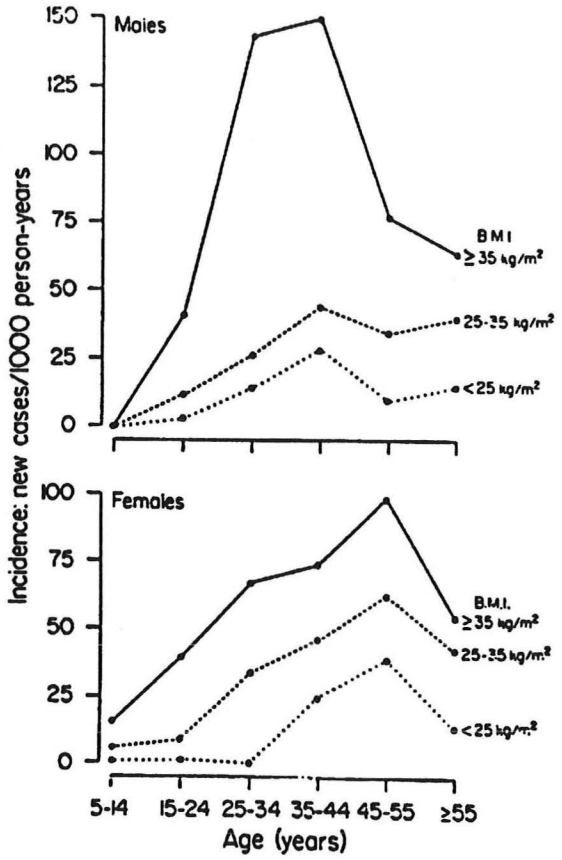

Figure 3 Diabetes incidence rates in Pima Indians (10).

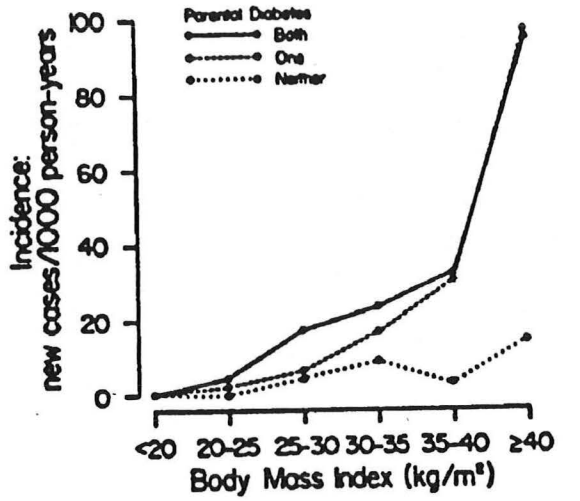

Figure 4 Age adjusted incidence rate of diabetes in Pima Indians related to parental diabetes (10).

All of these bits of evidence suggest that NIDDM or adult-onset diabetes is a genetic disease. However, it is not clear how many genes or what genes are involved in the pathogenesis of NIDDM. It is clearly more than a single gene defect, however, the genetic heterogeneity of the disease is unknown. To date attempts to identify genes that are linked to NIDDM have not yielded any definitive information. However, these studies are mainly limited to the analysis of the insulin and the insulin receptor genes. It is clear that these genes do not play a major role in the genetics of NIDDM.

EARLY MANIFESTATIONS OF NIDDM

Abnormalities in insulin secretion and action have been observed before fasting hyperglycemia and frank diabetes occur in individuals destined to get NIDDM. However, because of the slowly progressive nature of this disease and the fact that not all patients with early manifestations of glucose intolerance progress to develop diabetes the disease has been difficult to study. This has led to some controversy over which abnormalities

are functionally significant in the pathogenesis of NIDDM. Studies over the last decade have utilized a variety of techniques and patients to attempt to resolve some of these issues and have presented a general picture of the early phases in NIDDM. This picture is one in which two basic components are essential for the development of NIDDM. The first is insulin resistance that is initially compensated by increased insulin secretion. However, in the second phase of the disease insulin secretion falls and a relative insulin deficiency occurs. This leads to the clinical picture of NIDDM.

Insulin sensitivity is assessed by euglycemic clamp techniques in which a constant infusion of a fixed concentration of insulin is given and euglycemia is maintained by infusion of appropriate amounts of glucose. Such studies determine the rate of glucose clearance in response to a given and fixed level of insulin and thus illustrate the degree of insulin sensitivity in each individual. Several studies have shown that insulin sensitivity is reduced even in subjects with minimal elevations in fasting glucose (11-14). This is illustrated in figure 5 (11). The rate of glucose clearance is low in essentially all subjects with hyperglycemia and even among those subjects with normal glucose levels at least a two-fold difference is seen in the insulin sensitivity. This variation in the sensitivity to insulin can even be noted in apparently normal subjects.

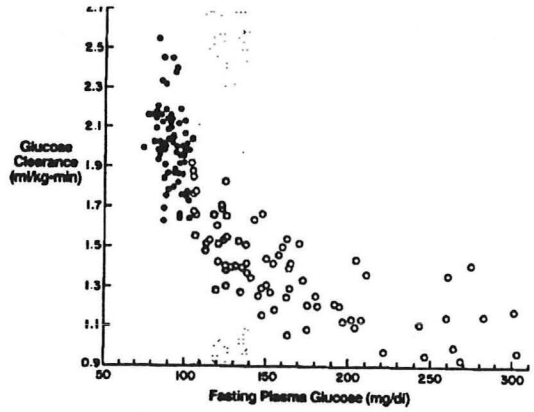

Figure 5 Glucose clearance rates in normal-weight NIDDM subjects (open circles) and controls (closed circles) (11).

Hollenbeck and Reaven (13) performed glucose clamp studies in 100 individuals with normal glucose tolerance as shown in figure 6. They divided these subjects into 4 quartiles based on the glucose uptake rates. When the glucose and insulin response to an oral glucose challenge was examined in these subjects it could be appreciated that the upper quartile of glucose clearance had the lowest insulin response, whereas those normal individuals who had the lowest glucose clearance rate had the highest insulin response despite an apparently normal glucose levels.

Insulin resistance in NIDDM results from decrease sensitivity in both muscle and liver. In the studies of DeFronzo decreased glucose clearance in peripheral tissues, especially muscle, appears to be responsible for most of the changes in glucose clearance during insulin infusion (figure 7) (11). However, other studies show that hepatic glucose production and total hepatic glucose output are altered in patients with NIDDM (15). In patients with mild NIDDM (fasting blood sugar 152±7 mg/dl) in the postabsorptive state (fasting) hepatic glucose and production were elevated in diabetics. Glucose infusion

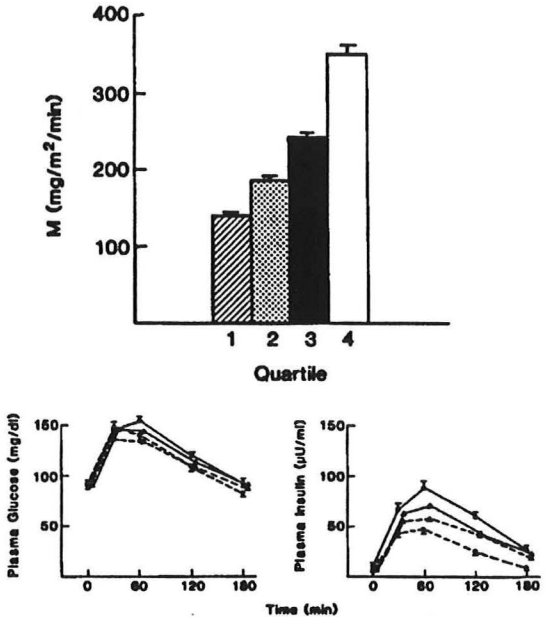

Figure 6 (Top) Glucose uptake values in individuals with normal glucose tolerance. (Bottom) Plasma glucose and insulin responses to an oral glucose load in the quartiles. (1, closed circle; 2, closed triangle; 3, open triangle; 4, open circle) (13).

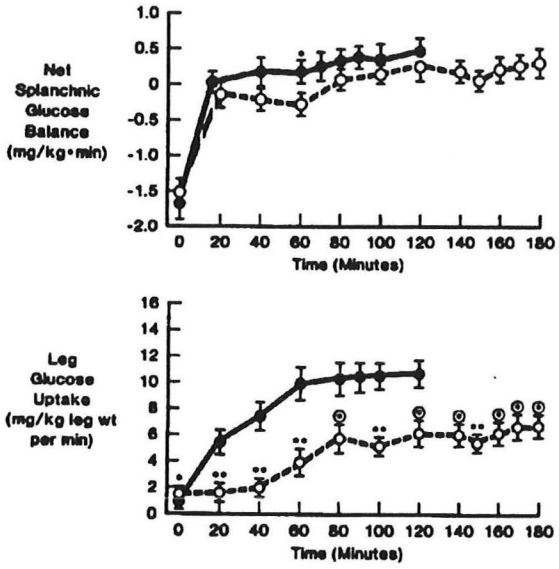

Figure 7 Glucose balance studies in splanchnic bed and the leg in control (closed circles) and NIDDM (open circles) subjects.

suppressed these activities much less in diabetics than in normals, even though insulin and C-peptide responses were comparable. Glucose cycling which measures the net rate of substrate cycling in the liver was elevated in diabetics in the postabsorptive state as well as after glucose infusion. The insulin resistance in NIDDM appears to be primarily related to post-insulin receptor defects. Although in subjects with glucose intolerance there is a slight decrease in insulin receptors in adipocytes, further progression of insulin resistance *in vivo* is not associated with a further change in insulin receptor number (14).

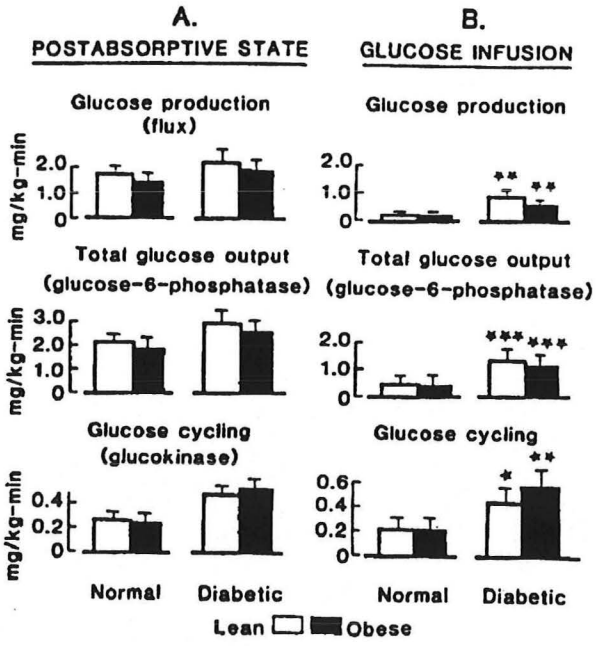

Figure 8 Glucose turnover and cycling (15).

In response to increasing insulin resistance there is initially an increase in the secretion of insulin. As shown previously in Figure 6, even in normals higher insulin responses to oral glucose are noted in those individuals with lower glucose clearance rates. In individuals with impaired glucose tolerance during an oral glucose tolerance test, there is an even greater secretion of insulin to compensate for the insulin resistance state. However, in those individuals that progress to diabetes the ability to secrete high levels of insulin is impaired. Insulin secretion falls and at that time fasting hyperglycemia begins to develop.

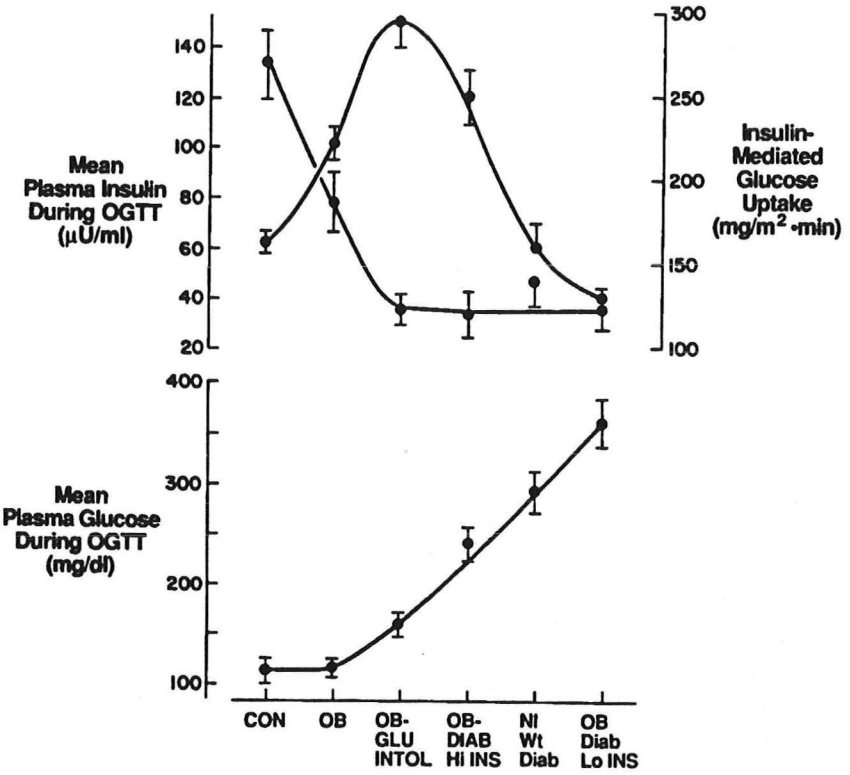

Figure 9 Responses to an oral glucose tolerance test and tissue sensitivity to insulin (11).

These changes in insulin secretion can also be seen in studies done by Polonsky and his colleagues that monitor insulin secretion throughout the course of the day. Both insulin and C-peptide levels are measured throughout the study and the rate of insulin secretion calculated from the clearance rates of these two peptides (15). In obese, nondiabetic subjects the glucose response to meals was similar, however the insulin secretory rate was increased both in the basal state and after meals (Figure 10) (16). However, when expressed as a ratio of the basal insulin secretion rate, the insulin response to meals was comparable to normal subjects. A different picture was evident

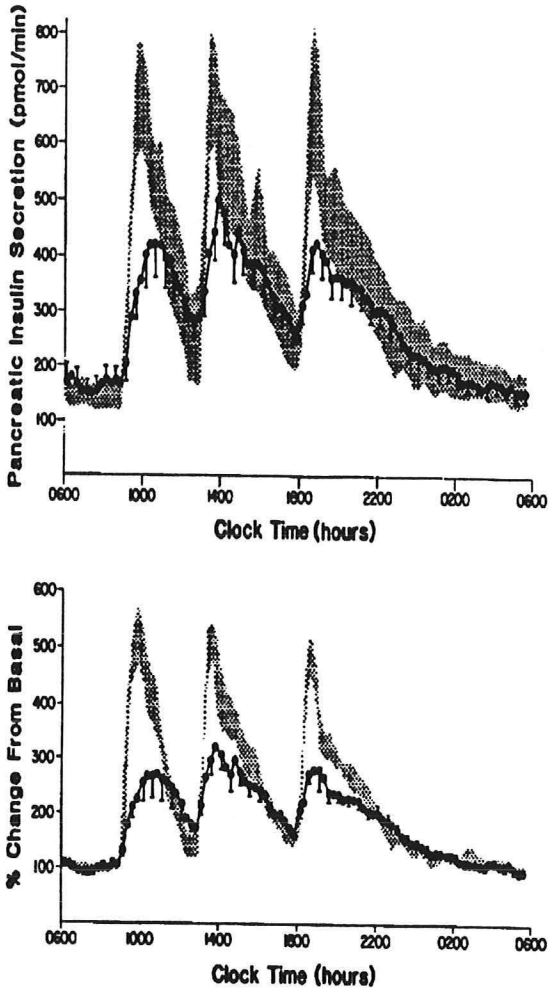

Figure 10 Insulin secretion rates in normal and diabetic subjects.

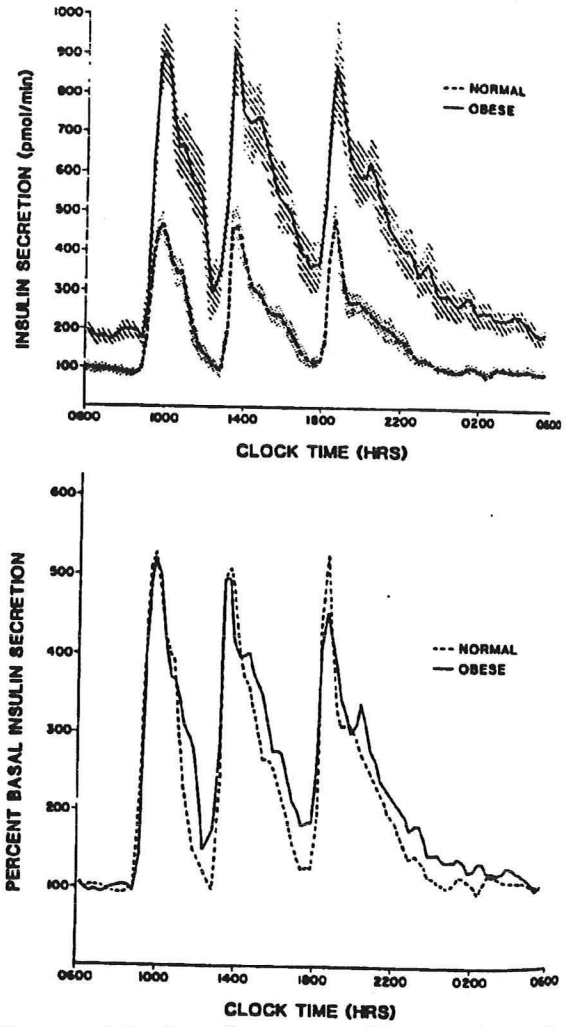

Figure 11 Insulin secretion rates in normal and obese subjects (16).

in subjects with NIDDM. The basal insulin secretory rate was similar to normal individuals, but after meals a decrease in insulin secretion in diabetics relative to normals was noted (17). This also suggests an initial ability to compensate for insulin resistance in obese subjects with a loss of compensatory insulin secretion leading to clinical NIDDM.

These studies have been based on individuals with either obesity, impaired glucose tolerance or clinical diabetes. The progression of the disease has not been followed in such subjects, however, utilizing population groups such as the Pima Indians such studies have been possible. Lillioja, et al, has followed a cohort at high risk for developing diabetes in a longitudinal manner (18). The observations in 24 individuals that developed impaired glucose tolerance are shown in figure 12. An increase the amount of insulin secreted in response to an oral glucose load is noted in conjunction with a decreased glucose uptake during hyperinsulinemic clamp studies. Variable responses were noted

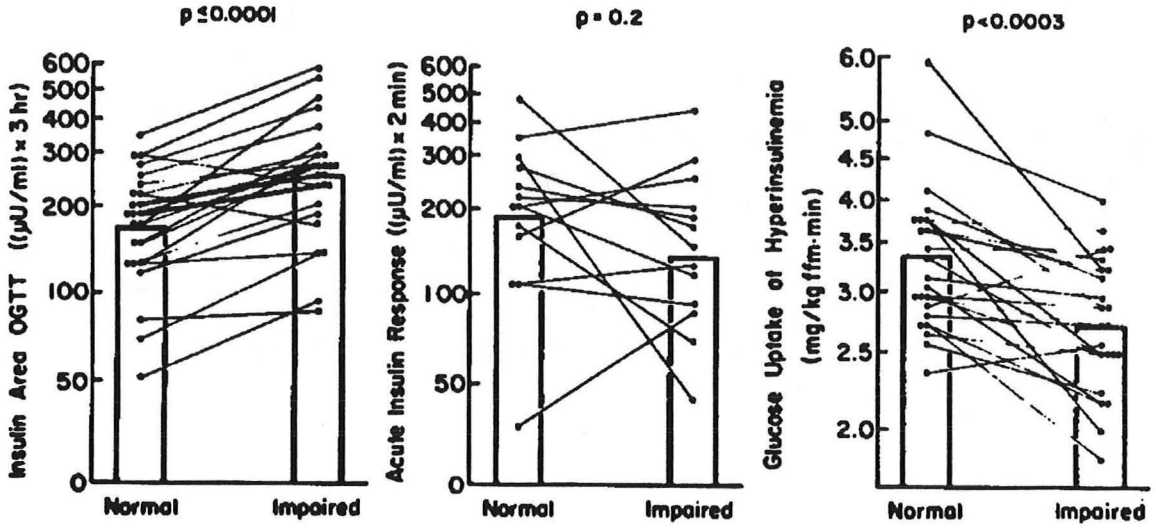

Figure 12 Longitudinal changes in 24 subjects with normal glucose intolerance in whom impaired glucose tolerance developed (18).

in the acute response of insulin, a measure of the first phase release of insulin. These observations suggest that in patients developing glucose intolerance, the main manifestation that is observed is a decreased sensitivity to insulin that is partially compensated by an increased secretion of insulin. In those individuals in the Pima Indian population that progress to impaired glucose tolerance, approximately one-third revert to normal whereas one-fourth have NIDDM at five years and two-thirds at ten years. The

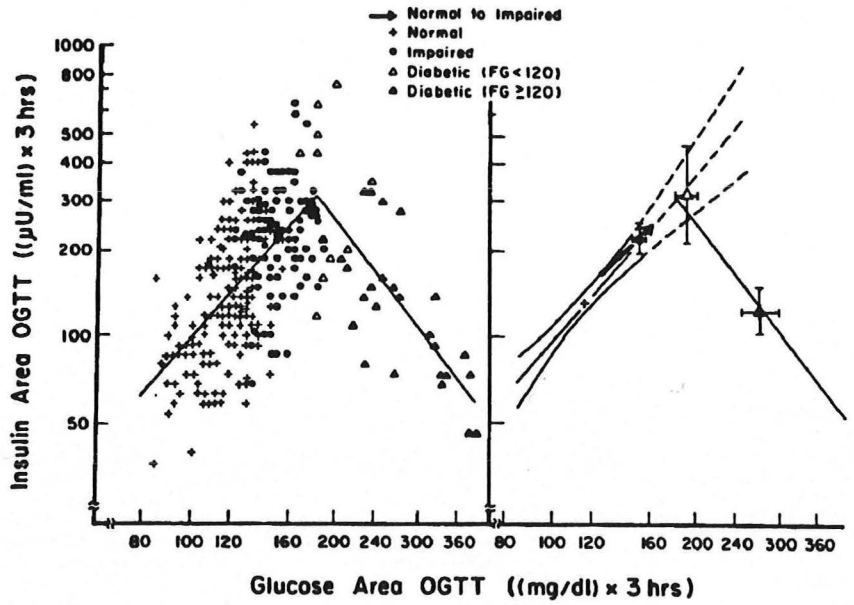

Figure 13 Insulin and glucose areas derived from oral glucose tolerance tests in Pima Indians (18).

best predictors of progression to NIDDM were age, the maximum risk peaking at ages 35-44; higher plasma glucose concentrations during fasting or after carbohydrate loading; and higher insulin levels after fasting and lower levels after carbohydrate loading (19).

In the Pima Indian population Lillioja and colleagues also studied 254 subjects that represented a whole range of glucose tolerance. Insulin sensitivity was assessed by glucose clamp studies and insulin secretion was assessed during oral glucose tolerance tests. As shown in figure 13, an increase in the insulin area during an oral glucose load is noted to a point; however, beyond this point the insulin secreted in response to glucose falls. Subjects with overt diabetes appear to have entered the downward part of the curve.

When the behavior of the insulin response to glucose is compared with the frequency distribution of glucose responses in the Pima Indians an interesting relationship is noted (figure 14). In subjects with glucose intolerance an increasing amount of insulin was observed whereas in the diabetic subjects the insulin decreased with increasing glucose concentrations. This resulted in two lines that intercept each other at a 2 hour glucose level of 195 mg/dl. When compared to the frequency of glucose responses in the Pimas, this intercept corresponded to the point that separates the bimodal curves in the population (18). This would tend to indicate that diabetes supervened when insulin deficiency developed. in the absence of insulin deficiency, hyperglycemia does not develop.

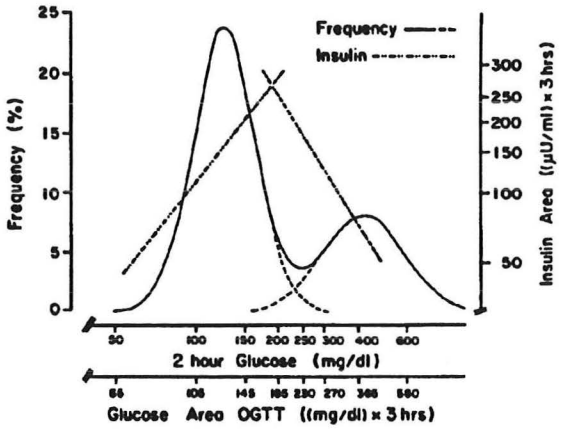

Figure 14 Frequency distribution of glucose levels and regression of insulin secretion relative to glucose levels in Pima women ages 35-45 (18).

A variety of mechanisms have been suggested for the molecular basis of insulin resistance in NIDDM. These include decreased insulin receptor number and function, glucose transport activity, and glycogen synthase activity. However, at present there is no definitive observation that localizes the defect to any of these mechanisms. Despite this it appears that insulin resistance does appear to have a genetic component. Utilizing glucose clamp studies to measure insulin sensitivity in the Pima Indians, a significant relationship to family membership is noted (Figure 15). Even when adjusted for age, sex, and obesity, family membership independently accounted for 34% of the variance in insulin action (20).

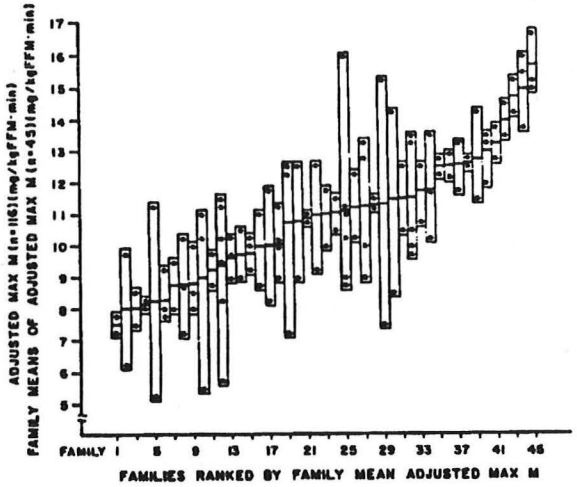

Figure 15 Glucose uptake rates adjusted for age, sex, and obesity grouped by families (20).

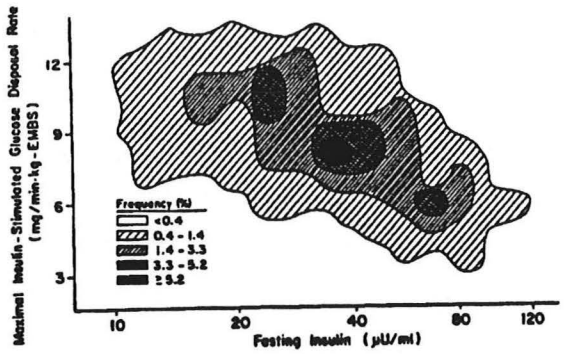

Figure 16 Contour plot of combined frequency distribution of insulin sensitivity and fasting insulin concentrations in nondiabetic Pima Indians (21).

Among 245 nondiabetic Pima Indians *in vivo* insulin action appears to be represented by three normal distributions accounting for 23%, 48%, and 29% of the total distribution (Figure 16). As shown in Figure 17, associated with differences in the maximal insulin-stimulated glucose uptake rates were fasting insulin concentrations. These results are consistent with the idea that insulin resistance among the Pimas id determined by a single gene with a codominant mode of inheritance (21).

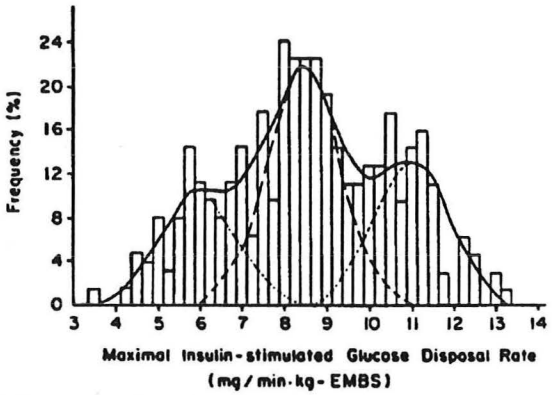

Figure 17 Frequency distribution of maximal insulin-stimulated glucose disposal rates among nondiabetic Pima Indians (21).

THE ISLET OF LANGERHANS IN NIDDM

In contrast to the β cell depletion present in Type I diabetes, secondary to autoimmune destruction of the β cell, there is not a dramatic change in β cell number in NIDDM (22). Although a decrease in the number of β cells is noted, the most striking finding is the presence of extracellular amyloid deposits. Islet amyloid was one of the first morphologic findings observed in the pancreas of diabetic patients, being described by Opie in 1900 (23). In the 1940's autopsy studies found islet amyloid deposits in about two-thirds of patients with NIDDM, and also in about 10% of nondiabetic subjects over the age of 50 (24).

Table III. Amyloid deposits in autopsy specimens (24).

	Amyloid-positive	Amyloid-negative	Total
Juvenile diabetic patients	1	25	26
Middle-aged or older diabetic patients	67	38	105
Nondiabetic patients over 50 years of age	5	45	50

The classic staining pattern of amyloid with Congo Red and under polarized light show green birefringence was confirmed in the 1960's by Ehrlch and Ratner (25). They found amyloid present in 49.5% of diabetics over the age of 50 and 3.9% of nondiabetics over the age of 60. The regions of amyloid deposition correspond to regions of the pancreas that contain β cells, rather than the pancreatic-polypeptide rich lobule of the head of the pancreas (26,27).

Despite the early recognition of islet amyloid, the molecular nature of the amyloid was not defined until recently. This was mainly due to inability to solubilize and purify the amyloid material by standard techniques. However, in 1987 two groups succeeded in purifying the amyloid material and determining the amino acid sequence of the peptide (28-32). This material was initially named diabetes associated peptide or islet amyloid polypeptide

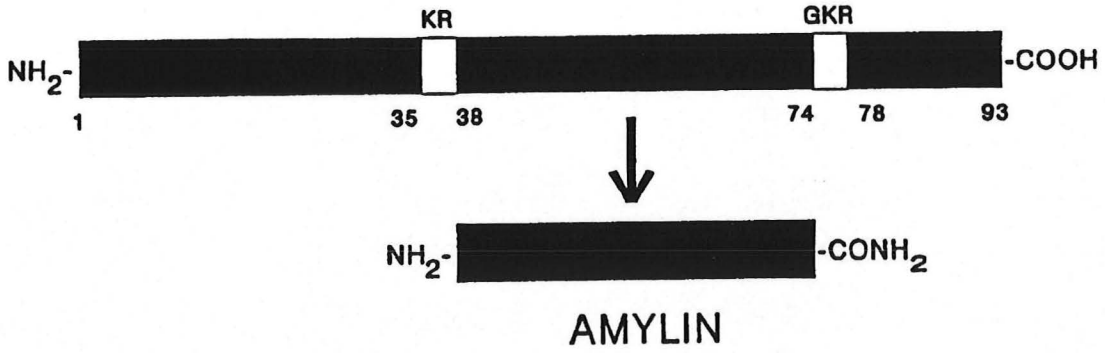

Figure 18 Rat amylin precursor structure.

(IAPP) by the two groups. Subsequently, the group that used the term diabetes associated peptide, has coined the name amylin. Analysis revealed that the primary component of the islet amyloid was a 37 amino acid polypeptide that was 46% identical with a previously described neurotransmitter, calcitonin gene-related peptide or CGRP. Several groups have cloned the cDNA for amylin or IAPP from several species (33-37). Sequencing a 900 bp cDNA derived from an pancreatic islet cell library revealed that amylin is derived from a precursor of 90 amino acids in the rat, as shown in Figure 18 (34), or 89 amino acids in man. Dibasic amino acids (lysine and arginine) flank the sequence of the 37 amino acid amylin molecule. Proteolysis of the precursor at these sites and amidation at the carboxy-terminal end of the cleaved peptide results in the production of the 37 amino acid amylin peptide. The site of synthesis of amylin appears to be mainly within the β cells of the pancreatic islet. Amylin mRNA is found in the islets at about 1/10th the amount of insulin mRNA. Small amounts of amylin mRNA and protein have been found in the stomach and intestine, but otherwise no other site appears to express the amylin molecule.

Immunoreactive amylin is found in normal β-cells copackaged with insulin in secretory granules (38,39). This finding suggests that amylin is cosecreted with insulin from the pancreas. Such secretion has been demonstrated in the isolated, perfused pancreas from normal rats. Using a specific radioimmunoassay for amylin secretion could be shown in response to glucose, arginine, or the combination (40). These

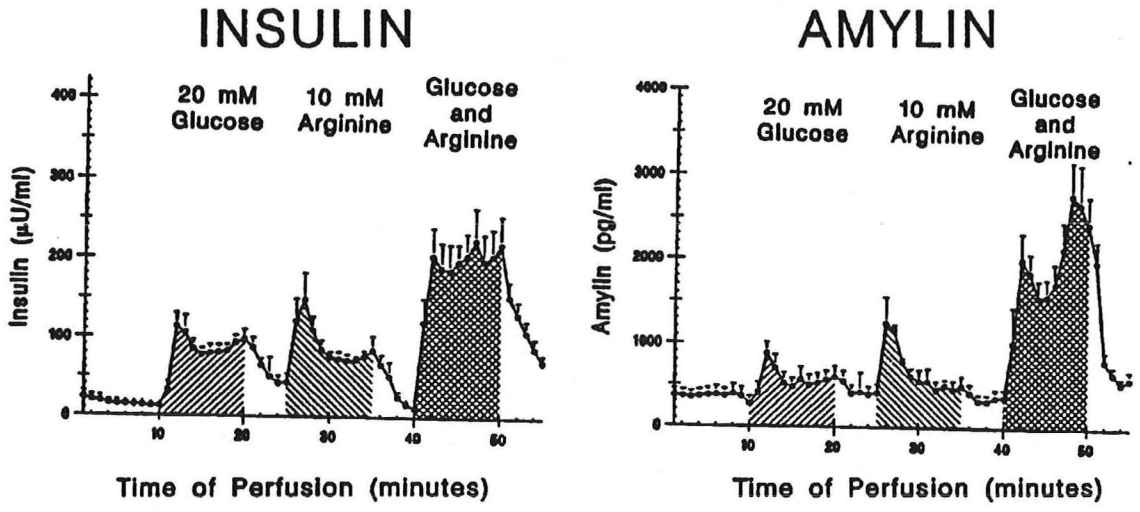

Figure 19 Insulin and amylin secretion from the isolated, perfused pancreas of normal rats (40).

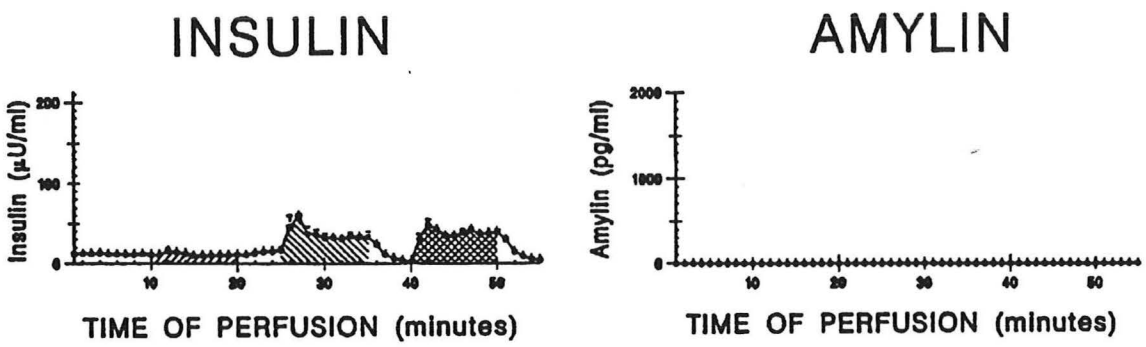

Figure 20 Insulin and amylin secretion in the isolated, perfused pancreas of rats rendered diabetic by treatment with 65 mg/kg of streptozotocin.

release of insulin and amylin in a parallel fashion, as shown in Figure 19. We estimate that the molar amount of amylin secreted is 25-37% the amount of insulin. When animals were treated with the β-cell toxin, streptozotocin, to ablate the β-cell population a severe, insulin-dependent diabetes resulted. Such animals had blood sugars of 450 mg/dl and required insulin to prevent ketoacidosis. Secretion studies in these animals showed a marked reduction in insulin secretion, and a total loss of amylin secretion (Figure 20).

Such studies clearly show that amylin is a product of the normal β-cell that is secreted in conjunction with insulin. If so, what potential role could it play in normal physiology and the pathogenesis of NIDDM. Unfortunately, these answers at present are not clear but some studies have shown interesting actions potentially relevant to the situation. Cooper and Leighton examined the effect of amylin and the CGRP, the neuropeptide that is 50% identical to amylin, on carbohydrate metabolism in skeletal muscle (41-43). In a preparation of isolated rat soleus muscle strips amylin inhibited basal and insulin-stimulated rates of glycogen synthesis without a significant change in the rate of glycolysis. It is interesting that both of these effects are insulin-regulated in the tissue, yet amylin appeared to affect glycogen synthesis preferentially. Of interest, previous

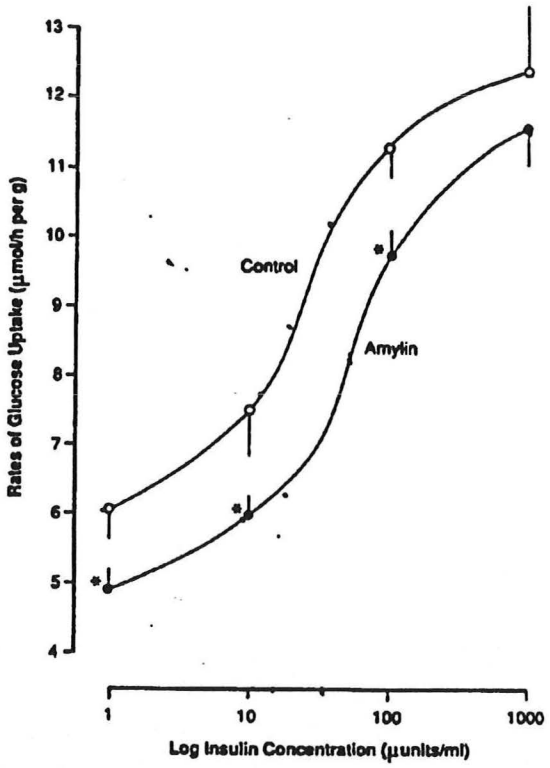

Figure 21 Effect of amylin on the insulin-stimulated rate of glucose uptake in isolated skeletal muscle (42).

studies in diabetic subjects using indirect calorimetry suggest that the primary manifestation of insulin resistance in skeletal muscle is in nonoxidative glucose metabolism (glycogen synthesis), rather than oxidative metabolism (glycolysis) (44,45). These effects were not observed in adipose tissue. These studies were conducted using concentrations of amylin in the 1-120 nM range. Such concentrations may be in excess of physiologic levels, however this has not been fully assessed to date.

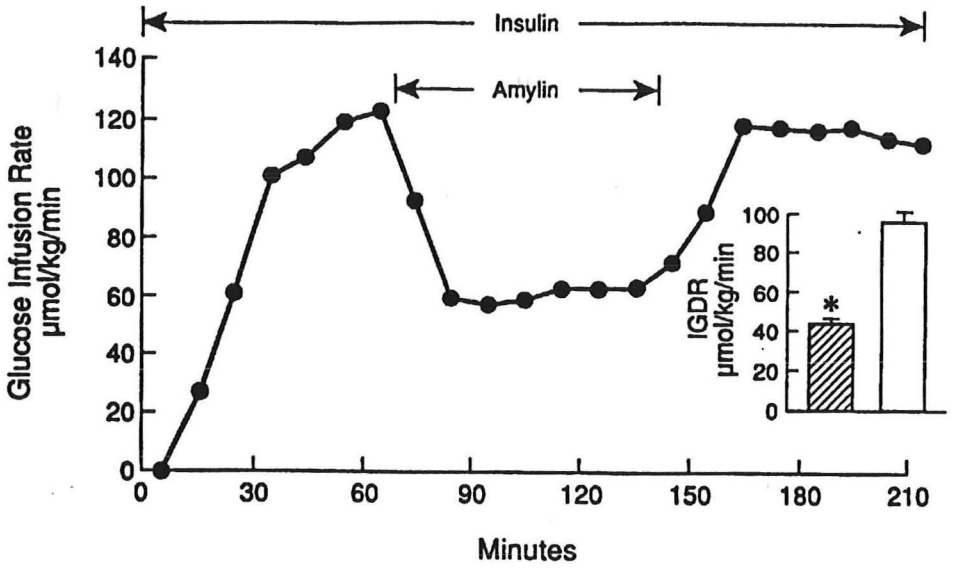

Figure 5 Effect of amylin administration on glucose disposal rate during euglycemic insulin clamp (46).

Additional studies have recently been conducted by Molina in which the effect of *in vivo* infusion of amylin or CGRP during a euglycemic insulin clamp has been performed (46). As shown in Figure 22, when amylin is infused at a rate of 500 pmol/min/kg a substantial decrease in the rate of glucose utilization is noted. This implies that amylin is inducing an insulin resistant state. Less glucose is required to maintain a constant blood sugar in the presence of a constant insulin level. Measurements of hepatic glucose output using radioactive glucose show that the infused amylin also appears to have

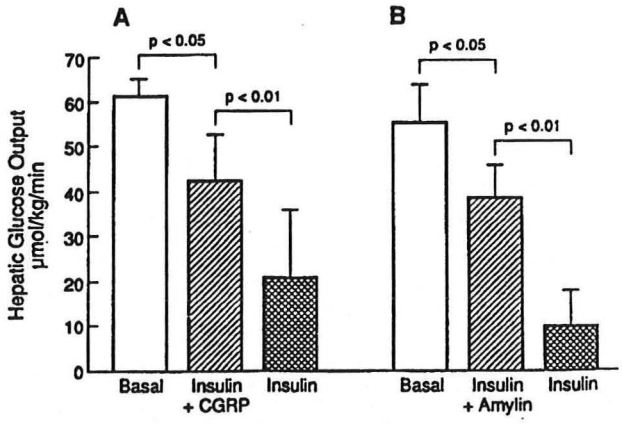

Figure 6 Effect of amylin on hepatic glucose output during a euglycemic clamp (46).

hepatic effects. Insulin suppresses hepatic glucose output, however when amylin or CGRP is infused together with insulin the decrease in hepatic glucose output. Thus in these studies amylin infusion appears to mimic manifestations of the insulin resistant state in NIDDM. Skeletal muscle insulin resistance and increased hepatic glucose output are both defects that have been observed early in NIDDM. However, it is not known if sufficient concentrations of amylin would circulate to result in such changes.

The other mechanism by which amylin might play a role in the pathogenesis is through the deposition of islet amyloid. Although one cannot follow the progression of NIDDM in the pancreas in human subjects, progressive amyloid deposition has been observed in two animal models. The Celebes black macques (*Macaca nigra*) develops NIDDM with a reasonable frequency. Animals have been observed that have developed glucose intolerance and then progressed to diabetes. In these animals pancreatic biopsies were obtained at several time points. In nondiabetic animals (mean age 8.9 years) only 1.4% of the islet contained amyloid. When these same animals progressed to a state of glucose intolerance (mean age 14.2 years) the amount of amyloid had increased to 31.4%. In animals that progressed from glucose intolerance (mean age 12.1 years) to diabetes (mean age 16.7 years) the amount of islet amyloid increased from 34.1% to 62.7%. Similarly, in cats with either glucose intolerance or diabetes immunoreactive islet amyloid was detected with increasing frequency in the diabetic state (48). Although again the consequence of the amyloid deposition is unknown the sequence of the amylin molecule in different species suggests a basis for the amyloid deposition. Species that develop NIDDM with islet amyloid deposits, such as man and cat, have a common sequence in the amylin molecule between residues 25-29 whereas rodents that do not develop amyloid deposits have diverged in this region (49,50). When peptides corresponding to this region have been observed in concentrated solutions the sequence of the human peptide spontaneously forms fibrils. That of rat amylin does not aggregate. It might be anticipated that since amylin and insulin are secreted together from the islet that as increasing amounts of insulin are secreted to compensate for the insulin resistance, increasing amounts of amylin would be secreted. If the molecule reached a critical level in the islet this would result in the formation of the amyloid deposit. This could be toxic to cells within the islet or merely be a marker of β-cell secretory activity.

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Amyloid-positive  1         10         20         30      37
      Human       KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY
      Cat         KCNTATCATQRLANFLIRSSNNLGAILSPTNVGSNTY

Amyloid-negative
      Rat         KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY
      Mouse       KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY
      Guinea Pig  KCNTATCATQRLINFLVRSSHNLGAALLPTDVGSNTY
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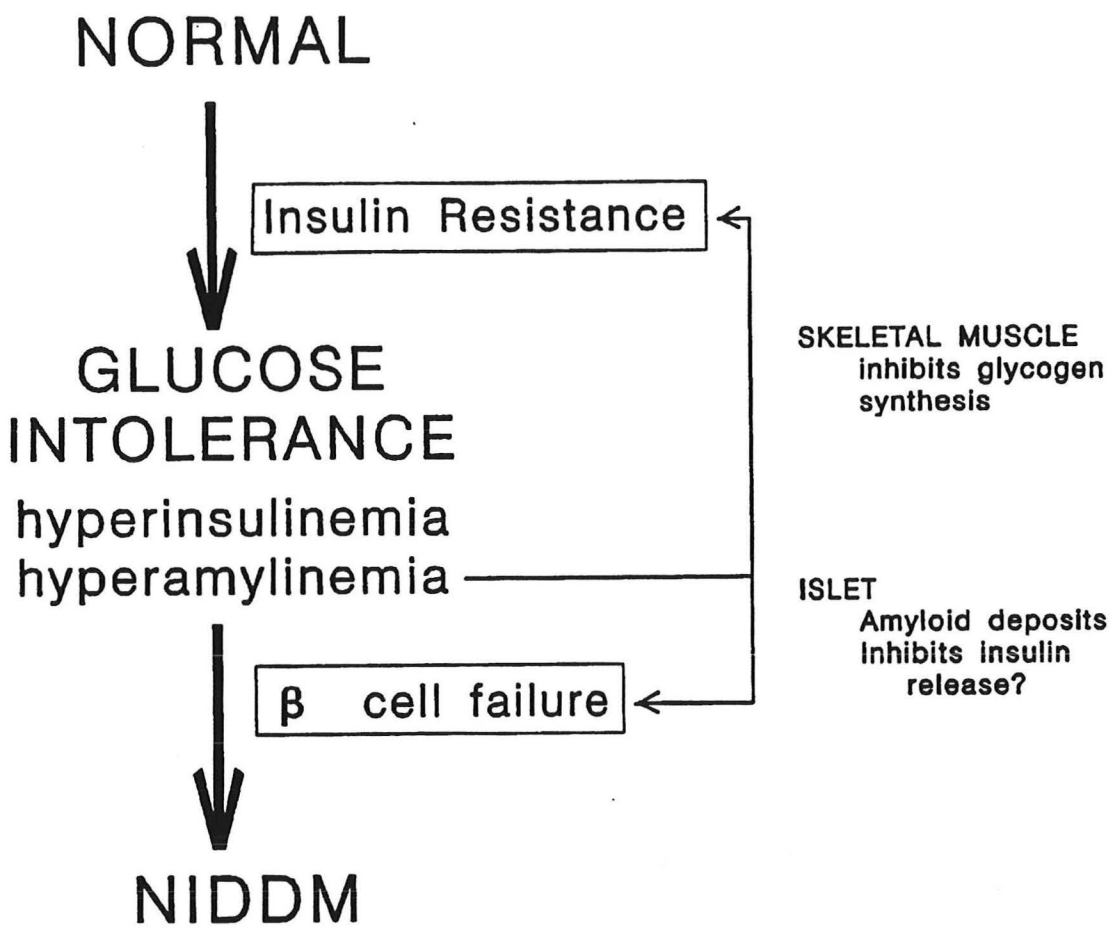

CONCLUSION

Previous studies on NIDDM indicate that genetic factors play a major part in the pathogenesis of the disease. Clinical studies show there are at least two distinct events necessary for the development of NIDDM - insulin resistance and a relative pancreatic β-cell failure. Amylin, through "hormone-like" actions, has been suggested to play a role in the early insulin resistance of NIDDM. It could also easily be imagined how amyloid deposits could play a role in the functional decline of the pancreatic β-cells. However a great deal of further studies are needed to define the normal expression and function of this molecule to see if the initial enthusiasm is appropriate.

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