Hyperinsulinemia—How Innocent a Bystander?

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Hyperinsulinemia is very much in the spotlight. Debate rages as to its significance and role in the etiology not only of NIDDM, but also other morphological and metabolic risk factors for atherosclerotic cardiovascular disease, including upper-body obesity, dyslipidemia, hypertension, and hyperuricemia. Epidemiological data support a key role for hyperinsulinemia in these disorders but it is far from conclusive except for the fact that hyperinsulinemia and insulin resistance may be present many years before the onset of impaired glucose tolerance and NIDDM, and clearly play a role in their etiology. The thrifty genotype hypothesis provides a plausible basis for a better understanding of how hyperinsulinemia and insulin resistance could lead to glucose intolerance and atherosclerotic cardiovascular disease, but the detailed biochemical mechanisms remain elusive. A role for increased sympathetic nervous system activity, resulting from hypothalamic stimulation as a primary event causing hyperinsulinemia, cannot be excluded as a cause of hyperinsulinemia. The current focus on hyperinsulinemia also has resulted in closer examination of the therapy of diabetes and hypertension, emphasizing the need to avoid hyperinsulinemia in both IDDM and NIDDM individuals because of the putative risk of atherosclerotic cardiovascular disease and hypertension. There is still a paucity of epidemiological data to support a role for hyperinsulinemia in the etiology of hypertension. However, clinical practice already is being influenced by the fact that ACE inhibitors have been shown to reduce insulin resistance in clinical research studies. The research reviewed here, particularly that relating to hyperinsulinemia, insulin resistance, and cardiovascular disease risk factors, has opened new vistas for the treatment and prevention of NIDDM and atherosclerotic cardiovascular disease. Appropriate exercise clearly is associated with improved insulin sensitivity, modification of CVD risk factors, and lower prevalence of NIDDM. Upper-body obesity, the latest culprit in the field, can also be reduced by exercise. Hyperinsulinemia and insulin resistance can be detected in children, adolescents, and young adults. NIDDM can be prevented, but clearly, intervention needs to commence in childhood, and intensive risk factor intervention in subjects with NIDDM can reduce the risk of atherosclerotic cardiovascular disease. It seems paradoxical that prevention of NIDDM and atherosclerotic cardiovascular disease are now possible even though the biochemical and molecular basis of these disorders is not fully understood.

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NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; ACE, angiotensin-converting enzyme; RIA, radioimmunoassay; FFA, free fatty acid; IGT, impaired glucose tolerance; MODY, maturity-onset diabetes of the young; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; CAD, coronary artery disease; CVD, cardiovascular disease; BMI, body mass index; GDM, gestational diabetes mellitus; CRF, corticotropin-releasing factor; ACTH, corticotropin hormone; CI, confidence interval.

Considerable epidemiological, human, and animal experimental data have been assembled to support a case for a key role for hyperinsulinemia in the etiology of various noncommunicable diseases, including NIDDM, hypertension, ASCVD (1–3), and perhaps even aging and immunodeficiency disorders (4). If glucose intolerance, hypertriglyceridemia, hypertension, and upper-body obesity constitute the "Deadly Quartet," as suggested by Kaplan (4), then hyperinsulinemia may prove to be the conductor of the ensemble.

The task of having to address the topic of hyperinsulinemia with all of its attendant implications is a formidable one given that it still is unclear whether hyperinsulinemia is an innocent bystander, partner-in-crime, or panacea in the etiology of these disorders. Thus, a major purpose of this review is to sift through the vast literature on this subject and discuss the contributions that have led to a better understanding of the putative etiological role of hyperinsulinemia. Some of these have already been highlighted in earlier reviews (1–3). It has already been suggested elsewhere (6) that, as yet, neither the epidemiological nor biochemical data provide a conclusive basis for many of the current claims and probably are also an insufficient basis for the major shifts in clinical practice; for example, use of ACE inhibitors to treat hypertension in individuals with diabetes, which are being recommended on the basis of recent but limited studies (7).

However, before delving further into the inventory and intrigue of the latest developments in the saga of the hyperinsulinemia and associated diseases, it is worth reviewing the earlier literature. Often the tendency is for contemporary authors—at any stage in history—to either dismiss or ignore earlier studies that may be relevant.

HYPERINSULINEMIA OR HYPOINSULINEMIA—THE CHARACTERISTIC METABOLIC ABNORMALITY IN NIDDM?

Background information

Over 50 years ago, Himsworth suggested that there were at least two clinical forms of diabetes, one was caused by true insulin deficiency, which he labeled "insulin sensitive" and the other was labeled "insulin insensitive" (8). This was a quite radical concept at that time. It was only after the development of a bio-assay for insulin in blood some 15 years later that Himsworth's original observation was validated. In 1951, Bornstein and Lawrence (9) reported their results on the absence of plasma insulin in 5 patients (with what would now be accepted as IDDM) and its presence in 5 NIDDM subjects. Further confirmation of the two major types of diabetes and their relative plasma insulin status came a decade later with the development of the RIA for insulin by Yalow and Berson (10,11).

Now, with a tool available to assess the insulin secretory status of subjects with diabetes, the stage was set for obtaining a clearer understanding of the natural history and pathogenesis. A significant barrier had been removed. However, just as the discovery of insulin did not solve the clinical problems of diabetes, the availability of an insulin RIA led to a major controversy that still continues today.

The controversy has centered around whether NIDDM is caused by β-cell dysfunction (characterized by hypoinsulinemia) or insulin resistance (characterized by hyperinsulinemia), or a combination of the two (12–14). Further confusion results from the fact that at different times in the progression of glucose intolerance to NIDDM, both islet cell dysfunction and insulin resistance can occur and coexist (13,14). Furthermore, debate continues as to whether hyperinsulinemia precedes insulin resistance in the natural history of NIDDM (2,15). These facts, coupled with the alleged heterogeneity of NIDDM (12), provide a veritable minefield for the uninitiated.

There have been strong proponents for the hypoinsulinemia concept, that is, that impaired secretory capacity of the β-cells is the major feature in the development of NIDDM (16–18). Yet, in their original report, Yalow and Berson (10) noted that after oral glucose, plasma insulin exceeded normal in patients with maturity-onset diabetes (now termed NIDDM), thus suggesting that insulin was unable to exert its full effect. Hales and Randle (19) also reported supranormal concentrations of plasma insulin in this form of diabetes, and they extended the concept of insulin resistance with the proposal that an abnormality of triglyceride metabolism led to increased release of fatty acids in adipose tissue and muscle. They suggested that this would cause resistance to the hypoglycemic action of insulin. What is now regarded as the pancreatic exhaustion hypothesis in the etiology of NIDDM can be found in their paper (19); they suggested that increased insulin resistance would result in a rise in plasma glucose and insulin, with eventual exhaustion of the pancreatic β-cells.

The case for hyperinsulinemia as the primary defect in NIDDM was further supported by numerous studies over the next few years (20–29). Rimoin demonstrated hyperinsulinemia in Navajo Indians and found a threefold difference in plasma insulin response between the Navajos and the Pennsylvania Amish (30). This ethnic variability in plasma insulin responses was subsequently confirmed in Pima Indians (31), Micronesians and Polynesians (32), Australian Aborigines (21), Asian Indians (6,33), and Chinese and Creoles (6).

Danowski, studying the evolution of diabetes from prediabetes, noted no change or increases in plasma insulin response and suggested that "these data supported the concept that diabetes can and does develop in adults despite a true increase, or at least no decrease, in the levels of apparent or immunoassayable insulin present in serum after oral glucose" (26).

Based on these data, it is reasonable to state that 20 years ago, a fundamental understanding of the natural history of NIDDM and a strong case for hyperinsulinemia as the most likely characteristic feature already existed. The proposal that increased FFA concentrations cause insulin resistance (Randle's cycle) (19) has resurfaced more recently and the evidence has been reviewed elsewhere by Reaven (35). Circulating FFA concentration is suppressed quickly by insulin in normal subjects. However, individuals with NIDDM have a reduced capacity to suppress FFAs thereby increasing hepatic glucose output and contributing to hyperglycemia in these subjects. This could further exacerbate hyperinsulinemia and insulin resistance. However, contemporary opinion and data do not support a major role for this mechanism in the insulin resistance of NIDDM, although such an effect can be induced acutely (36).

The confusion and controversy as to whether hypoinsulinemia or hyperinsulinemia is the fundamental defect in NIDDM can, in part, be explained not because of heterogeneity but rather at what point in the natural history of NIDDM glucose tolerance is studied (21,32,37, 38). Hyperinsulinemia is a well-documented feature of IGT (39–42), and in longitudinal studies in several ethnic groups, it clearly precedes decompensation to diabetes (15).

Studies in established NIDDM patients will usually demonstrate hypoinsulinemia as a result of the natural history of the disorder. Reaven and his colleagues have been the champions of the hyperinsulinemia/insulin resistance faction. They have consistently questioned the hypoinsulinemia hypothesis (21,43,44) and demonstrated clearly that the discrepant results were attributable to the degree of glucose intolerance in existence when the studies were conducted. Reaven and Miller (21) studied

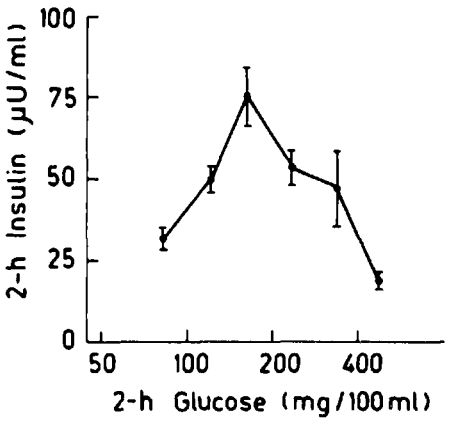

Figure 1—*The relationship of mean logarithmic 2-h plasma glucose with 2-h plasma glucose insulin response (mean ± SE) in Micronesian Nauruans showing the typical inverted U-shaped curve.*

responses to an oral glucose load and demonstrated first an increase, then a decrease in the insulin response through progressive degrees of hyperglycemia. This typical inverted U-shaped pattern was subsequently confirmed in another group of Europids (45), Pima Indians (31), and Micronesians and Polynesians (32) (Fig. 1). This phenomenon was more recently labeled the "Starling curve of the pancreas" (14). Thus, a person with NIDDM studied at the stage when pancreatic decompensation has taken place will show hypoinsulinemia; whereas an individual at the transition point of IGT to NIDDM will exhibit hyperinsulinemia. Consequently, the recent study of Temple et al. (46), claiming that insulinopenia was the characteristic defect in NIDDM, is partly flawed because the subjects studied were severely hyperglycemic and pancreatic decompensation already would have occurred in most.

At the risk of being judged either a fool or a sentimentalist, the above data have been included to demonstrate a firm basis for the current position that hyperinsulinemia is the predominant and initial abnormality in the natural history of NIDDM. This is not to say that there is not a subgroup of NIDDM subjects in which deficient insulin secretion plays a role (13,14). This certainly appears to be the case in certain families with MODY in which a nonsense mutation in the glucokinase gene has been demonstrated (49).

However, summarizing the situation in 1979, Reaven (47) noted that the accumulated data suggest that "insulin resistance is the cause of glucose intolerance in the majority of adult, nonobese patients with chemical diabetes and in obese subjects. The insulin resistance in both situations is associated with a reduced number of insulin receptors, and this decrease in number of insulin receptors can account for the insulin resistance and glucose intolerance."

HYPERINSULINEMIA AND INSULIN RESISTANCE—THE PATHOPHYSIOLOGY— What are the pathophysiological mechanisms underlying this scenario, and how could they account for the various metabolic abnormalities and disease states now attributed to hyperinsulinemia and insulin resistance? As early as 1972, Reaven et al. (44) suggested that persistent hyperinsulinemia in subjects with "chemical diabetes" could lead to increased hepatic triglyceride production and endogenous hypertriglyceridemia and could accelerate atherogenesis. They noted that therapy for this group should include control of the hyperinsulinemia because of this possibility.

The definition of hyperinsulinemia is difficult and varies between populations because of ethnic variability in insulin concentrations (31–34). Invariably, however, hyperinsulinemia represents a situation in which the plasma insulin is higher than that expected for a given plasma glucose concentration. This may occur in the presence of normoglycemia or hyperglycemia. Certainly, a raised plasma insulin in the presence of a normal plasma glucose indicates a state of insulin resistance (48).

Insulin resistance can be defined as a situation in which a normal amount of insulin produces a subnormal biological response (48). The accumulated evidence strongly supports the fact that resistance to the effect of insulin is a fundamental feature of NIDDM and obesity as well as some rarer metabolic and endocrine states (48). It also occurs in people with normal glucose tolerance (15,50). In addition, convincing data now indicate that insulin resistance is a marker for subsequent development of NIDDM (6,15), and that it has a genetic basis (51).

The possible causes of insulin resistance have been reviewed in detail elsewhere (3,12,14,48) but can be broadly subdivided into *1*) an abnormal β-cell secretory product, 2) circulating insulin antagonists, or 3) a target-tissue defect in insulin action. Only the latter situation will be discussed in this review as it appears to be the most likely cause (14,48).

When hyperinsulinemia is coupled with insulin resistance, what may happen metabolically? In brief, when insulin secretion is stimulated by glucose ingestion, the combination of hyperglycemia and hyperinsulinemia promotes glucose uptake by splanchnic (liver and gut) and peripheral (mainly muscle) tissues and suppresses hepatic glucose production (14). Although there is considerable debate as to which comes first in NIDDM—hyperinsulinemia or insulin resistance (15)—the dilemma is not easily resolved. If the primary defect is in tissue sensitivity of muscle or liver, hyperinsulinemia would be a secondary and compensatory response. On the other hand, evidence also suggests that hyperinsulinemia may be the primary defect and insulin resistance is secondary (2,6,15). It is quite possible that these are two independent, genetically determined mechanisms for the development of NIDDM, with the former being more evident in nonobese subjects and the latter in the obese. However, whatever the sequence, the primary event leads to the emergence of the other, and the subsequent metabolic derangement is similar.

With insulin resistance in the peripheral tissues, the plasma glucose rises and the pancreas responds by increasing circulating insulin concentrations. This rise causes downregulation of the insulin receptors and exacerbates the tissue insensitivity to insulin. A vicious cycle ensues with a progressive rise in plasma glucose up to a point, the apex of the "Starling curve of the pancreas," at which time the β-cell decompensates, insulin secretion falls, and hyperglycemia is further exacerbated (1,3,14). It seems quite possible that hyperglycemia per se plays a role in causing reduced insulin secretion—a phenomenon called glucotoxicity (13,14).

Why the β-cell decompensates at this point is still the subject of debate. It is possible that a lower β-cell reserve or a defect in insulin synthesis or secretion may be present (6,52). Any of these could result from a genetically determined molecular abnormality in the pancreatic β-cell.

CELLULAR MECHANISMS OF INSULIN RESISTANCE

Carbohydrate metabolism

The cellular mechanisms of insulin resistance have been elegantly reviewed by De Fronzo (14). Both binding and postbinding defects in insulin action appear to contribute to insulin resistance in NIDDM, and diminished insulin binding occurs primarily in individuals with IGT or very mild diabetes. However, in NIDDM subjects with fasting plasma glucose ≥7.8 mM (140 mg/dl), postbinding defects are primarily responsible for the insulin resistance. Documented postbinding defects include diminished tyrosine kinase activity, decreased glucose transport, impaired glycogen synthase activity, and reduced pyruvate dehydrogenase stimulation (14).

Shulman et al. (53) have demonstrated that muscle glycogen synthesis is the principal pathway of glucose disposal in normal and diabetic subjects, and that defects in muscle glycogen synthesis have a dominant role in the insulin resistance that occurs in NIDDM. Using nuclear magnetic resonance spectroscopy, they were able to demonstrate significant reduction of insulin-mediated muscle glycogen synthesis in NIDDM subjects, and these findings were compatible with the degree of insulin resistance. Whether the site of insulin resistance is extracellular or intracellular still must be established.

An intriguing aspect of insulin resistance in muscle is the marked improvement in insulin sensitivity in NIDDM subjects after exercise (54). This has important implications in both the therapy and prevention of NIDDM (6). The possibility that exercise results in the production of a humoral substance that modulates peripheral insulin sensitivity cannot be excluded.

Lipid metabolism

Insulin resistance also affects lipid metabolism through enhanced lipolysis. The resulting rise in FFA was suggested as a putative inhibitor of glucose oxidation in muscle by Randle et al. (55) many years ago, and Reaven (56) has suggested that elevated plasma FFA concentration, through a mass-action effect, increases the cellular uptake of FFA and results in stimulation of lipid oxidation. The accelerated fat oxidation inhibits insulin-mediated glucose disposal in muscle, but stimulates gluconeogenesis in liver, with a resulting increase in hepatic glucose output. In contrast, another report (57), although confirming that excess FFA oxidation inhibits glucose oxidation and disposal, does not support the role of FFAs in the etiology of insulin resistance in subjects with NIDDM.

Hyperinsulinemia and/or insulin resistance result in dyslipidemia (1,3, 35). The characteristic lipid abnormalities seen include decreased HDL cholesterol and increased VLDL synthesis, which result in elevated serum triglyceride concentration.

Although evidence exists to suggest that hyperinsulinemia is secondary to upper-body obesity (4,6), hyperinsulinemia could cause a preferential deposition of adipose tissue in the upper-body region (58). Given the well-documented association of upper-body obesity with risk of NIDDM, hypertension, and CAD (6), the cascading effect of hyperinsulinemia as an etiological agent for these disorders becomes clearer (Fig. 2).

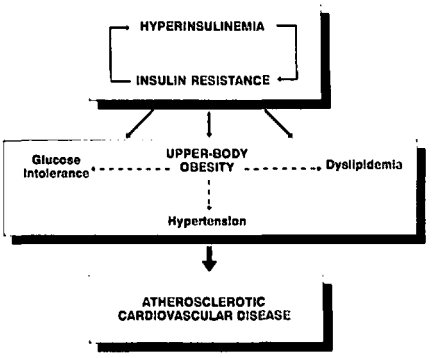

Figure 2—*The putative role of hyperinsulinemia in the etiology of atherosclerotic CVD.*

HYPERINSULINEMIA—THE TELEOLOGICAL RELATIONSHIP TO THE DEVELOPMENT OF NIDDM

— Hyperinsulinemia has been widely heralded as the possible key factor for the development of the CVD risk factor cluster of glucose intolerance, dyslipidemia, hypertension, upper-body obesity, and hyperuricemia (1–4,59,60). Thus, it might be considered naive to address its role in the development of NIDDM in isolation. On the other hand, this is one instance where excellent and convincing data from epidemiological studies indicate an important etiological role for hyperinsulinemia (15).

Hyperinsulinemia is a characteristic feature of populations with a high prevalence of NIDDM, as demonstrated in Pima (31) and other American Indians (22), Micronesian Nauruans (32,39), Mexican Americans (41), Australian Aborigines (29,61), Hispanics (62), Asian Indians (6,27), and American blacks

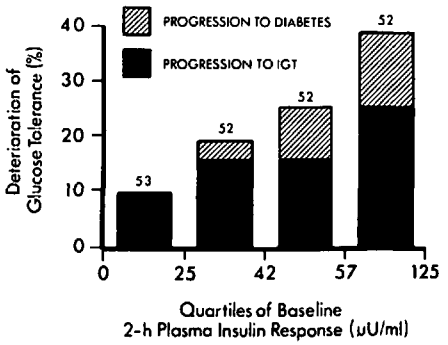

Figure 3—*The proportion of Nauruan subjects progressing to IGT and NIDDM in relation to quartile of baseline 2 h plasma insulin. From Sicree et al. (39) © by the American Diabetes Association.*

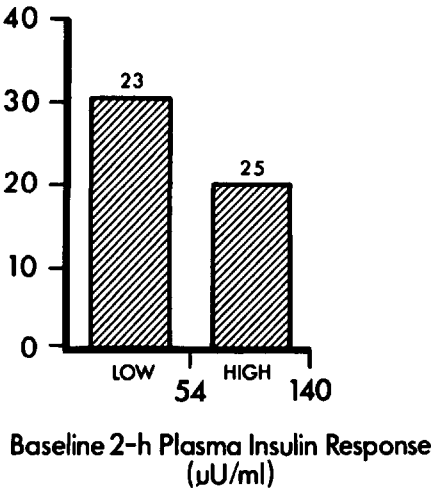

Figure 4—*Proportion of Nauruans developing NIDDM from IGT according to baseline 2-h insulin response. Value above each bar represents the number of people in that category. From Sicree et al. (39) © by the American Diabetes Association.*

(63). Because these reports were cross-sectional, only limited inference can be made from them regarding the etiological role of hyperinsulinemia. However, longitudinal studies provide a more substantive basis to permit the conclusion that hyperinsulinemia has an important role in the natural history of glucose intolerance (15). Hyperinsulinemia predates the onset of both IGT and NIDDM by many years in Micronesian Nauruans (39), Pima Indians (40), Mexican Americans (41), and Europids (42). Nauruans with hyperinsulinemia, i.e., those in the higher quartiles of baseline 2-h plasma insulin, were more likely to develop both IGT and NIDDM over time (Fig. 3).

Somewhat surprisingly at first, but quite compatible with the concept of β-cell exhaustion, was the fact that progression from IGT to NIDDM could be predicted by lower (but still high relative to normal) basal postglucose load insulin response (39) (Fig. 4). This apparent paradox has now been confirmed in other populations (40–42,64) and it clearly provides a basis for a better understanding of the natural history of glucose intolerance.

It has been suggested that the major site of insulin resistance may be muscle and/or adipose tissue (14). It has been previously accepted that hyperinsulinemia is secondary to insulin resistance. However, a very open mind should be kept on this issue. Although data exist to support this order of events (3), only a most meticulous longitudinal study in humans could prove whether hyperinsulinemia or insulin resistance is the primary defect.

On the other hand, substantial evidence from animal models (65,66) indicates that hyperinsulinemia is the primary event. Hyperinsulinemia predates insulin resistance in rodent (65) and monkey (66) models of NIDDM. Indeed, hyperinsulinemia appeared to precede insulin resistance by several years in a longitudinal study of onset of NIDDM in monkeys (*Macaca mulatta*) (66). In the progression from normal glucose tolerance to overt diabetes, the earliest change noted was a slight and progressive increase in fasting plasma insulin. This preceded any change in the fasting plasma glucose or glucose disappearance during an intravenous glucose tolerance test. Based on data from a 7-yr surveillance, Hansen and Bodkin (67) have implicated a primary defect in β-cell control or sensitivity, as evidenced by increased insulin release in response to glucose, and a slight and subsequent significant increase in fasting plasma insulin, abnormalities that precede the fasting plasma glucose elevations and the decrease in plasma insulin and insulin response and the development of glucose intolerance. In addition, some studies in humans support the contention that hyperinsulinemia per se can cause insulin resistance (68,69).

The combined animal data and human epidemiological and clinical data suggest that NIDDM develops in a progressive fashion (70). Thus, in subjects with genetic susceptibility to NIDDM, whatever the initial defect (i.e., hyperinsulinemia or insulin resistance), a vicious cycle develops between hyperinsulinemia and insulin resistance in the attempt to maintain normal glucose homeostasis. Eventually, however, pancreatic decompensation occurs, resulting in deterioration of glucose tolerance through IGT to diabetes. Whether the hyperinsulinemia, if primary, is attributable to increased CNS sympathetic activity or a primary β-cell phenomenon, or a combination of the two (Fig. 5), still must be elucidated. Although insulin receptor molecular defects have been shown in rare instances (71), it is most unlikely that these or an abnormal insulin gene (71,72) play a role in the wider scenario. Reduced hepatic clearance of insulin in the cause of hyperinsulinemia also should be considered and further investigated.

HYPERINSULINEMIA AND THE THRIFTY GENOTYPE HYPOTHESIS—A UNIFYING EXPLANATION FOR NIDDM AND CVD

— Having considered the relationship between hyperinsulinemia and the development of diabetes in isolation, it is clear that other metabolic abnormalities also may result, including dyslipidemia, hypertension, and upper-body obesity. After all, NIDDM is a disorder with multiple metabolic defects

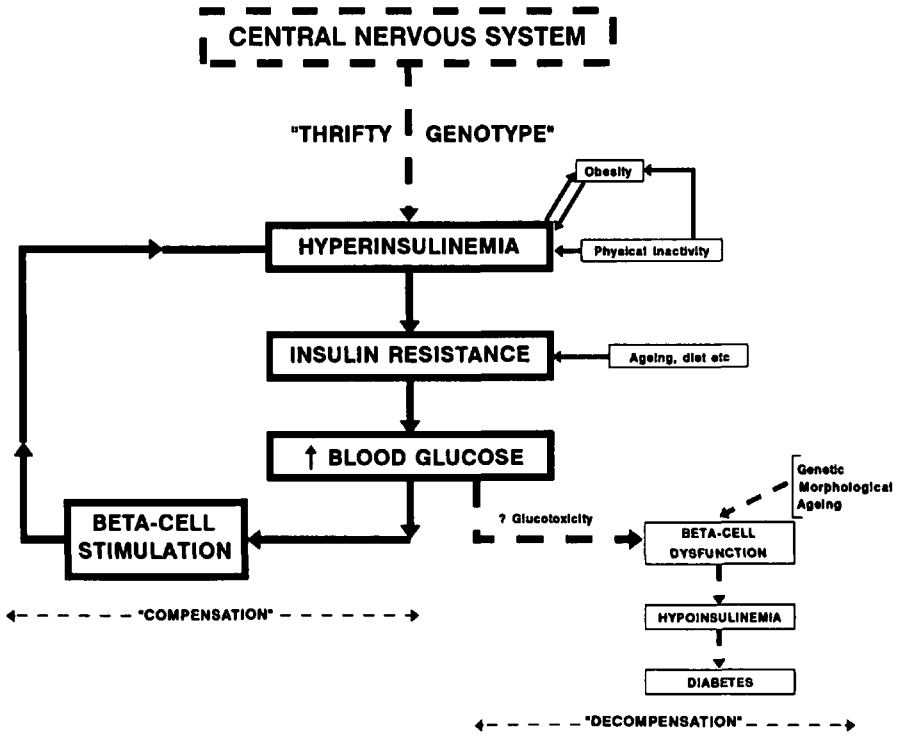

Figure 5—*The proposed pathogenetic sequence of events that leads to NIDDM; it combines a primary defect implicating hyperinsulinemia and insulin resistance with subsequent glucotoxicity and β-cell decompensation.*

(1–3) and the major cause of mortality in NIDDM is CAD (73,74).

How does this information fit in the larger picture? How is hyperinsulinemia linked to the etiology of upper-body obesity, ASCVD, hypertension, and glucose intolerance? It has been suggested that there may be an anthropological basis for these associations. Neel (75) hypothesized that hunter-gatherers who relied on the feast-and-famine cycle of food sources and availability developed a thrifty genotype. This provided a selective advantage during periods of variable food supply in earlier times in history. With life-style changes (constant and abundant food supply, and physical inactivity of our contemporary society), many previously hunter-gatherer or peasant agriculturist populations now exhibit a high prevalence of NIDDM; and Neel suggested that the thrifty genotype has become a disadvantage, which contributes to the high frequency of NIDDM. There are several animal models of the thrifty genotype that develop diabetes in the laboratory situation (76,77). In addition, Wendorf and Goldfine (78) have suggested that insulin resistance may be the phenotypic expression of this genotype.

This hypothesis may explain the high prevalence of glucose intolerance now seen in certain populations. However, could the thrifty genotype also explain the other components of the CVD risk factor cluster? O'Dea (79) demonstrated striking improvements in all of the metabolic abnormalities of NIDDM and reduction in other CVD risk factors in a study in which 10 diabetic Australian Aborigines reverted to their traditional hunter-gatherer life-style for 7 wk (Table 1). Hyperinsulinemia and insulin resistance have been demonstrated in Australian Aborigines (29,80) and the effect of traditional life-style—either dietary factors, exercise, or both—on reducing the hyperinsulinemia and insulin resistance may have played a role in the improvement in the CVD risk factor profile. The fact that these improvements occurred simultaneously supports their linkage to and a possible central etiological role of hyperinsulinemia.

Table 1—*Improvement in metabolic and morphological CVD factors in 10 Australian Aborigines after a 7-wk reversion to traditional life-style*

Parameter	Before	After
Plasma glucose (mM)	11.6	6.6*
Plasma insulin (mU/L)	23	12†
Plasma cholesterol (mM)	5.65	4.98
Plasma triglyceride (mM)	4.02	1.15*
Weight (kg)	81.9	73.8†
BMI (kg/m^2)	27.2	24.5†

Adapted from O'Dea (80).
*$P < 0.05$.
†$P < 0.001$.

A better understanding of how the thrifty genotype operates in a survival mode and in contemporary society is required; however, O'Dea (80) has suggested how it might operate. Survival would have depended on the ability to maximize feast periods by the efficient conversion of excess energy into fat for use as a supplemental energy source during times when food was scarce. In most hunter-gatherer groups, the "feast" foods would have been those high in protein and relatively low in fat and carbohydrate. Given both the diet composition and the pattern of food intake, there could have been two metabolic adaptations that relied on selective insulin resistance to help survival. The first adaptation would be hepatic gluconeogenesis that was insensitive to suppression by insulin, coupled with an increased capacity for hepatic lipogenesis that was sensitive to stimulation by insulin. The second adaptation could be efficient fat

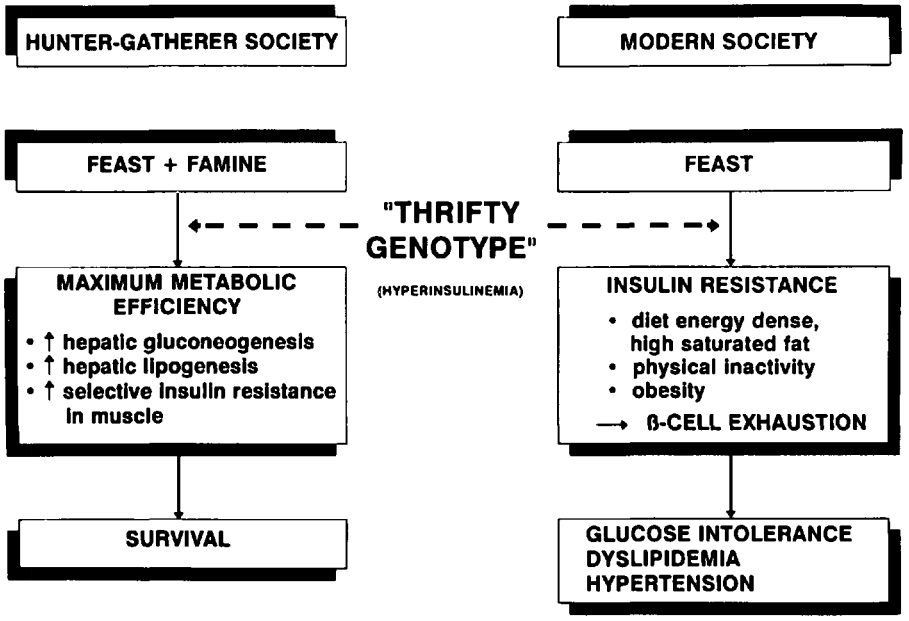

Figure 6—*The proposed mechanisms for the operation of the thrifty genotype in the etiology of glucose intolerance and other key CVD risk factors in former hunter-gatherer populations.*

accumulation to take advantage of feast periods that could be facilitated under conditions of hyperinsulinemia, when there was resistance to the hypoglycemic effect of insulin but relatively normal sensitivity to actions involving fat deposition. Therefore, if there was a selective insulin resistance in muscle, a blunting of insulin's glucose-lowering effect would result during fasting, but active hepatic gluconeogenesis and lipogenesis would still be allowed. The net result would be the efficient facilitation of vital energy storage during feast times.

In modern times, with overnutrition and sedentary physical activity patterns—factors that exacerbate insulin resistance—the selectivity of the insulin resistance may be lost, resulting in secondary insulin resistance in liver and adipose tissue (78). This would initiate a vicious cycle with a cascade effect of exaggerated hyperinsulinemia, insulin resistance and dyslipidemia (with hypertriglyceridemia and lower HDL cholesterol), upper-body obesity, hypertension, and, therefore, increased risk of CAD (Fig. 6). Thus, the components of the thrifty gene that once favored survival of the hunter-gatherers have become the risk factors for CAD and other forms of CVD in modern man.

If insulin does play a role as a survival hormone, then the presence of hyperinsulinemia predating the onset of NIDDM by many years in certain populations (6,39–42) may also explain its presence in Papua, New Guinea (81), Nauruan and Tuvaluan (82), Australian Aboriginal (83), and Pima Indian children (84). These are all populations in which high rates of NIDDM have been reported with a modernization of lifestyle (6). This finding may be of potential importance in relation to the primary prevention of NIDDM, as it appears that the cascade of risk factors for NIDDM and other associated noncommunicable diseases could commence in childhood. Clearly, more detailed studies of this possibility are needed.

HYPERINSULINEMIA—AN ETIOLOGICAL ROLE IN ATHEROSCLEROSIS?— This subject is much more complex than it appears. The interrelationship between glucose intolerance and ASCVD alone (85), and glucose intolerance, dyslipidemia, hypertension, upper-body obesity, and hyperinsulinemia and ASCVD (23,85) is quite complicated because these conditions tend to cluster and both direct and indirect mechanisms may be implicated. The relationship of hyperinsulinemia to yet another CVD risk factor, namely hyperuricemia (86), has received scant attention although it has been suggested as another consequence of hyperinsulinemia (59). Other variables complicate the equation, including ethnic and cultural factors, sex, physical activity, cigarette smoking, and nutritional factors to name but a few.

The biological effects of insulin on arterial tissues include 1) proliferation of smooth muscle cells, 2) stimulation of growth factors, 3) stimulation of connective tissue production, 4) enhanced LDL-receptor activity and cholesterol synthesis, and 5) increased formation and decreased regression of lipid plaques (3,87). However, it should be emphasized that most of the evidence for a link between hyperinsulinemia and atherosclerosis is circumstantial. It would be hard to get a conviction in a court of law (88)!

Three epidemiological studies (89–91) are regularly cited as evidence for this relationship. Jarrett (88) has discussed the inconsistencies between these studies and cautioned against overinterpretation of their significance. However, the 15-yr follow-up of the Paris Prospective Study (92) has confirmed the relationship. Here, 2-h post-load plasma insulin was an independent predictor of CAD deaths in subjects not known as having diabetes mellitus. This has very important implications given that there appears to be high CAD risk (related to hyperinsulinemia and/or other factors) long before diabetes develops (2,85,93).

The clock starts ticking for CAD many years before the onset of clinical disease. Because ASCVD is responsible for the majority of deaths in NIDDM

(73,74), this has very important implications for the primary prevention of CAD in people with diabetes. For example, subjects with IGT exhibit hyperinsulinemia (39–42,49,82) and their enhanced risk of CAD may relate to this. Therefore, prevention needs to start long before glucose intolerance ensues yet, at this time, no specific or sensitive test is available to predict the development of IGT or NIDDM.

Haffner et al. (93) have assessed the association of hyperinsulinemia and risk of CVD in the San Antonio Heart Study. They documented the CVD risk factor profile of 614 Mexican Americans who did not have diabetes when the study commenced. In 43 subjects who had developed NIDDM by 8 yr of follow-up, higher baseline levels of a number of CVD risk factors were noted, including fasting and 2 h glucose, fasting insulin, total and LDL cholesterol, BMI, and lower levels of HDL cholesterol compared with subjects who remained normal. Most of these differences persisted after adjustment for obesity and/or level of glycemia but disappeared after adjustment for fasting insulin. When subjects with IGT at baseline were eliminated, this atherogenic pattern of CVD risk factors persisted. This study confirms that subjects who are destined to develop NIDDM are at increased risk of CAD many years before onset of diabetes and this may be related to baseline insulin concentration.

A potentially exciting area of investigation is that of GDM. If CVD risk factors predate the onset of diabetes by many years, then subjects with GDM should be studied in greater detail to establish whether they have other CVD risk factors; and, indeed, if they are at greater risk of developing ASCVD in the longer term.

Other epidemiological studies support the contention that NIDDM subjects are predestined for CVD. Ferrannini et al. (94) have demonstrated, in the San Antonio cohort, that insulin sensitivity, glucose tolerance, blood pressure, body fat mass and distribution, and serum lipids are a network of mutually interrelated functions; and that an insulin resistance syndrome underlies all six disorders, carrying an increased risk of CAD. We have recently confirmed the majority of these findings in Asian Indians, Creoles and Chinese in Mauritius, although, in these ethnic groups, no significant association was observed between the hyperinsulinemia and blood pressure (95). Similar findings from other populations are discussed later in this review.

CVD risk factors and IGT also were studied in Hispanics and whites participating in the San Luis Valley Diabetes Study in Colorado (96). In both ethnic groups, individuals with IGT had CVD risk profiles that fell in between subjects with normal glucose tolerance and those with NIDDM. Similarly, in the Rancho Bernardo study, a less favorable CVD risk factor profile preceded the diagnosis of both NIDDM and IGT (97). Adverse CVD risk factor levels among subjects with minor degrees of glucose intolerance (less than IGT) also have been reported in Europids (98), Asian Indians, Chinese and Creoles (6), Australian Aborigines (80), Fijian Melanesians and migrant Asian Indians (99), and Micronesians (100).

As IGT is also associated with hyperinsulinemia and insulin resistance (74), it seems likely that the increased frequency of CVD risk factors in these IGT subjects is a manifestation of these metabolic abnormalities. These accumulated data may explain, in part, the finding that subjects with NIDDM have an excessive risk of mortality from CVD, given that a substantial proportion of IGT subjects will eventually develop diabetes (39–41). They highlight the need to review the concept that macrovascular disease is a "chronic complication" of NIDDM rather than part of the natural history of the disease and also stress the underlying issues involved in management over and above the therapeutic goal of normoglycemia in people with NIDDM (i.e., the need to also reduce hyperinsulinemia and insulin resistance as part of the therapeutic strategy).

If this were a case in court, there would still be gaps in the prosecution of hyperinsulinemia in the etiology of atherosclerosis. An obvious example of these gaps is the low prevalence of CAD in the American Pima Indians, a population with well-documented high NIDDM prevalence and hyperinsulinemia (101). Could an ethnic factor exist that protects them against CAD (85)?

Conversely, at the opposite end of the spectrum of CAD risk and prevalence are the migrant Asian Indians (102,103). McKeigue et al. (103) have reviewed global reports of CAD in migrant Asian Indians (104). High CAD prevalence is common in migrants from the Indian subcontinent and rates often are higher than those of the indigenous population, e.g., in Fiji (102), United Kingdom (103), Singapore (104), and Mauritius (105). In many of these populations, the high rates of CAD cannot be explained on the basis of conventional risk factors, such as serum lipids, cigarette smoking, obesity, or hypertension (85).

Although it has been suggested that the high prevalence of NIDDM in migrant Asian Indians may be a major factor (106), it seems just as likely that hyperinsulinemia and/or insulin resistance, which are well-documented features in Asian Indians (6,26,33,98), may have an important etiological role, which could also explain the dyslipidemia and high prevalence of NIDDM in this ethnic group.

Now several population-based studies show that high insulin concentrations constitute a predictor of future CAD (89–91). It was long considered that increased CAD risk associated with NIDDM was secondary to the diabetes or glucose intolerance (85). Now, considerable evidence exists to refute this theory (107). For example, considerable circumstantial evidence supports the fact that ASCVD and NIDDM are associated

disorders, and evidence summarized earlier suggests that hyperinsulinemia and/or insulin resistance may be the common etiological factor.

HYPERINSULINEMIA, INSULIN RESISTANCE, AND THE CVD RISK FACTOR CLUSTER—IMPLICATIONS FOR PREVENTION

— In 1936, Himsworth suggested that decreased insulin sensitivity was a characteristic feature of what is now known as NIDDM (8). Over 50 years later, it was proposed that insulin resistance or the concomitant hyperinsulinemia may be a central etiological factor for a group of CVD risk factors—glucose intolerance, dyslipidemia, hypertension, and upper-body obesity (1–3,5). Suddenly, hyperinsulinemia has been acclaimed the culprit, the panacea, and the putative key factor. Or is it really just an innocent bystander, or partner-in-crime?

NIDDM and IGT commonly occur in association with other CVD risk factors, such as dyslipidemia, hypertension, and upper-body obesity (1–3,5). The question is whether the main significance of IGT and NIDDM is their contribution of hyperglycemia as a CVD risk factor. For example, glucose intolerance is a key component of the recently described syndrome X or a similar but larger CVD risk factor cluster (2,6). But does it operate directly or indirectly via the accompanying hyperinsulinemia? Various combinations of these CVD risk factors (Table 2) have been described by a number of workers over the last 40 years and are reviewed elsewhere (1–3,5,6).

The omission of upper-body obesity from syndrome X, as described by Reaven (1), is difficult to comprehend given its frequent association with the other CVD risk factors in epidemiological studies (2,3,6,59,86,94). This omission is all the more important because both weight reduction and exercise can reverse a number of these CVD risk factors, including hyperinsulinemia, insulin resistance, and dyslipidemia (6,54,107). In addition, weight reduction becomes an essential component in the integrated intervention strategy for the prevention of glucose intolerance and ASCVD. However, though uncommon, the features of syndrome X are sometimes seen in nonobese individuals. O'Dea et al. (161) have reported the presence of hyperinsulinemia and hypertriglyceridemia in young, lean, Australian Aborigines with IGT.

Table 2—*Syndrome X plus: the CVD risk factor cluster associated with hyperinsulinemia and insulin resistance*

Syndrome X plus
Hyperinsulinemia
Insulin resistance
Glucose intolerance
Increased VLDL—triglycerides
Decreased HDL—cholesterol
Hypertension
Upper-body obesity
Hyperuricemia
Physical inactivity
Aging

HYPERINSULINEMIA AND INSULIN RESISTANCE IN THE ETIOLOGY OF HYPERTENSION

— Of particular interest is the suggested, and biologically plausible, association between hyperinsulinemia and hypertension. This is based on the observation that a higher frequency of obesity and glucose intolerance exists in hypertensive subjects (3). Modan et al. (59) suggested that hyperinsulinemia may have an etiological role in hypertension and Reaven has provided further supportive data (1).The relationship is still not completely understood, although increased activity of the sympathetic nervous system and enhanced renal tubular sodium reabsorption, as well as a number of other mechanisms, have been proposed (1–3,5,59) (Table 3). The possibility of this association has led to suggestions that certain ACE inhibitors (e.g., captopril) may have an advantage in the treatment of hypertension in diabetic patients because they cause a reduction in insulin resistance (7).

Table 3—*Possible mechanisms through which hyperinsulinemia may play a role in the etiology of hypertension*

Stimulation of CNS sympathetic activity
Increased renal sodium retention
Effects on membrane ion-transport systems: e.g., decreased sodium-potassium–adenosine triphosphate and increased sodium-hydrogen activity
Hypertrophic effect on vascular smooth muscle.

However, the suggestion that increased sympathetic nervous system activity may be the mechanism by which hyperinsulinemia causes hypertension may be interpreted otherwise. Some evidence indicates that hyperinsulinemia also may be caused by increased nervous system activity (65); thus, the association with hypertension could be coincidental. Torlone et al. (109) also have demonstrated that captopril improved insulin sensitivity in NIDDM associated with hypertension; this occurred at the level of the liver and extrahepatic tissues, primarily muscle and adipose tissue.

The fact that clinical practice is being influenced by an association that has not yet withstood the test of detailed scientific examination should be cause for concern. Do the epidemiological data stand up to closer examination? Donahue et al. (11) have reviewed the existing data and posed the question, "Hyperinsulinemia and elevated blood pressure: cause, confounder, or coincidence?" There is some support for an association in Europid populations and rodent models (1,35). This hypothesis is further supported by studies showing that insulin plays a physiological role in mechanisms that may result in elevated blood pressure (1,3). In contrast, studies in a number of ethnic groups do not support the hypothesis. Such groups include another Europid group in the U.S. (111); Micro-

nesians, Polynesians, and Melanesians in the Pacific (112); Asian Indians, Chinese, and Creoles in Mauritius (95); and Pima Indians and blacks in the U.S. (63).

As most studies cited here are cross-sectional, prospective studies in these populations will be vital. Particularly important are studies that assess the relationship of blood pressure and insulin independent of regional fat distribution and overall body mass because these are likely to exert a confounding influence on the association. No prospective data show that hyperinsulinemia precedes the onset of hypertension in otherwise healthy adults. However, the biological plausibility and the data discussed above support further studies to resolve the controversy.

HYPERINSULINEMIA—IMPLICATIONS FOR THE TREATMENT OF DIABETES MELLITUS AND IGT— With hyperinsulinemia receiving so much attention as a possible etiological factor for atherosclerosis and hypertension, it is natural for attention to turn to the question of iatrogenic hyperinsulinemia resulting from treatment of diabetes both in IDDM and NIDDM patients. For example, does excessive insulin therapy resulting in hyperinsulinemia in IDDM or NIDDM subjects increase risk of ASCVD? This is still a controversial area, with only limited information available. Certainly, there was a close correlation between macrovascular disease prevalence and daily dose of insulin in insulin-treated NIDDM subjects in the Schwabing Study (113). However, in the absence of more information, clinicians would be wise to monitor both sulfonylurea and insulin therapy closely in NIDDM subjects because hyperinsulinemia may result in weight gain and dyslipidemia, thereby increasing the risk of ASCVD. Of the oral hypoglycemic agents in common use, metformin may have an advantage because it may reduce both hyperinsulinemia and insulin resistance (114).

The optimal treatment for an obese NIDDM patient is weight reduction and appropriate exercise. Both of these strategies result in lowering of plasma insulin levels (6,54,108) and increased insulin sensitivity (54), and exercise also reduces other CVD risk factors (108). This remains the best advice we can offer to this group of patients.

On the other hand, insulin therapy often plays a major role in the treatment of NIDDM, and is a lifesaver for the person with IDDM. There continues to be an urgent need to develop more efficient and physiological ways of delivering insulin to minimize periods of hyperinsulinemia in the insulin-treated diabetic (e.g., implantable insulin pumps). The full scientific evidence to implicate hyperinsulinemia as the main causative factor for the Deadly Quartet (4) is not yet available; but, it would be foolish for clinicians to ignore the data that already exist. They do so not only at their risk but even more important, the risk of ASCVD in their patients.

Although the achievement of normoglycemia in subjects with diabetes appears to be the clinician's "Holy Grail," the importance of associated hyperinsulinemia should not be ignored. CVD is common in both IDDM and NIDDM and is a major cause of mortality (74). Diabetic patients, either IDDM or NIDDM, receiving insulin therapy, and possibly even NIDDM subjects on sulfonylureas, are likely to be hyperinsulinemic for a significant part of each day.

As hyperinsulinemia may either cause or exacerbate other CVD risk factors, it would seem prudent to attempt to optimize hypoglycemic therapy, maintaining a delicate balance between achieving normoglycemia and minimizing hyperinsulinemia. In addition, as it is well established that exercise results in a reduction of insulin levels and increased insulin sensitivity (6,54,108), there is a rationale for exercise in the therapy of both IDDM and NIDDM.

There are still only limited data to suggest that hyperinsulinemia resulting from insulin therapy is harmful but the possibility should be born in mind and until evidence is found to the contrary, it is sensible to take a conservative view for the possible benefit of patients. Equally important is the idea that certain therapeutic agents for hypertension (e.g., thiazide diuretics and β-blockers) may exacerbate insulin resistance and dyslipidemia (4,7). It seems logical to consider this when selecting drugs for the treatment of hypertension.

The clinical relevance of the demonstrated improvement in insulin sensitivity in hypertensive diabetic patients after using certain ACE-inhibitor hypotensive agents (7,109) is still an open question. Prospective studies will be very important in determining whether the use of drugs (such as captopril) improve long-term glycemic control and reduce the incidence of adverse outcomes, such as dyslipidemia, obesity, and ASCVD. Again, an open mind is necessary, but the demonstration of a possible mechanism with a beneficial effect (109) suggests a biologically plausible rationale for the use of ACE inhibitors in treating NIDDM subjects with hypertension.

Subjects with IGT also are hyperinsulinemic and have a substantially increased risk for ASCVD compared with individuals with normal glucose tolerance (85). This group should be carefully screened for other CVD risk factors, and should they be present, both weight reduction and exercise are indicated as preventive measures. To what extent such intervention measures reduce the chance of progression to NIDDM still must be determined.

THE NEW DIMENSION—THE ROLE OF THE CNS IN THE DISEASES OF CIVILIZATION— The above discussion on the putative role of hyperinsulinemia in the etiology of a cluster of CVD risk factors leads us to question the underlying mechanism(s) and to form a unifying hypothesis. Is hyperinsulinemia just the overt expression of an underlying CNS disorder, which is attributable to psychosocial mechanisms that result

in neuroendocrine dysfunction? Björntorp has recently addressed this issue and has hypothesized that upper-body obesity results from chronic hypothalamic arousal, which is caused by a defeat reaction to psychosocial pressures (115). He points out that some evidence suggests that visceral fat accumulation may be a somatic sign of chronic hypothalamic arousal in the CRF-ACTH-cortisol axis, along with an inhibition of gonadotrophin secretion. Upper-body obesity, apart from being a risk factor for most of the established risk factors for ASCVD and NIDDM (115), is itself a risk factor for these disorders (2–4). As the endocrine abnormalities associated with upper-body obesity produce hyperinsulinemia and insulin resistance (2–4), the chain of events triggered by psychosocial factors could directly generate the components of the CVD risk factor cluster (i.e., upper-body obesity, hyperinsulinemia, insulin resistance, dyslipidemia, and hypertension) (Fig. 7) and, thus, be implicated in the etiology of NIDDM and ASCVD (115).

Thus, despite the name—the New World Syndrome (2), the Deadly Quartet (4), syndrome X (1), syndrome X plus (2), or the Big Four (116)—these metabolic and morphological risk factors and disease end points are now frequently seen in populations where modernization as a way-of-life has occurred (2,6). This may be the result of the expression of neuroendocrine responses acting on a genetic background that favors the development of these disorders (115).

The thrifty genotype might provide the genetic basis for these disorders (117). If this is so, then the decline in incidence of epidemic glucose intoler-

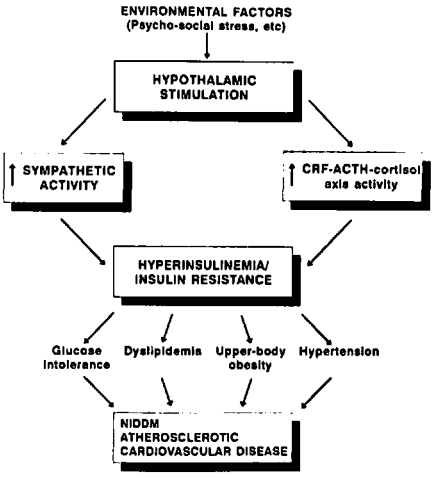

Figure 7—*In this proposed sequence of events, hypothalamic stimulation leads to hyperinsulinemia, insulin resistance, and the risk factors for the so-called diseases of civilization—NIDDM and ASCVD disease. Adapted from Björntorp (115).*

Table 4—***Changes in the incidence and natural history of glucose intolerance in Nauruans between 1975/1976–1982 and 1982–1987 (sexes combined)***

Category and period	Person-yr	Incident cases (*n*)	Crude incidence rate (cases/1,000 person-yr)	Age-standardized incidence rate (cases/1,000 person-yr)	Incidence rate ratio*	95% CI	X^2_1
Normal							
IGT							
1975/1976–1982	876	32	36.5	41.4	0.55	(0.36–0.84)	7.5†
1982–1987	3,299	64	19.4	21.6			
NIDDM							
1975/1976–1982	876	15	17.2	17.1	0.46	(0.24–0.85)	6.0‡
1982–1987	3,299	27	8.2	7.4			
IGT							
NIDDM							
1975/1976–1982	390	22	58.3	35.2	1.23	(0.72–2.10)	0.6
1982–1987	959	58	60.5	56.1			
Normal							
1975/1976–1982	390	23	59.0	69.8	1.28	(0.80–2.04)	1.0
1982–1987	959	77	80.3	88.1			
All							
NIDDM							
1975/1976–1982	1,266	37	29.2	26.2	0.77	(0.52–1.16)	1.5
1982–1987	4,258	85	20.0	22.5			

From Dowse et al. (118).
*Mantel-Haenszel incidence density rate ratio and test-based CI (19).
†$P < 0.05$.
‡$P < 0.01$.

ance (Table 4) that we have reported in the high NIDDM prevalence population of Nauru (118) has important implications for newly industrialized nations with high rates of noncommunicable disease. Prevention programs could lengthen survival of those with the thrifty gene and tend to perpetuate the chronic disease burden. On the other hand, in countries with limited curative medical care and poorly developed prevention programs, the noncommunicable disease problem could recede with time. Thus, a powerful moral dilemma faces public health workers while the molecular biologists and clinical research scientists attempt to understand the role of hyperinsulinemia in the etiology of these noncommunicable diseases.

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