SUMMARY - Two definitions of normality (“isolated” or “correlated”) are considered. The boundaries of “isolated” normality were determined by a statistical procedure, whereas the “correlated” approach was related to a clinical or predictive definition. In the latter case, the biological variations were considered abnormal if they implied a hazard with some significant future ailment as a risk factor. In this pragmatic approach, the upper limit of normal/abnormal variations is the point beyond which medical strategy is related to the most expected benefit when applied to a definite population or to an individual patient. The capacity of a diagnostic test to discriminate between patients with a defined risk and those without risk depends strictly on the value of the parameter chosen. In medical care for the prevention of vascular complications in diabetic patients or with foetal risks in pregnant women, the limits of the so-called normal range of glycaemia and other parameters should be determined according to the objective of the preventive and/or therapeutic measures to be prescribed. Diabetes & Metabolism 1998, 24, 60-66.

RÉSUMÉ - Les limites normales de la glycémie - Quel but clinique ? Deux définitions de la normalité peuvent être utilisées. Selon la définition « autonome », les limites de la normalité ne reposent que sur des données et calculs statistiques. À l’inverse, selon la définition « corrélée », la définition de l’étendue des valeurs normales est liée à des arguments cliniques prédictifs : les valeurs retenues comme anormales sont celles qui sont liées à la probabilité significative d’un risque clinique, une évolution défavorable ou une complication définie. Dans une telle définition pragmatique, les bornes des variations dites normales, sont celles au-delà desquelles la décision d’une intervention médicale, appliquée à une population ou à un sujet déterminé, peut se justifier par la probabilité d’un bénéfice supérieur aux risques courus. La capacité d’un test diagnostique pour identifier au sein d’un groupe de patients, ceux qui courent un risque défini – son pouvoir discriminant – est directement liée à la valeur qui, sur un paramètre choisi comme séparateur, a été choisie comme point de partage. Au cours de la surveillance et du traitement des sujets atteints de diabète sucré, à la recherche des risques vasculaires, et dans le traitement des risques fœtaux au cours de la grossesse, les bornes des valeurs dites normales de la glycémie et autres paramètres doivent être établies et justifiées en fonction du but spécifique poursuivi, de dépistage, de prévention ou de traitement. Diabetes & Metabolism 1998, 24, 60-66.

Key-words : normality, medical decision, diabetes mellitus.

Mots-clés : normalité, décision médicale, diabète.
“Could God make a better world than ours?
To answer the question, firstly we have to know what we mean by “world”; secondly what we mean by “better”; thirdly, we shall have to answer the question” (William of Ockham 1290-1349).

Diabetes mellitus is the first disease identified in relation to the disturbance of a main component of the “milieu intérieur” (internal environment), as formulated by Claude Bernard (1813-1878). Diabetes is related to a prolonged “excessive” concentration of plasma glucose. The question remains as to the variations which must be considered as “excessive”, and the values that are in the suitable normal range. In other words, what are the limits of the healthy or normal range beyond which the disease state prevails?

The ranges of normal and abnormal are the pillars of medical decision-making, and the practitioner’s understanding of variations is fundamental to the practice of medicine. However, the range suggested for measurement of a specific medical condition is often unsuitable for the stated goals, and the basic concept of normality is ambiguously or inconsistently applied.

Two definitions of normality – “isolated” or “correlated” – will be considered here. For the “isolated” form the range of normality constitutes a zone representing the average or conventional values found in the spectrum. The boundaries can be usefully defined by a purely statistical procedure based on a particular mathematical principle chosen for this purpose. In the “correlated” approach, the idea of normality is associated with an ideal or medical characteristic of health. According to a clinical or predictive definition, biological variations can be regarded as abnormal when they are associated with clinical phenomena or imply the hazard of some future ailment as a risk factor. Rather than involving an intellectual decision about a predictive diagnosis, a distinct correlated approach depends on justifying a medical decision about a definite treatment or other act. In the context of such a pragmatic approach, the upper limit of normal/abnormal variations is the optimal point beyond which the medical decision may be considered as that associated with the greatest net expected benefit (providing more good than harm) when applied to a definite population or to an individual patient. Correlated normality is the suitable method for making decisions about normal or abnormal conditions since it leads to active decisions about prevention and treatment rather than intellectual decisions about diagnosis.

Despite an appealing medical sensitivity, correlated approaches for decision boundaries are often difficult to use in an era of continuously improving knowledge and technology. To maintain appropriate limits, normal/abnormal values need to be altered according to new epidemiologic knowledge and therapeutic progress. Together with different predicted risks and expected benefits, boundaries cannot be demarcated alone. Decision boundaries of anormality/abnormality are substantially dependent on the complications to be predicted and prevented. Moreover, they are related to the concomitant data that may or should be considered simultaneously.

For all of these good and bad reasons, normality ranges are usually (and more easily) defined by an isolated demarcated zone that serves as a type of screening test. Values that fall inside the zone are accepted as normal, and those outside the zone are brought to the clinician’s attention and appraised accordingly, sometimes together with the additional correlated information mentioned above.

### Statistical Boundaries of the Normal Blood Glucose Range

There is no standard answer to the question as to what proportion of the variations in glucose plasma concentration should be regarded as normal, and what proportion of high values as abnormal. The usual statistical strategy considers as common, and hence normal, 95% of the inner values of the measurements in so-called normal subjects; the remaining 5% are regarded as significantly abnormal. Clinicians have become conditioned to accept the same magical boundary marker of 95% for normality. Besides, the investigator must choose whether the 5% abnormal values lie at both ends or one end of the frequency distribution. In diagnostic considerations of diabetes, in which only high values are to be searched for, it is rational to leave all of the abnormal 5% in the upper end of the distribution curve. Accordingly, the rational boundary of normal/abnormal values may be the 95th centile of frequency distribution. For a screening policy concerning diagnosis of impaired glucose tolerance among a population of asymptomatic male subjects 40 to 64 years old, the defined diagnostic threshold ($\geq 96$ mg/l; 5.4 mmol/l) was found to be the 95th centile of the distribution of blood glucose concentration 2 h after an oral glucose load.

Like most biological components of the “milieu intérieur”, the frequency distribution of plasma glucose concentration in individual subjects, as in populations, is not symmetrical on both sides of the curve. Being “positively” skewed on the right side along with high glucose concentration values. This asymmetrical distribution of plasma glucose concentration, expressed in mg/dl or mmol/l, precludes direct use of the Gaussian model, unless the data are mathematically transformed into logarithms of the measured concentration values. This logarithmic transformation...
implies that the data must be subsequently back-transformed into the original scale. Such a procedure is cumbersome and unfamiliar to practitioners reluctant to use such complex computations. Thus, even though inappropriate, Gaussian parameters are currently applied to glucose concentrations expressed in mg/100 ml or mmol/l. In such a parametric distribution, the 95th centile is given by a 1.64 standard deviation (SD) above the mean value (m ± 1.64 SD). Clinicians have retained two zones for the decision about diagnosis, but, despite such a clinical inconsistency, there are actually three zones for decisions about normality: a central zone, called “normal”, between two boundaries on both sides of the mean value ± 1.96 SD; and two symmetrical zones of abnormal values beyond these statistical limits. Needless to say, these statistical standards of normality are inconsistent with requirements for arguable decision-making, either with diagnostic approaches or therapeutic procedures.

**BOUNDARIES OF NORMALITY/ABNORMALITY RELATED TO PREDICTED RISKS**

The vascular complications of non-insulin-dependent diabetes mellitus (NIDDM) in developed countries present a public health problem greater than that of any infectious disease. Most of these complications may be prevented by early diagnosis of diabetes and prolonged medical surveillance and care. However, half the patients who develop cardiovascular complications do so before their NIDDM is diagnosed [4]. In order to afford early prevention and care for such complications, many attempts have been made to refine both the diagnostic tests and the criteria of asymptomatic NIDDM and the prediabetic state [5-7].

The capacity of the diagnostic procedure depends on two factors: Firstly, the frequency distribution of the adverse event at a defined time in relation to the varying values of the diagnostic parameter. The main adverse outcomes are related to the incidence of a cardiovascular disease (CVD) and to such microvascular complications as retinopathy and nephropathy. A second factor is the discriminant power of the test, i.e. the capacity of test results to separate the subjects who have a significant risk or probability of a definite complication from those with no or low probability of such a complication.

Three parameters are commonly used to define diabetic mellitus and prediabetic states: fasting plasma glucose concentration, 2-h glucose concentration after an oral load of 75 g glucose (50-100 g), and the percentage of glycated hemoglobin (HbA1c %). The intrinsic qualities of diagnostic tests, i.e. sensitivity and specificity, are strictly related to the value of the cutoff point which defines “negative” or “positive” results for the values of the parameter, respectively lower or higher than the cutoff value. The discriminant capacity of a test result is directly expressed by its likelihood ratio (LR). The LR of a definite result (T + or T –) is the ratio of the probability of that result among patients at risk (M), i.e. those who have or will develop the defined complication, in relation to the probability of the same result among subjects not at risk (non-M), i.e. the patients who will not develop that complication during the study period.

The LR of the positive result is LR(+) or

\[ L_+ = \frac{P(T + | M)}{P(T + | \text{non} M)} = \frac{\text{Sensitivity}}{1 – \text{Specificity}} \]

The LR of the negative result is LR(–) or

\[ L_- = \frac{P(T – | M)}{P(T – | \text{non} M)} = \frac{1 – \text{Sensitivity}}{\text{Specificity}} \]

The informative value of each result is expressed by the natural logarithm ln (actually 100*ln) of its respective LR [8-10]. Considering that, among (M) searched patients, every imperfect diagnostic test may give either a true-positive or a false-negative result, the total expected informative capacity (EIC) of such a test to identify a disease or risk (M) is the sum of the logarithms of the two LR weighted by the respective frequencies of these two results among (M) patients:

\[ \text{EIC} = 100*\ln(LR +)*P(T + | M) + 100*\ln(LR –)*P(T – | M) = 100*\ln(L)^*\text{Se} + 100*\ln(\lambda)^*(1 – \text{Se}). \]

For example, the informative capacities of the results of three tests to predict the prevalence of retinopathy at the end of a five-year period are reported in Table I [after 5].

The data reported in Table I show that, among all the test results, the highest informative value is given by the “positive” result (≥ 6.8 mmol/l) of fasting plasma glucose concentration: 100*ln(L) = 172. The same test affords the greatest “expected total informative capacity” (86.2 conventional units) to predict the risk of retinopathy at the end of 5 years.

Sensitivity and specificity are conditional probabilities depending on the cutoff point, i.e. the value that dichotomises the continuous variations of the parameter, so that values ≥ cutoff point are said to be “positive” results and the others “negative” ones. The informative capacity of the test is strictly conditioned by the cutoff point, i.e. the glucose concentration which is considered to be the upper limit of the normal range.

Let us look at the 2 × 2 table illustrating the effects of sensitivity and specificity variations when the cutoff point is moved toward higher or lower values of the parameter (Fig. 1): moving the cutoff point toward more pathologic values reduces both the true-positive rate (sensitivity) and the false-positive rate (1 – specificity). Conversely, lowering the cutoff value reduces
the true-negative rate (specificity) and the false-negative rate (1 – sensitivity). The choice of the optimal cutoff value, i.e. the upper limit of the suitable normal range, is conditioned by the relative clinical effects of the two diagnostic errors, respectively the first-order alpha (α) error expressed by the false-positive rate b/n2, and the second-order beta (β) error expressed by the false-negative rate c/n1. The overall discriminant capacity of a diagnostic parameter and the value which is the most informative cutoff point are illustrated by a receiver operating characteristic (ROC) curve [10]. ROC curve analysis has shown that the three parameters have a better discriminant ability to predict retinopathy than nephropathy [5].

The prevalence of the positive result P(T +) is a linear function of the prevalence "p" of the disease M in the studied population. The slope of the straight line [Se – (1 – Sp)] is the algebraic difference between the two positive rates of the diagnostic test, respectively the true-positive rate Se = (1 – α) and the false-positive rate α = (1 – Sp). The vertical intercept is equal to the false-positive rate. The linear function of P(T +) relative to the prevalence P(M) = p of the disease is illustrated by Figure 2 for a diagnostic test with a sensitivity Se or true-positive rate = 0.90, a specificity Sp = 0.80, and a false-positive rate α = (1 – Sp) = 0.20. The function is compared with the “identity line”, i.e. the function of a supposed perfect diagnostic test in which the probability of the positive result P(T +) is equal to the true prevalence of the searched disease.

Figure 2 shows that the quality of the diagnostic estimation is related to the true prevalence rate of the disease in the studied population, or to the respective risk for an individual patient. The function of the imperfect test crosses the “identity line” at a point A corresponding to the prevalence p* of the disease. The diagnostic test overestimates the prevalence of the disease to the extent that true prevalence is lower than p*, and understates it when p > p*.

For a given sensitivity, decreasing the false-positive rate reduces the intercept and increases the slope of the line, thus creating a lower crossover point at which the estimated rate of the searched disease understates the true rate. For a given specificity and a false-positive rate, a rise in the true-positive rate increases the slope of the line and also lowers the crossover point [12].

The 2 x 2 table shows that the prevalence of the positive result of an imperfect diagnostic test in the studied population is

\[ P(T +) = \frac{f_1}{N} = P(a) + P(b) = P(M)*P(T + \text{ si } M) + P(\text{non } M)*P(T + \text{ si non } M) = p*Se + (1 – p)*(1 – Sp) = p*[Se – (1 – Sp)] + (1 – Sp) \]

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The 2 x 2 table shows that when cases b and c have an equal numerical size (b = c), then P(T +) =
P(M) = p, which does not imply that the false-positive rate \((b/n_2 = \beta)\) and the false-negative rate \((c/n_1 = \alpha)\) have an equal value.

\[
P(T+) = \frac{f_1}{N} = \frac{a + b}{N} = \frac{a + c}{N} = P(M) = p.
\]

Such a situation occurs when odds

\[
P(M) = \frac{p}{1 - p} = \frac{\alpha \text{ error rate}}{\beta \text{ error rate}}
\]

The prevalence \(P(T+)\) of the positive result is equal to the true prevalence of the disease at point A when the prevalence of the disease is

\[
p^* = \frac{\alpha}{\alpha + \beta} = \frac{1}{1 + \alpha} = \frac{1}{1 + 0.10} = 0.66.
\]

The value of the prevalence \(p^*\) only depends on the ratio of the two diagnostic error rates, respectively the false-negative error rate \(\beta\) and the false-positive error rate \(\alpha\).

The reliability of a screening or diagnostic procedure depends on both the true prevalence of the searched disease and the ratio of the two diagnostic errors related to the defined cutoff point on the diagnostic parameter. The choice and the appropriate interpretation of any diagnostic test depend on knowledge of its aim and its prognostic importance. Depending on the risks to be estimated and precluded by the diagnostic procedure, the cutoff point for negative versus positive results of the test (and the upper limit of the agreed normal range) is conditioned by the presumed prior probability of the disease and also by the respective clinical severity of false-positive and false-negative results. As far as feasibility allows, this ensures the appropriateness and the suitability of the aimed preventive or therapeutic measures.

### THE SCIENCE OF MEDICAL CARE

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients [David L Sackett, 1997].

**Cardiac and vascular risks** – Data from longitudinal studies suggest that the risk of cardiovascular disease (CVD) in NIDDM patients is two to four times as great as in subjects without diabetes. The risk is independent of the duration of diagnosed diabetes, because even before that time patients would have been classified as having impaired glucose tolerance, a prediabetic state is also associated with an increased risk of CVD [7]. Actually, there is a continuous relation between the risk of CVD and raised glucose concentrations, that extends from barely elevated values into the diabetic range since it includes a range of glucose concentrations previously not thought to be abnormal. The non-linear pattern of cardiovascular risk associated with hyperglycaemia has been confirmed by diverse prospective studies [13]. The data reported in Table II show that attributable risk is the same regardless of the cutoff point [7]. Neither cutoff point nor risk threshold may be worked out. The postprandial glucose value above which patients are at increased cardiac risk may be as low as 5.4 mmol/l, which is lower than the value conducive to a diagnosis of impaired glucose tolerance. The prevalence of such “dysglycaemias” might exceed 50% of middle-aged adults, depending on the cut-off used to define the risk factor.

The decision to take into account the results of such investigations is a matter of the demands of the society and its capacity to afford them. An apparent health paradox is that patients’ needs and demands for security tend to be greater as medical care becomes safer in a society [14].

A clinical reference should define an operative cutoff value as the minimum degree of abnormality or risk that will result in initiating treatment for the disease. Hence, such a cutoff point depends on the “dysutilities” or clinical costs of respectively false-positive and false-negative results, i.e. the net expected benefit of treating the patient (sometimes an asymptomatic subject) and his/her expressed preferences. From an individual patient’s viewpoint, there is some evidence that mild or moderate hyperglycaemia is less important than severe or elevated hyperglycaemia. In public health terms, however, the former may be more important since it is much more common and thus accounts for a greater proportion of the deaths and serious non-fatal vascular events associated with hyperglycaemia [15].

**Risks in pregnancy** – Counseling and surveillance of pregnant diabetic women is a cornerstone of medical decision-making in order to prevent gestational complications such as perinatal mortality, spontaneous
abortion, foetal macrosomia and congenital anomalies. Compliance of pregnant women is generally reliable since they are disturbed by the prospect of an adverse outcome. The results of medical intervention are easily measurable in a rather short time.

A fourfold higher rate of perinatal mortality is observed in untreated diabetic women than in pregnant women with a normal glucose tolerance test. Several studies have suggested that a threshold > 115 mg/dl (6.44 mmol/l) is associated with a linear increase in perinatal mortality [1]. However, even with an acceptable control of glycaemia, these patients are still at higher risk for perinatal mortality because of additional risk factors.

The risk of spontaneous abortion in insulin-dependent diabetes is substantially higher than in the general population. Maternal HbA1c values greater than two standard deviations above the mean (with reference to isolated normality) are the sole variable in ascertaining the risk of spontaneous abortion. The threshold for prevention of spontaneous abortion is 10-12 %, whereas normal HbA1c in pregnancy ranges from 4 to 7 % depending on laboratory standards [1].

Table III

Table II. Incidence of coronary heart disease (CHD) attributable to serum glucose concentration (1-h after 50g glucose challenge) [from 7].

<table>
<thead>
<tr>
<th>cutoff of serum glucose 1 h after oral challenge</th>
<th>% with value in the category</th>
<th>12-year CHD frequency</th>
<th>attributable risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>above cutoff</td>
<td>79.6 %</td>
<td>5.11</td>
<td>1.82 %</td>
</tr>
<tr>
<td>below cutoff</td>
<td>20.4 %</td>
<td>3.29</td>
<td>-</td>
</tr>
<tr>
<td>10.6 mmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>above cutoff</td>
<td>20.2 %</td>
<td>6.20</td>
<td>1.83 %</td>
</tr>
<tr>
<td>below cutoff</td>
<td>79.8 %</td>
<td>4.37</td>
<td>-</td>
</tr>
</tbody>
</table>

Congenital malformations are the main cause of perinatal mortality and one of the greatest concerns among adverse outcomes of Type I and Type II diabetic pregnancies. Decreasing the risk of congenital malformations includes both preconceptual counseling and achievement of the appropriate level of glycaemic control. The correlated cutoff points for predicting malformations are an initial HbA1c concentration > 12 % (6.2-7.5 standard deviations above the mean) or a median first-trimester fasting plasma glucose concentration > 120-130 mg/dl (6.7-7.3 mmol/l). A combination of preconceptual treatment and targeting the level of glycaemia to a fasting level < 120 mg/dl (120 mmol/l) and a postprandial mean < 140 mg/dl (7.8 mmol/l) might result in an anomaly rate comparable to that of the nondiabetic population [1]. However, medical intervention to prevent the risk of congenital malformations may be quite frustrating. It implies an early, prolonged, stringent and cumbersome control of glycaemia by the patient.

Table III. Glycaemic thresholds for prevention of diabetic complications of foetal disease.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Mean blood glucose (mg/dl)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>&lt;110</td>
<td>-</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>&lt;140</td>
<td>&lt;13</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>&lt;160</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Macrosomia/LGA</td>
<td>&lt;100</td>
<td>-</td>
</tr>
<tr>
<td>Metabolic complication</td>
<td>&lt;110</td>
<td>-</td>
</tr>
</tbody>
</table>
Moreover, ROC curve analysis shows that the two suggested index tests (fasting plasma glucose and post-load glucose mean concentrations) are poorly informative and offer a quite low discriminant power [16]. As self-reporting of blood glucose measurements is unreliable, the expected benefit is statistically small; hence beta II error risk is still significant if the number of recruited patients is not large enough. The causal relationship of outcome with actual glycaemic control is unreliably assessed, and the psychological cost of medical intervention might be detrimental for a prolonged period [17]. Analysis of the association between glycaemia level and adverse foetal outcomes should include values used to initiate the specific intervention, type of intervention, threshold for glucose targeted by investigators, and the frequency and timing of blood glucose measurements. Such a difficult implementation makes the clinical significance of these preventive measures less consistent and often unreliable.

**CONCLUSION**

A diagnostic criterion suitable for testing an etiological hypothesis may not be adopted for clinical purposes in diseased individuals. Medical intervention should rely on criteria consistent with the aims of medical intervention. This is particularly true when the disease of interest is defined by specifying a diagnostic cut-off for a continuous variable. Normal ranges and thresholds for decision-making are not “isolated” values but must be correlated with the objective of optimizing the medical assignment, relative to the scientific evidence afforded by clinical research. They must also take into consideration the predicaments of individual patients and their rights and preferences [18].

« En matière de pathologie... le dernier mot revient à la clinique. 
On ne dicte pas scientifiquement des normes à la vie. »

*(Georges Canguilhem - 1966)*

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