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Response from the authors

Dear Sir,
Remarks regarding the pessimistic view expressed by Sternberg et al. in their letter on the future of glucose sensing with an implanted microsensor appear appropriate.

1. The delay between changes in blood glucose and those in the signal produced by the glucose sensing system may depend strongly on the nature of the system (i.e. implanted glucose sensor vs microdialysis system, size of the implanted glucose sensor). In rats, a sharp increase in the current generated by a miniaturized sensor (0.4 mm diameter wire) implanted in the subcutaneous tissue was consistently observed within 5 min following an i.p. glucose load (see Figs. 2 and 5 in [1], not quoted in Sternberg's review, showing the results observed for sensors implanted over 3 or 10 days, respectively).

2. The nature of the "true" glucose concentration in extracellular fluid is a controversial issue nicely reviewed by Schmidt et al. [2]. It is clear that the value obtained depends partially on the method of measure (i.e. Wick technique, dialysis or ultrafiltration method), and, if an implanted glucose sensor is used, on the geometry of the sensor.

3. Clinical trials of a glucose monitoring system [3] (quoted as reference [9] by Sternberg et al.) were performed approximately 14 h after implantation. Thus, the fact that the sensitivity of this sensor was lower when assessed during implantation than when observed in vitro may be related to Pfeiffer factor Q. This low sensor sensitivity is not a novel observation, and nothing but a confirmation of what we have already observed in rats [1] and dogs [4]. We are currently investigating its significance.

4. The fact that the sensor's sensitivity is not identical in vivo and in vitro on one hand, and that the "true" glucose concentration in situ cannot be directly measured on the other hand, highlights the issue of calibration in the field of glucose sensing. We were sad (but not surprised) to learn that "the one point in vitro, one point in vivo calibration method [5, 6] is rather easy to accomplish but is not considered to be accurate because both the zero in vitro and the actual blood glucose value do not correspond to their respective subcutaneous values". By contrast, the two-point calibration method [1, 3, 7, 8] yields accurate estimation of blood glucose concentration and is now being used by others [9, 10], and this should encourage Sternberg and his colleagues to use it. Indeed a) there is no need to obtain a long plateau (such as that achieved by the clamp technique), if the delay between the change in blood glucose concentration and the response of the signal is short, as shown above. b) The method is not difficult to perform since only two blood glucose measurements are needed. c) It is difficult to imagine that patients using a continuous glucose monitoring system will not check at least twice that their system is working. We do agree, however, that efforts to make the method user-friendly are needed.

5. We previously published [1] the proof that the sensor we are currently evaluating in vivo in the animal and in man works for at least 10 days when implanted in the s.c. tissue of normal rats. Others consider the possibility of a permanently implanted device using the same type of sensors [11]. We therefore do not share the pessimistic view that "it is not possible to get a long term response with this type of sensor". Using a glucose sensor for the detection of nocturnal hypoglycaemia, as proposed by J. Pickup, may be viewed not as a drawback, but as an important progress in diabetes management, if one considers the recent results of the Diabetes Control and Complications Trial.

6. Finally, although it is understandable that Sternberg and his colleagues defend the future of microdialysis [5, 6], they should not be so pessimistic considering other strategies for glucose sensing such as the use of implanted microsensors [12]. They should instead meditate on the conclusion of the balanced editorial published by Pickup in a recent issue of the Lancet [13]: "Thus, despite the promise of microdialysis and near infrared spectroscopy, it would be premature to abandon research into implanted electrochemical sensing devices". According to Ambrose G. Bierce (1842–1914), "there is but one way to do nothing and diverse ways to do something".

Yours sincerely,
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