Both the National Diabetes Data Group (NDDG) and the World Health Organization (WHO) have included in their classification schemes for diabetes an entity labeled “impaired glucose tolerance” (IGT). The presumed significance of this entity is twofold: first, it is commonly believed that IGT represents a transitional state between normality and diabetes; and second, IGT is also believed to be a risk factor for cardiovascular disease, either in its own right, or as a consequence of its presumed precursor relationship to diabetes. These relationships will be critically examined in this editorial. Our thesis is that IGT is not a homogeneous category, but consists of at least three entities which, although conceptually distinct, cannot be distinguished by glucose tolerance testing alone. The arguments in defense of this viewpoint rest heavily on the concept that plasma glucose concentrations are biomodally distributed in populations. Therefore, the evidence for bimodality will be briefly reviewed.

Bimodality of plasma glucose distributions has now been reported in several populations, most of which are of New World or Pacific Island origin. In addition to having a high prevalence of diabetes, these populations are relatively isolated genetically. While the high prevalence of diabetes facilitates detection of the second (hyperglycemic) mode, the highly selected nature of these populations raises the possibility that bimodality is somehow unique to them. We have recently reported bimodality in San Antonio Mexican Americans, a population which, although it contains substantial New World genetic admixture, is nevertheless more than 50% Caucasian. Moreover, Mexican Americans are a much larger and genetically less isolated population than those in which bimodality has previously been reported, since they live side-by-side with other ethnic groups and thereby have greater opportunities for intermarriage. It could still be argued that bimodality in Mexican Americans is somehow a consequence of their New World genes. We feel, however, that our findings do tend to move the bimodality argument in the direction of greater generalizability to include populations such as Caucasians and blacks. Bimodality in these populations would, if present, be difficult to detect because of the much lower prevalence of diabetes and the second mode. Apart from the data, which are admittedly still incomplete, bimodality is theoretically appealing, since it fits with the clinicians’ view that diabetes is a discrete clinical entity and not merely the right-hand tail of a continuous distribution of glucose values.

Assuming the reader is willing to accept the concept of bimodality as a general phenomenon, we will now explore the implications of this phenomenon as they relate to IGT. From Figure 1 it is clear that the IGT category contains many individ-
A theoretical representation of the relationship of impaired glucose tolerance (IGT) to bimodally distributed plasma glucose concentration.

Figure 1.

Cut off Point for Diabetes

Plasma Glucose Concentration

uals who are, in fact, normal although their glucose tolerance happens to fall in the upper portion of the normal range. We will refer to these individuals as "IGT normals."

A second group in the IGT category consists of genuine diabetics who have "false-negative" glucose tolerance values, i.e., they already have diabetes even though their glucose tolerance values do not exceed the currently accepted NDDG or WHO cutoff points. Because of the overlap between the normal and abnormal range — a familiar phenomenon to clinicians — there will always be a small percentage of genuine diabetics of this type. We will refer to these individuals as "false-negative (FN) diabetics." In general, these FN diabetics will be outnumbered by the IGT normals.

The final group in the IGT category consists of individuals who are truly in transition from normal to diabetic, a group we will refer to as "IGTs in transition." For reasons to be discussed below, we postulate that at any given point in time (i.e., cross-sectionally) only a minority of IGT subjects are of this third type, although in a longitudinal study the cumulative percentage of individuals who pass through this stage could be much larger. It is important to emphasize that at present it is impossible to distinguish between these three types of IGT subjects on the basis of their glucose tolerance values. Such a differentiation will, in all probability, have to await the development of a definitive marker for the prediabetic state.

It has often been noted that less than half of IGT subjects progress on to so-called "clinical diabetes." This is precisely what would be predicted on the basis of the statistical principle known as "regression to the mean." This principle states that, because of an inevitable degree of error in any measurement, individuals selected from one or the other extreme of a distribution will, on repeat measurement, tend to lie closer (i.e., regress) to their overall population mean. Regression to the mean explains why abnormal laboratory tests are so often normal when repeated, a phenomenon quite familiar to most clinicians. Since IGT normals are in the upper portion of the normal range, they will, on repeat measurement, tend to have lower plasma glucose values, i.e., values closer to the mean of the normal population. By contrast, since FN diabetics are in the lower portion of the diabetic range, these individuals will, on repeat measurement, tend to have higher plasma glucose values, i.e., values closer to the mean of the diabetic population. In addition, these latter individuals may also undergo genuine disease progression, which would increase their plasma glucose values still further.

A theoretical, but not much discussed, implication of bimodality is that the transitional state between normal and diabetic is relatively short-lived. If this were not the case, IGTs in transition would tend to accumulate in the population, thereby obscuring the nadir between the normal and the diabetic mode. Thus, bimodality implies that diabetes is not the result of a slow, gradual deterioration of glucose tolerance. This point is of more than merely theoretical interest, since the speed of decompensation to diabetes may have important implications with respect to pathogenetic

*Even though we believe that the majority of IGT subjects are in fact normal, we will continue to use the term IGT. However, we will interpret it to mean "indeterminate" rather than "impaired" glucose tolerance to reflect the fact that, for a given individual in the IGT range, we can not distinguish by present means if he is an IGT normal or a FN diabetic.
mechanisms. In theory, the dynamics of the conversion process could be studied empirically by giving IGT subjects frequent glucose tolerance tests (perhaps every 6 months) to see if those who convert do so slowly or rapidly. The results of such a study might not be entirely clear-cut, however, since IGTs in transition (who may convert rapidly) could not be readily distinguished from FN diabetics (who may progress slowly). Most follow-up studies of IGT have reported only cumulative decompensation rates.10-12 Knowler et al.14 however, have studied progression to diabetes at 2-year intervals in Pima Indians. Their data suggest that decompensation occurs relatively rapidly, i.e., over a 2-year period or less.

An important question is whether the increased cardiovascular risk associated with overall IGT is solely attributable to increased risk among FN diabetics and IGTs in transition. Conceivably, IGT normals might have no increased cardiovascular risk whatsoever. This is a question that could be answered empirically. All that is necessary is to ascertain whether those IGT subjects who subsequently develop cardiovascular disease do so only after having first converted from “test-negative” to “test-positive” diabetics. In fact, it is possible that this question could be answered by a re-analysis of the existing data bases from large, prospective epidemiologic studies of cardiovascular disease in which subjects, having been characterized initially at baseline, were subsequently given periodic glucose tolerance tests until cardiovascular disease occurred.

Recently, Jarrett15 has called attention to the similarity in cardiovascular risk between IGTs and diabetics. Based on these and related findings, he has argued that diabetes is not itself a cause of cardiovascular disease, but rather that atherosclerosis and diabetes share a number of common antecedents. In any case, it is still possible that the IGTs who later develop cardiovascular disease are drawn principally, or even exclusively, from the FN diabetics and IGTs in transition and not from the IGT normals.

A major problem in defining IGT is the lack of concordance between the NDDG and the WHO criteria for this entity.1,2 The upper limit presents little problem, since the NDDG and WHO cut-points for diabetes are identical. It is in defining the lower limit that the two sets of criteria diverge. (The uncertainty about the lower limit is indicated in Figure 1 by the wavy left-hand border for IGT.) Because of the disparity between the two definitions, the prevalence of IGT measured in a population varies markedly depending on whether the NDDG or the WHO criteria are used.16,17 This is an unfortunate situation and should no doubt be rectified, but it should be realized that any resolution will inevitably be arbitrary and not well-grounded in theory. This is because the bimodal glucose distribution provides a theoretical basis for choosing an upper limit for IGT, but it provides no similarly compelling basis for choosing a lower limit.

What practical implications flow from these theoretical considerations? First, the clinician should recognize that IGT is not a homogeneous entity: the patient with IGT could have one of three distinct conditions which cannot be readily differentiated. The clinician should communicate to the patient that: 1) the test result was inconclusive; 2) the patient is probably normal but may be developing diabetes or already have it in a mild form (Figure 1 shows that, except when diabetes is highly prevalent in the population, most subjects in the IGT range are normal, albeit in the upper portion of the normal range); and 3) follow-up with periodic glucose tolerance tests is indicated until the situation is clarified. The traditional advice to maintain ideal weight, to get more exercise, and, for that matter, to quit smoking if the patient is a smoker and to eat less cholesterol and saturated fat seems reasonable, since these are health maintenance measures that most preventive medicine authorities subscribe to.

Certain areas for research are also suggested. Specifically, the dynamics of the conversion process from normal to diabetic should be studied. If, as we postulate, the conversion process is relatively rapid and if patients could be “captured” in the midst of this process, it would obviously be of interest to identify any changing patterns of insulin secretion and insulin resistance that might occur coincident with the transition from normal to diabetic. It would also be of interest to determine if the increased cardiovascular risk among IGT subjects is confined to IGTs in transition and FN diabetics, or whether IGT normals also experience an increased risk of cardiovascular disease,
References

15. Jarrett RJ. Type 2 (non-insulin-dependent) diabetes mellitus and coronary heart disease — chicken, egg or neither? Diabetologia 1984;26:99–102

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