The definition of diabetes mellitus that is found in our textbooks and in the opening statements of our medical communications is usually, “Diabetes is a chronic metabolic disease characterized by high blood sugars with long-term complications.” Is this a reasonable description of this seemingly epidemic problem?

The diagnostic criteria for both Insulin Deficient Diabetes (Type 1) and Insulin-Resistant Diabetes (Type 2) are an elevated fasting blood sugars above 126 mg% (7mmol), an abnormal glucose tolerance test with an elevated blood glucose at two hours over 200 mg% (11.1mmol), an elevated hemoglobin Alc over 6.5% or random blood sugars over 200 mg%. It is recommended that these abnormalities be shown at least twice before the diagnosis of diabetes is made.

In this day of rather significant scientific advances and with medical therapies which seem to defy Mother Nature and cure diseases right and left, these simple diagnostic criteria seem absurd to some of us—especially, since the disease has obviously been present for a long time before we are able to collect the hyperglycemic ‘diagnostic’ numbers.

Most of us realize that the criteria for the blood glucose levels now used for diagnosis were postulated by clinicians who were observing the end results of chronic hyperglycemia. The ophthalmologists were foremost in relating the apparent effects of long-term hyperglycemia to ‘diagnostic levels of glucose.’ Diabetic retinopathy was the benchmark on which we rested the validity of our diagnostic glucose criteria. This is history and is not of scientific interest to us today.

What is of interest is that there seems to be an epidemic of insulin resistant diabetes mellitus Type 2 (DM2) with attendant complications and co-morbidities, which is overwhelming the ability of our medical system to provide appropriate service. It is important that we treat and defeat DM2. This might be done more effectively by starting our therapies before the disease is overtly manifest by hyperglycemia.

So, maybe the diagnostic criteria need tweaking. It is known that diabetes is a genetically modulated disease. The initiating causes of clinical hyperglycemia DM2 are in part: 1. genetic abnormalities, 2. aging, 3. stressful situations, and 4. excessive obesity.

There are other factors that are contributory to the progression of the condition; but, like so many other diseases, the main cause should be uncovered, displayed and explained. It would appear to many of us that the underlying and main pathophysiological cause of diabetes is genetic aberrations. We read of many genes that seem to be connected with hyperglycemia – adiponectin 3q27, insulin gene, HNF-1a, PPARG gene, TCF7L2, melanocortin gene, apoprotein L1, TCF7L2, IRS1, G6PC2,etc.

Several years ago, a geneticist told me, “Dick, there are over 100 genes that seem to be associated with hyperglycemia. Most of us think it takes four or five to cause persistent hyperglycemia that we can call diabetes.” The Finnish report in Diabetes, 2011, studied 24 gene loci and found that different combinations seemed to cause various diabetic complications. This would detract from our simple suggestion that chronic hyperglycemia or glucotoxicity (>170mg%) cause the complications of DM2. It may well be that specific genetic loci determine which ill effects a patient will develop, and that many combinations of the ‘facilitating’ genes cause the diagnostic characteristic of hyperglycemia.

I suppose the point of this ramble is to suggest that if we are really interested in controlling DM2 and inlimiting the long term complications, we should look to our genetic data and try to develop a methodology to identify highest-risk patients early. Perhaps identifying the hundred most implicated genes would provide enough of a basis to develop an algorithm to diagnose occult diabetes—eg. five of 100 selected causative genes in anyone’s genome would be ‘diagnostic’ of impending diabetes. If that were the case, we have at our disposal drugs that should delay the overt symptoms and perhaps complications of diabetes for years.

Instead of beginning the DM2 patient, who already has advanced— diagnostic— hyperglycemia, on metformin, which merely inhibits the genetically induced excessive production of glucose from a mal-regulated liver; we might treat with a Thiazolidinedione TZD PPAR-gamma enhancing medicine. This would improve the sensitivity of endogenous insulin and prevent the hyperinsulinemia, abnormal glucagon feedback and beta cell dysfunction that seem to be the hallmarks of early DM2. Likewise, GLP-1 medications could be used earlier to enhance the pancreatic production of insulin and critical regulatory hormones and probably delay overt diabetic symptomatology—with the added advantage of satiety and weight loss. A very early diagnosis—before overt signs and metabolic abnormalities—might lead to new drugs or to gene-altering techniques that would negate the development of DM2.

Continued on page 6
The longer the overt symptoms and signs of the disease are delayed, one would suppose, the less the complications and the less impact the disease would have on our society. We would still have to periodically measure the blood sugar—or some critical marker hormone, insulin, c-peptide or A1C—to evaluate our therapies. But, by controlling the basic underlying pathophysiologic mechanisms very early in the disease and by preventing the development of hyperglycemia (now necessary to make the diagnosis and start therapy,) we should be better able to control the development of complications.

A few years from now the diagnosis of DM2 may not be dependent upon blood sugars and A1C but, rather, upon a single drop of blood taken from an infant’s foot and tested for the critical genes that are associated with the disease.

Obviously it is a multifaceted problem, and there must be hundreds of different combinations of genetic material that result in the condition we call diabetes mellitus. In this day of computers, electronic medical records and data overload, it seems to me that a concentrated push by our genome-studying geneticists would be most welcome.

Of course, we would probably find that our society has a 50% or higher chance of developing hyperglycemia and some subtype of diabetes on a genetic basis — unfortunately, this is a fact we are already experiencing when we study that segment of our society which is being overfed.

There are, however, very obese persons who do not develop hyperglycemia, hyperinsulinemia and the overt co-abnormalities associated with DM2. Their genotype and distribution of diabetic causing genes must be interesting — another area for study by our geneticists and genome studying colleagues.

In the meantime, we can at least try to educate ourselves and our patients to the advantages of weight control, exercise and earlier utilization of those drugs that can reverse the hormonal abnormalities causing the disease.

It may be that the cost to our system would be overwhelming, and that onerous controls would be developed for who could receive therapy—maybe it is still too soon to really know what causes and what might prevent such a pervasive disease. But, what would our world be with less DM2?

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**CDC recommendation:**

**Test everyone born from 1945-1965 for Hepatitis C**

People born from 1945-1965 account for 3 out of every 4 people with Hepatitis C, and more are unaware of their infection.

- Testing only patients with elevated ALT’s may miss 50% of infection
- Hepatitis C is a leading cause of liver cancer and liver transplants
- Care and treatment can help prevent Hepatitis C-related disease and deaths

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*Texas Department of State Health Services*