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To the Editor

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I was surprised to find no mention of Fig. 7 from the article by Turner et al. [1] in any of three recent discussions dealing with the ‘hyperbolic relationship’ between insulin sensitivity and insulin release [2], ‘the hyperbolic law of glycaemia’, most neatly defined as a quasi-hyperbolic relationship in subjects with NGT between beta cell function and insulin sensitivity [3], and the hyperbola paradigm [4]. The article [1] would seem to have as good a claim to be quoted in the history of the ‘hyperbola’ as that most often cited [5], which was published 2 years later.

As shown (Fig. 1), hyperbolae were plotted for three different levels of basal plasma glucose to relate an ‘insulin resistance factor’ to the ‘fraction of functioning beta cells’, which is how beta cell function was expressed. The curves were derived from a mathematical model based on a dynamic feedback loop describing the interactions between glucose and insulin in the plasma and the two main organs that regulate glycaemia, the liver and pancreas. This model was also used to calculate the factors for insulin resistance and beta cell function for 65 patients newly referred to a hospital diabetic clinic. Their values lay within the curves, and were distributed so that, approximately, the hyperglycaemia of one quarter was predominantly due to increased resistance to the hypoglycaemic effect of insulin, while that of another quarter was mainly due to diminished beta cell function, and in the remaining half, both effects contributed substantially.

The hyperbolic shape originated in the ‘insulin response to a steady state glucose concentration’ [1], an origin that forecasts the failure to keep to the hyperbolic course (when the current equilibrium of a subject is disturbed) that concerns the above authors [2–4]. But the disturbance brought about, for instance, by a decrease in insulin sensitivity is most unlikely to be completely compensated because, if so, the compensating forces would cease to act, and the original disturbance would again shift the position. The proviso ‘most unlikely’ is inserted because sensitive receptors linked to effective responses as well as to a coordinating effector agency outside the feedback loops could achieve adherence to the hyperbolic curve, but cellular and organ functions have not been shown to be capable of such sophistication, most likely seen when either sensitive instruments and/or competent neuronal organisations are involved.

The main residual concern about this early formulation [1] is its ‘Premise 3’, which ‘requires that any defect of insulin secretion is characterised by a reduced maximal secretory insulin response to glucose (low $V_{\max}$) with normal beta cell sensitivity’, though it is but weakly supported in the text by the unconvincing Fig. 3. If both the $V_{\max}$ and the K_m of the curve relating insulin secretion to glycaemic level are free to vary, then the equations cannot be solved unequivocally either in that paper [1] or where the HOMA factors are calculated after some refinement but with the same premise included [6].

Thankfully, variation in the sensitivity of the insulin response to glucose was given as much prominence as alterations in the active mass of beta cells in the most recent of the above reviews [4].

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Fig. 1 The insulin resistance and insulin deficiency calculated from the fasting plasma sample in 65 consecutive new patients (35 female, 30 male) referred to a diabetic clinic with a fasting plasma glucose of more than 5.5 mmol/l, excluding those who had current infection, liver disease or high alcohol intake. Their ages ranged from 24 to 65 years (mean 52 years), and percentage of ideal body weight ranged from 89% to 249% (mean 154%), with 12 patients weighing less than 115% of their ideal body weight. Insulin resistance is expressed in relation to the average normal person (set as 1), and beta cell dysfunction is similarly expressed as if there were reduced numbers of beta cells. "Isoglycaemia" lines are drawn from three different basal plasma glucose concentrations. Thus, a given basal

plasma glucose value is produced by a particular decrease in effective insulin concentration arising from a spectrum of combinations of increased insulin resistance and decreased beta cell function, illustrated by the lines. Each dot represents one patient, and the radiating broken lines represent the relative contributions to a patient's diabetes of insulin resistance and reduced insulin secretory capacity. In approximately one-third of the new diabetic patients, there appears to be a modest reduction in insulin secretory capacity, and the diabetes is predominantly due to insulin resistance. One year later, four patients required insulin and 14 required sulphonylureas to prevent symptoms arising from glycosuria, and 47 remained on diet therapy alone

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