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COMMENTARY

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The hyperbolic law—a 25-year perspective

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In people with normal glucose tolerance, a decrease in insulin action is accompanied by up-regulation of insulin secretion, and vice versa. This is interpreted as a compensatory increase of insulin secretion, which maintains normoglycaemia despite decreased insulin sensitivity. In this issue of *Diabetologia* [1], Dr Hockaday deplores the fact that a landmark paper by the late Robert Turner and colleagues (himself included), which dates back to 1979, is rarely cited when this quasi-hyperbolic relationship is under discussion [2]. And Dr Hockaday is right, because the "hyperbola" in Fig. 7 of that paper, after two algebraic transformations (the insulin resistance factor being equivalent to 1/[insulin sensitivity] plus switching axes, the fraction of functioning beta cells being equivalent to beta cell function with opposite orientation), becomes the hyperbola now commonly used with acute insulin response (AIR) as a function of insulin sensitivity (Fig. 1a and b). In their abstract the authors already claim that "the height of basal plasma insulin is a function of the degree of insulin resistance." Hence, Dr Hockaday appropriately claims that the concept was already shaped in their paper, which was published 25 years ago, 2 years before the classical paper of Bergman and co-workers [3].

However, it is not surprising that this paper went somewhat unnoticed by the "hyperbola aficionados," because its main focus, and that of Fig. 7 in particular, was on factors involved in the pathogenesis of hyperglycaemia. In contrast, the concept of the hyperbola is now used to illustrate the fact that in a healthy individual any decrease in insulin sensitivity is compensated by up-regulation of beta cell function, and vice versa [4, 5]. The concept is self-sufficient at this level, and does not necessarily explain the development of hyperglycaemia. Its fundamental importance remains, however, because measurements of beta cell function can only be interpreted appropriately when a (more or less) simultaneous measure of insulin sensitivity is available [6]. These ideas were not fully developed in the 1979 paper. The beauty of Bergman's simplification lies in the introduction of the so-called disposition index as the mathematical product of insulin action and beta cell function [7]. The disposition index is a way of measuring the ability of the beta cells to compensate for insulin resistance. This compensation is thought to be perfect when the disposition index remains constant in the face of decreasing insulin action; only when glucose tolerance becomes impaired, does the disposition index actually fall.

Turner and co-workers used "HOMA factors" for insulin resistance and per cent beta cell function, which, in essence, are the product and ratio respectively of basal insulin and glucose concentrations. This is to some extent a self-fulfilling construct, because the product and ratio of any set of numbers will inevitably produce a hyperbola. The intrinsic dependence of the two HOMA factors thus limits the validity of any conclusions drawn from the data they provide. The "modern" hyperbola is clearly more informative, because it arose from variables that are not only independent but also employ stimulated measures of insulin secretion (or beta cell function) and insulin sensitivity such as the IVGTT and the euglycaemic clamp. It leads to the remarkable conclusion that the stimulated beta cell somehow knows whether the organism it belongs to can dispose of more or less glucose during the hyperinsulinaemic–euglycaemic clamp, i.e. whether it is in an insulin-sensitive or in an insulin-resistant person. The burning question relates to the nature of the signal that alerts the beta cell to the presence of insulin resistance. This latter point is addressed with acuity by Dr Hockaday in his next paragraph: "The disturbance brought about, for instance, by a decrease in insulin sensitivity is most unlikely to be completely compensated, for if so, the compensating

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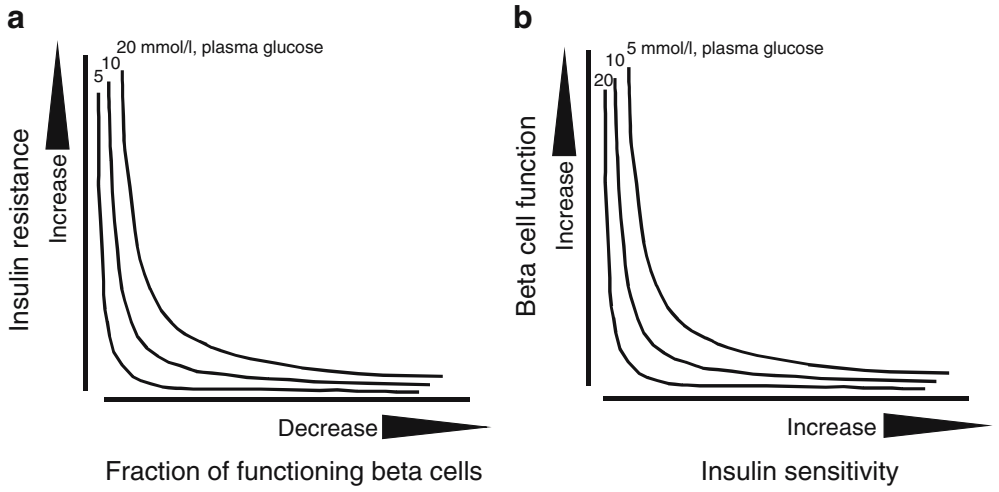

Fig. 1 Maturation of the "hyperbola." **a** In the original concept by Turner and co-workers, the relationship was constructed from basal glucose and insulin concentrations. Isoglycaemia lines were drawn for three plasma glucose concentrations [2]. **b** Today's concept of the hyperbola reflects the natural relationship between beta cell function and insulin sensitivity and illustrates beta cell compensation for insulin resistance. It is usually constructed using independent and stimulated measures of beta cell function and insulin sensitivity. It is essentially identical to Turner's concept after two algebraic transformations (the insulin resistance factor being equivalent to 1/[insulin sensitivity] plus switching axes, the fraction of functioning beta cells being equivalent to beta cell function with opposite orientation)

forces would cease to act...". This is perfectly in line with the concept we recently put forward under the name of "glucose allostasis" [8].

The term "allostasis" was originally introduced by Sterling and Eyer [9], who considered the morning rise in blood pressure from overnight levels to be allostatic, since the upright posture assumed during the day requires a higher systemic blood pressure to guarantee adequate cerebral blood flow. They postulated that over time this generates "feed-forward" increases in blood pressure, which in turn promote atherosclerosis. More recently, McEwen and others developed the concept of allostasis to help explain adaptive neuroendocrine responses to chronic stress: these ensure that an individual can cope from one day to the next, but at the price of cumulative damage to that individual's health [10]. We have brought this terminology more into line with modern thinking, and use "homeostasis" for mechanisms essential for survival and "allostasis" for a chronic process that maintains and adapts the homeostatic system.

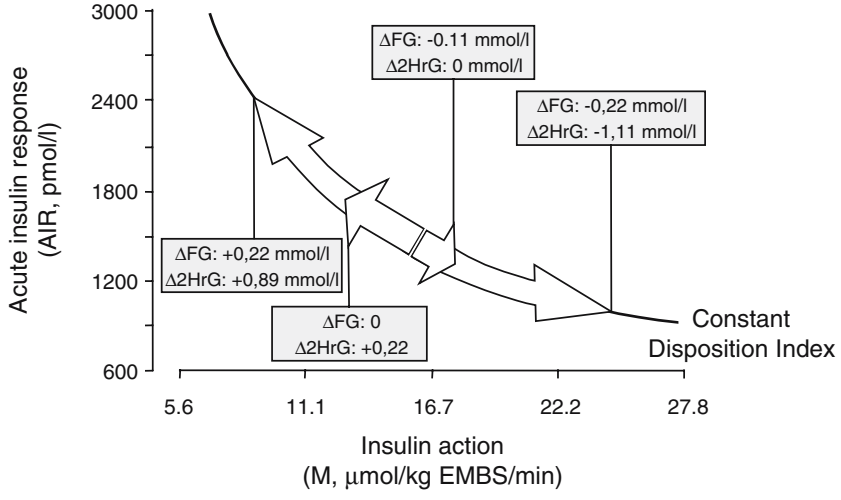

Fig. 2 Movement along the hyperbola. The hyperbola reflects the situation of perfect compensation of beta cell function (acute insulin response, AIR) in response to changes in insulin sensitivity (*M*, insulin-stimulated glucose disposal). The disposition index (DI, product of AIR×*M*) is constant in this situation. Data from 187 Pima Indians who had normal glucose tolerance at baseline and at follow-up (~5 years) were modelled. Any deviation from the hyperbola was mathematically adjusted for (details in [8]). Subjects were divided into four groups by "movement" along the curve of "normal compensation." The magnitude and direction of movement is represented by the *arrows*. The resulting change in glycaemia (*ΔFG* fasting glucose concentration; *Δ2HrG* 2-h glucose concentration) is shown in the *grey-shaded boxes* (adapted from [8]). Thus, even perfect compensation over time of insulin secretion by the beta cell in response to changes in insulin sensitivity is associated with changes in glycaemia

Consistent with Dr Hockaday's statement, we have presented evidence that glycaemia must increase in the face of insulin resistance, and despite normal beta cell compensation [8]. Insulin action and secretion were analysed in large cohorts of healthy Pima Indians and Caucasians with normal glucose tolerance, and the analysis was controlled for variability in appropriateness of beta cell compensation. When all other factors were kept constant, higher demand on the beta cell due to reduced insulin action was positively associated with glucose levels in cross-sectional analyses in both Pima Indians and Caucasians. Longitudinal studies have also shown that glycaemia increased with increasing beta cell demand (and vice versa) over a wide range of almost 0.55 mmol/l for fasting and 2.22 mmol/l for 2-h plasma glucose concentrations in the extreme groups (Fig. 2). Necessary to guarantee acute homeostatic regulation, this built-in increase in glycaemia can be referred to as "glucose allostasis" [11].

Like Dr Hockaday, we felt that our data confirmed what should be obvious from theoretical reasoning alone: a chronic stimulus responsible for a chronic compensation cannot be fully removed, or there would be no further need for the compensation. This implies that compensatory mechanisms, although physiologically normal and appropriate, cannot possibly restore the original state completely. This is a challenging concept, and one reviewer of this paper categorically refused to accept "that a rising glucose value is an inevitable characteristic of insulin resistance." It is probably impossible to get any closer to the truth of that matter than we came in our paper, because any experimental manipulation of insulin action in real life will not take place without concomitant changes in the disposition index, i.e. over- or undercompensation. And naturally, any change in disposition index would have a far greater impact on glycaemia than a realistic movement along the hyperbola.

Allostatic systems are the price we pay for a chronic adaptive mechanism. With glucose, however, the price is particularly high, because the very parameter that entrains the regulation (increased glycaemia) is damaging over time (increased glycaemia = allostatic load), thus increasing the burden that persistent increases in insulin secretion place on the beta cell and perhaps other parts of the system. And there is good evidence that even mild increases in glycemia are associated with increased all-cause mortality. For example, in more than 16,000 healthy men, a 2-h post-load plasma glucose concentration of 5.94 mmol/l was associated with a 15% increase in all-cause mortality compared to 5.44 mmol/l [12].

Thus 25 years after Robert Turner's observation, the hyperbola remains as topical as ever, and provides a convenient conceptual framework within which to discuss and perhaps advance our understanding of regulation and dysregulation of glycaemia.

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