Why Syndrome X? From Harold Himsworth to the Insulin Resistance Syndrome

Historical Perspective

Gerald M. Reaven*

Division of Cardiovascular Medicine, Falk CVRC, Stanford Medical Center, 300 Pasteur Drive, Stanford, California 94305
*Correspondence: greaven@cvmed.stanford.edu

Although the concept of Syndrome X was introduced in the Banting Medal address of 1988 (Reaven, 1988), the notion that led to its genesis had started approximately 50 years earlier. In this short history, an attempt will be made to trace the two paths of scientific discovery that were formally merged in New Orleans in 1988 to form the scientific foundation of Syndrome X. In addition, the developments in the last 16 years that have led from the notion of Syndrome X to the broader concept of an Insulin Resistance Syndrome (IRS) will be briefly summarized.

The two faces of diabetes mellitus

In the spring of 1939, just before the beginning of World War II, Himsworth summarized in the Goulstonion Lectures on the "Mechanism of Diabetes Mellitus" to the Royal College of Physicians of London the results of the work that he and his colleagues had initiated in 1936. The substance of these lectures was later published in *The Lancet* (Himsworth, 1939a, 1939b, 1939c, 1939d) and offered a startlingly modern view of the pathophysiology of diabetes mellitus. Specifically, Himsworth concluded "diabetes mellitus is a disease in which the essential lesion is a diminished ability of the tissue to utilize glucose. The high blood sugar is a controlled and compensatory phenomenon, the object of which is to facilitate the utilization of glucose by the tissues." He went on to question the general belief that "all cases of human diabetes could be explained by deficiency of insulin," and raised the possibility that "a state of diabetes might result from inefficient action of insulin as well as from a lack of insulin."

Based upon the general principles outlined above, Himsworth reviewed the results of a series of simple, but elegant, experiments aimed at understanding why hyperglycemia occurred in patients with diabetes. Summarizing these findings, he proposed "the diminished ability of the tissues to utilize glucose is referable either to a deficiency of insulin or to insensitivity to insulin, although it is possible that both factors may operate simultaneously." Given this distinction, he concluded by pointing out that diabetes should be subdivided into two categories "according to which of these disorders predominates into insulin-sensitive and insulin-insensitive types." Himsworth also differentiated the two types on clinical grounds, pointing out that "insulin-sensitive diabetes, which is thought to be due to a deficiency of insulin, tends to be severe," whereas insulin-insensitive diabetes, "due not to a lack of insulin but to insensitivity of insulin, is generally less severe."

World War II essentially ended Himsworth's experimental studies of the relationship between insulin resistance and diabetes mellitus, but in 1949 he delivered the Oliver-Shappey lectures to the Royal College of Physicians (Himsworth, 1949), concluding that "it appears we should accustom ourselves to the idea that a primary deficiency of insulin is only one, and then not the commonest, cause of the diabetes syndrome." In retrospect, it is difficult to comprehend that the view of diabetes outlined by Himsworth in the Goulstonion Lectures antedated by approximately 40 years the imprimatur given by the National Diabetes Data Group to a remarkably similar division of patients with diabetes mellitus into two major subtypes (National Diabetes Data Group, 1979).

Insulin resistance and type 2 diabetes

To support the suggestion by Himsworth that not all diabetes was secondary to absolute insulin deficiency, it was necessary to establish the fact that circulating insulin was present in those patients classified by Himsworth as being insulin insensitive. In an effort to address this issue, bioassays were developed to estimate plasma insulin-like activity, and results were published indicating that normal, or greater than normal levels of insulin-like activity were present in patients with what was then referred to as maturity-onset diabetes (Bornstein and Lawrence, 1951; Vallance-Owen et al., 1955). However, these methods for estimating plasma insulin concentrations were far from ideal: as experience with the different methods increased, the situation became less clear, and there was continuing controversy as to what actually were the circulating plasma insulin concentrations in patients with diabetes mellitus. This uncertainty ended abruptly with the publication of an immunoassay study of endogenous plasma insulin in man (Yalow and Berson, 1960). In this groundbreaking work, Yalow and Berson described an immunological method for measuring insulin that combined specificity with the degree of sensitivity needed to measure the minute concentrations of insulin present in the circulation. Using this new method to compare plasma immunoreactive insulin levels in normal subjects to those of patients with maturity-onset diabetes, they found that the insulin levels were on the average higher in the diabetic patients. On the basis of these results they concluded "that the tissues of the maturity-onset diabetic do not respond to his insulin as well as the tissues of the nondiabetic subject respond to his insulin." Or, to use Himsworth's terminology, patients with this form of diabetes were "insulin insensitive."

Although the results of the initial publication by Yalow and

Berson were soon confirmed by many other research groups, it became apparent that the relationship between plasma glucose and insulin concentrations in patients with type 2 diabetes was not a simple one, and that plasma insulin responses to oral glucose could not be simply divided into two categories—absent or present. Specifically, in individuals with relatively minor elevations of fasting plasma glucose concentration, plasma insulin responses to oral glucose in absolute terms were equal to or greater than normal, but, with increasing degrees of glucose intolerance, and the appearance of significant fasting hyperglycemia, the plasma insulin response became attenuated, and with severe fasting hyperglycemia, the insulin response was less than in normal control subjects (Buchanan and McKiddie, 1967; Chiles and Tzagournis, 1970; Hales and Randle, 1963; Reaven and Miller, 1968).

Furthermore, the observation that essentially no patients with type 2 diabetes were as insulin deficient as those with type I diabetes was not necessarily translated into the belief that resistance to insulin-mediated glucose disposal was present in patients with type 2 diabetes. Thus, at various times it has been argued that hyperglycemia in patients with type 2 diabetes had nothing to do with insulin resistance but was totally a function of (1) delay in rate of appearance of insulin in plasma; (2) lack of "appropriateness" in the pancreatic β cell response to glucose (the absolute increase in plasma insulin was not high enough given the coexisting plasma glucose concentration); or (3) the preferential secretion of proinsulin (Melani et al., 1970; Perley and Kipnis, 1966; Seltzer et al., 1967). Further confounding the situation was the fact that a variety of different insulinogenic stimuli were used to compare the plasma insulin response of various experimental groups, including oral glucose, intravenous glucose, amino acids, glucagon, sulfonylurea compounds, and mixed meals.

It became apparent that the controversy as to whether or not insulin resistance existed in patients with type 2 diabetes was not going to be solved by philosophical arguments as to the meaning of plasma insulin measurements. Instead, it was necessary to develop an experimental approach that would quantify in an unambiguous manner the ability of an individual to dispose of fixed glucose load under the influence of identical insulin stimuli during steady-state conditions (Shen et al., 1970). This was accomplished by infusing subjects for 180 min with constant amounts of insulin, glucose, epinephrine, and propranolol. Steady-state plasma concentrations of insulin and glucose were achieved within 90 min after the start of the infusion and were measured every 10 min during the final 30 min of the study. This approach was based upon the ability of epinephrine and propranolol to suppress endogenous insulin secretion and inhibit hepatic glucose output. Under these conditions, it was possible to assess the ability of plasma insulin concentrations, similar in terms of both quantity and quality, to promote the disposal of comparable glucose loads in a variety of subjects. With this experimental design, the height of the steady-state plasma glucose concentration (SSPG) is a direct reflection of a subject's overall efficiency of insulin-mediated glucose disposal. Once this approach was validated, it was possible over the next few years to demonstrate that patients with impaired glucose tolerance and type 2 diabetes, as a group, were insulin resistant (Ginsberg et al., 1974, 1975; Shen et al., 1970). Subsequently, similar results were obtained as to the existence of insulin resistance in patients with type 2 diabetes when measurements of insulin-mediated glucose disposal were made with the euglycemic clamp technique (DeFronzo et al., 1979; Kolterman et al., 1981; Reaven, 1983). As a result, a consensus was soon reached, approximately 40 years after the initial studies of Himsworth, that a defect in the ability of insulin to increase tissue utilization of glucose was present in the vast majority of patients with type 2 diabetes (Reaven, 1983).

Cross-sectional studies published shortly after introduction of the radioimmunoassay for insulin were consistent with the hypothesis that patients with type 2 diabetes, as a group, were insulin resistant, and that hyperglycemia supervened in these individuals when the pancreatic β cell was no longer capable of maintaining the degree of compensatory hyperinsulinemia needed to overcome the defect in insulin action (Buchanan and McKiddie, 1967; Chiles and Tzagournis, 1970; Hales and Randle, 1963; Reaven and Miller, 1968). Once it had been established that resistance to insulin-mediated glucose disposal was a characteristic of patients with type 2 diabetes (Reaven, 1983), longitudinal studies were initiated to test the hypothesis that this defect antedated the development of hyperglycemia in individuals at increased risk to develop type 2 diabetes. Evidence in support of this formulation was soon available from the results of prospective studies showing in nondiabetic individuals that hyperinsulinemia, as a surrogate marker for insulin resistance, predicted the development of type 2 diabetes (Haffner et al., 1990; Saad et al., 1989; Sicree et al., 1987). The story initiated by Himsworth was completed with publication of the results of prospective studies showing that the best predictor of the development of type 2 diabetes in nondiabetic individuals was the presence of insulin resistance and hyperinsulinemia at baseline (Lillioja et al., 1993; Warram et al., 1990).

Perhaps the most fitting way to end this section is with the following quote from a brilliant paper by Himsworth and Kerr, published approximately 65 years ago (Himsworth and Kerr, 1939):

> On the whole the insulin-sensitive diabetics tend to be younger, thin, to have a normal blood pressure and healthy arteries; in them the disease is sudden and severe at onset; they easily develop ketosis and react to a slight excess of insulin with a hypoglycaemic attack. The insulin-insensitive diabetics on the other hand tend to be older, obese, to have hypertension and to exhibit arteriosclerosis; in them the onset of the disease is insidious; they rarely develop ketosis and can tolerate over-dosage of insulin without showing symptoms of hypoglycaemia.

Insulin resistance, compensatory hyperinsulinemia, and cardiovascular disease (CVD): Syndrome X

The notion that resistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia could play a role in CVD began with an attempt to formulate a general hypothesis to explain the following four apparently disparate observations.

(1) In the late 1950s, Albrink and Mann demonstrated that hypercholesterolemia was not the only abnormality of lipid metabolism associated with CVD risk, and that hypertriglyceridemia was as common, if not more so, in patients with manifest CVD (Albrink and Mann, 1958a, 1958b).

Table 1. Syndrome X—Increased risk of cardiovascular disease

Insulin resistance
Compensatory hyperinsulinemia
Varying degrees of glucose tolerance
↑ Plasma TG concentration
↓ Plasma HDL cholesterol concentration

(2) At the same time, Ahrens and colleagues demonstrated that hypertriglyceridemia in patients with "essential lipemia" could be divided on the basis of their response to formula diets into two forms: carbohydrate (CHO)-induced and fat-induced lipemia (Ahrens et al., 1961). Furthermore, and contrary to conventional wisdom, they pointed out that the vast majority of hypertriglyceridemic individuals had the CHO-induced variety.

(3) Once the insulin immunoassay was introduced, it became clear that a significant number of individuals with relatively minor degrees of glucose intolerance had significantly elevated plasma insulin concentrations (Yalow and Berson, 1960).

(4) Evidence was published showing that individuals with a documented myocardial infarction, studied several months after the acute coronary event, at a time when they were asymptomatic, were somewhat glucose intolerant and hypertriglyceridemic when compared to an appropriately matched control group (Reaven et al., 1963).

Based upon the four findings outlined above, the following schema was formulated in an attempt to tie them all together. It was argued that resistance to insulin-mediated glucose disposal is frequently present in apparently healthy individuals, but that the majority of insulin-resistant individuals can secrete enough insulin to compensate for their defect in insulin action, thereby preventing frank deterioration of glucose tolerance. Unfortunately, the compensatory hyperinsulinemia in insulin-resistant persons acts on the liver to stimulate very low density lipoprotein triglyceride (VLDL-TG) synthesis and secretion, leading to hypertriglyceridemia and increased CVD risk. The untoward effects of daylong hyperinsulinemia in insulin-resistant/hypertriglyceridemic individuals are accentuated in response to low-fat/high-carbohydrate diets, leading to even further increases in plasma TG concentration.

The necessary first step in evaluating the hypothesis outlined above was to develop an isotopic method to quantify VLDL-TG secretion rate (Farquhar et al., 1965). Once this was accomplished, it was shown that the greater the VLDL-TG secretion rate, the higher the plasma TG concentration (Reaven et al., 1965). The next step was the demonstration that the higher the plasma insulin response to meals, the greater the VLDL-TG secretion rate, and the higher the plasma TG concentration (Reaven et al., 1967). During this period, further evidence was provided in support of the earlier findings of the existence of CHO-induced lipemia (Ahrens et al., 1961), and, more importantly, to demonstrate that the dietary-induced increase in plasma TG concentration was highly correlated with the associated elevation of plasma insulin concentrations that occur in response to low-fat/high-CHO diets (Farquhar et al., 1966). Finally, once the method to quantify insulin-mediated glucose disposal was available, it was shown that the more insulin resistant the individual, the higher was the plasma insulin response to meals, the greater the VLDL-TG secretion rate, and the more elevated the plasma TG concentration (Olefsky et al., 1974).

Table 1 lists the components of Syndrome X as defined in 1988, and it can be seen that the major elements had been shown to exist by 1974. The importance of a low high-density lipoprotein cholesterol (HDL-C) concentration as a CVD risk factor, and the frequency with which it was associated with an elevated TG concentration, became clear over the next few years (Castelli et al., 1986; Miller and Miller, 1975; Reaven, 1988).

The possibility that essential hypertension was also related to insulin resistance/compensatory hyperinsulinemia should have been appreciated following the report that 19 individuals with essential hypertension had significantly higher plasma insulin concentrations than a control population (Welborn et al., 1966). However, approximately 20 years elapsed before there was confirmation of the initial observation that hyperinsulinemia was present in patients with essential hypertension (Lucas et al., 1985; Modan et al., 1985). Given these findings, and the earlier demonstration that glucose intolerance occurred with greater frequency in patients with essential hypertension (Jarret et al., 1978), it was not surprising that evidence was soon published showing that the prevalence of resistance to insulin-mediated glucose uptake was also increased in patients with this clinical syndrome (Ferrannini et al., 1987; Shen et al., 1988). The fact that patients with essential hypertension, as a group, were insulin resistant, hyperinsulinemic, and somewhat glucose intolerant not only suggested that essential hypertension be added to the abnormalities listed in Table 1 but also provided further support for the notion that all of these changes were likely to cluster within the same individual. Direct evidence in support of the concept of Syndrome X was soon provided by the results of a population-based study, in which apparently healthy individuals were stratified into hyperinsulinemic and normoinsulinemic groups (as surrogate measures of insulin resistance and insulin sensitivity), showing that the hyperinsulinemic (insulin-resistant) individuals were somewhat glucose intolerant, with mildly elevated blood pressure, and had higher plasma TG and lower HDL-C concentrations (Zavaroni et al., 1989).

From Syndrome X to the Insulin Resistance Syndrome

By 1988, there was widespread recognition that (1) being insulin resistant increased the risk of developing type 2 diabetes; (2) most patients with type 2 diabetes were insulin resistant; and (3) type 2 diabetes occurred when insulin-resistant individuals could not maintain the degree of hyperinsulinemia necessary to maintain normal glucose tolerance. The fact that most insulin-resistant individuals continued to sustain the degree of compensatory hyperinsulinemia needed to prevent gross decompensation of glucose tolerance, and were thereby at increased CVD risk, was not well appreciated and is why the concept of Syndrome X as shown in Table 1 was introduced.

There were two reasons for designating the abnormalities listed in Table 1 as Syndrome X. In the first place, it was based on the use of the algebraic term for the unknown (let X equal the unknown) to emphasize that the importance of insulin resistance and its associated abnormalities as CVD risk factors was largely unrecognized. Secondly, in order to draw attention to the CVD risk factors associated with insulin resistance/hyperinsulinemia, and avoid distractions concerning the pathogenesis of each of the components seen in Table 1, it seemed best to use a nonspecific descriptor term. However, since the introduction of Syndrome X, considerable new information has

Table 2. The Insulin Resistance Syndrome

Metabolic abnormalities associated with insulin resistance/hyperinsulinemia
Some degree of glucose intolerance
Impaired fasting glucose
Impaired glucose tolerance
Dyslipidemia
↑ Triglycerides
↓ HDL-C
↓ LDL-particle diameter (small, dense LDL-particles)
↑ Postprandial accumulation of TG-rich lipoproteins
Endothelial dysfunction
↑ Mononuclear cell adhesion
↑ Plasma concentration of cellular adhesion molecules
↑ Plasma concentration of asymmetric dimethylarginine
↓ Endothelial-dependent vasodilatation
Procoagulant factors
↑ Plasminogen activator inhibitor-1
↑ Fibrinogen
Hemodynamic changes
↑ Sympathetic nervous system activity
↑ Renal sodium retention
Markers of inflammation
↑ C-reactive protein, WBC, etc.
Abnormal uric acid metabolism
↑ Plasma uric acid concentration
↓ Renal uric acid clearance
Increased testosterone secretion (ovary)
Sleep disordered breathing
Clinical manifestations of insulin resistance
Type 2 diabetes
Essential hypertension
Cardiovascular disease
Polycystic ovary syndrome
Nonalcoholic fatty liver disease
Certain forms of cancer
Sleep apnea

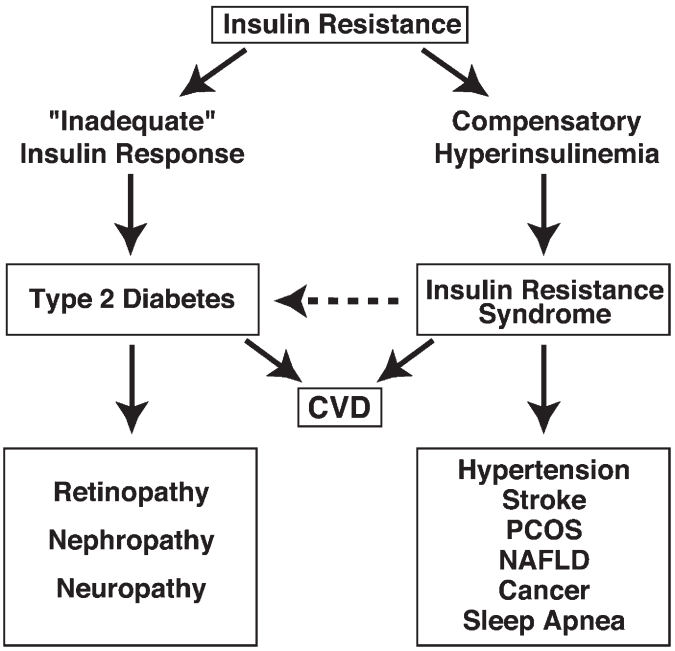

Figure 1. A schematic description of the clinical syndromes that occur more commonly in association with insulin resistance (current clinical manifestations of the Insulin resistance Syndrome)

Insulin resistance is depicted as leading to type 2 diabetes, as well as a number of other syndromes, associated with the defect in insulin action, in which the magnitude of the compensatory hyperinsulinemia prevents loss of glucose homeostasis. It should be noted that while being insulin resistant may lead to type 2 diabetes, the microangiopathic complications only occur when frank hyperglycemia is present. The Insulin Resistance Syndrome is used to provide a physiological framework with which to help understand the link between insulin resistance/compensatory hyperinsulinemia and the abnormalities and clinical syndromes listed in Table 2.

PCOS = polycystic ovary syndrome; NAFLD = nonalcoholic fatty liver disease; CVD = cardiovascular disease.

evolved relevant to the role of insulin resistance in human disease. These findings, in addition to solidifying the role of insulin resistance as increasing CVD risk, have greatly expanded the abnormalities and clinical syndromes more likely to occur in insulin-resistant individuals, as shown in Table 2. It is not possible to review the experimental data that supports the information in Table 2, but a detailed discussion of these issues can be found in a recently published review (Reaven, 2004). As a result of all the information now available, the relatively simple formulation shown in Table 1 is no longer appropriate, and the modification illustrated in Figure 1 is a more accurate depiction of the current situation. Finally, as a consequence of the experimental findings since the introduction of Syndrome X, it seems reasonable that this term be replaced with the notion of the Insulin Resistance Syndrome (IRS), a pathophysiological construct under which the abnormalities and clinical syndromes more likely to occur in insulin-resistant/hyperinsulinemic individuals that do not develop type 2 diabetes can be appropriately subsumed.

It must be emphasized that insulin resistance is not a disease but rather a description of a physiological state. An insulin-resistant individual has a greater likelihood of developing the closely related abnormalities and associated clinical syndromes shown in Table 2. The IRS is a designation to describe the abnormalities and clinical syndromes more likely to occur in association with insulin resistance. It must be clearly understood that any individual component of the IRS can occur in the absence of insulin resistance, and being insulin resistant does not *necessarily* lead to any of the manifestations of the IRS. Of great importance is the fact that not all tissues in any given individual are equally insulin resistant, and many of the manifestations of the IRS are secondary to the compensatory hyperinsulinemia acting on normally insulin-sensitive tissues.

Conclusion

Approximately 65 years have elapsed since Himsworth first proposed that patients with diabetes mellitus could be divided into two categories—insulin sensitive and insulin insensitive. His focus was on the role of insulin insensitivity in the pathogenesis of hyperglycemia, and it is now clear that this was simply the first of what is an ever-growing list of clinical syndromes associated with insulin resistance. Given that insulin action varies more than 6-fold in apparently healthy individuals (Yeni-Komshian et al., 2000), and that differences in level of adiposity (25%) and physical fitness (25%) account for approximately 50% of this variability (Bogardus et al., 1985), it should be obvious that as the world becomes more obese, and less active,

the problems associated with the IRS are the plague of the 21st century.

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