cannot be ascribed to different changes in glycaemic control which improved similarly in the two groups during the follow-up interval. The significance of the increased rate of loss of GFR within or above the normal range in the hyperfiltering patients remains uncertain; whether it will continue through and below the normal range will be determined by continuation of our study.

Yours sincerely,
S. L. Jones, M. J. Wiseman and G. C. Viberti

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Glucose infusion rates during euglycaemic clamps do not precisely reflect action profiles of subcutaneously injected insulin

Dear Sir,

In a recent paper Heinemann et al. [1] report on their attempts to quantify the action profile of insulin analogues which were presumed to be absorbed faster than human insulin. They conclude from their results that the analogues B9Asp/B27Glu and B10Asp exhibit "significantly faster onset of action as compared to regular insulin". However, due to a major drawback of the experimental design, this conclusion does not appear to be justified.

According to the experimental protocol employed in this study [2], plasma glucose was clamped in healthy subjects at 5 mmol/l by means of a Biostator-GCIIS for 8 h, while insulin was infused intravenously at 0.1 mU/kg × min. Thus, plasma insulin concentrations of about 10 mU/l were attained [2]. Insulin preparations to be tested were injected subcutaneously 90 min after starting the clamp procedure. Increases of glucose infusion rates above basal are interpreted by the authors as representing the action profile of the insulin under study.

From the literature it can easily be inferred [3], that an experimental protocol like this will result in only partly suppressed endogenous glucose production under both basal and post-injection periods. Moreover, due to variations of plasma insulin concentrations, it must be assumed, that the suppression of endogenous glucose production will change during the experiment at variable degrees. In addition, it cannot be presumed that insulin analogues and unmodified insulin inhibit endogenous glucose production as well as endogenous insulin secretion to the same extent. The glucose infusion rates necessary for maintaining euglycaemia are at best rough estimations for glucose metabolism, but they by no means reflect it quantitatively. Therefore, glucose infusion rates are not valid measures for comparing the action profiles of different insulins, especially when the values obtained differ by a small amount as in the present study.

In our opinion, the study design has to be modified (e. g. by inclusion of glucose turnover measurements) before definitive conclusions regarding faster absorption of these insulin analogues can be drawn.

Yours sincerely,
W. Kerner, F. S. Keck and E. F. Pfeiffer

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Response from the authors

Dear Sir,

Kerner et al. are wrong in suggesting that the determination of glucose infusion rates during a euglycaemic clamp as used by us in studies on insulin pharmacokinetics [1] is an invalid measure for characterizing insulin action profiles. They are correct in noting that hepatic glucose production is not completely suppressed according to our experimental protocol and that it may indeed vary during the experiment due to changes in circulating insulin concentrations. In fact, a further decrease of an initially incompletely suppressed hepatic glucose production rate is to be expected if bioactive insulin preparations are subcutaneously injected during the experimental protocol, as it represents part of the physiological in vivo response to exogenous insulin. The aim of our experimental protocol was to measure the overall effect of bioavailable insulin, i. e. the biological action of different insulin preparations after being absorbed into the circulation following its subcutaneous injection. In this context, a complete suppression of basal hepatic glucose production is neither necessary nor desireable, since peripheral glucose utilization rates would steadily increase during prolonged clamp studies at higher basal insulin concentrations [2]. In our euglycaemic clamp studies on insulin pharmacokinetics, we have therefore routinely used basal low dose insulin infusions in order to suppress endogenous insulin secretion which might otherwise be inadvertently stimulated during glucose infusions. Any additional information concerning absolute rates of hepatic glucose production and peripheral glucose metabolism appear to be of minor relevance. It is up to the personal judgement of Kerner et al. to describe a twofold increase of insulin action

within 45 to 60 min following its subcutaneous injection as a "small amount".

If genetic bioengeneering would ever succeed in developing insulin analogues with differential activities on hepatic and skeletal muscle tissues, detailed glucose turnover measurements, as apparently favoured by Kerner et al., may become potentially useful tools.

Yours sincerely,
L. Heinemann and A. A. R. Starke

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Human cell lines from families available for diabetes research

Dear Sir,

Diabetes mellitus is a major health problem. In its most common form of Type 2 (non-insulin-dependent) diabetes the disease shows strong genetic determinants. Although the patterns of inheritance are unclear, this late onset disease may be caused by a dominant autosomal gene. In the less common form of diabetes, Type 1 (insulin-dependent) diabetes, which develops at any age but primarily affects the young, certain HLA specificities are known to provide an increased risk. These HLA determinants are necessary, but not sufficient for the disease to develop. A second or third gene for Type 1 diabetes may be necessary. In addition, rare forms of diabetes mellitus due to single point mutations in either the insulin or the insulin receptor gene have been documented. These monogenic forms of diabetes mellitus, however, hardly contribute to the overall prevalence of the disease.

Progress in understanding the patterns of inheritance of diabetes has been slow. Many scientists have attributed the lack of progress not so much to the lack of genetic markers and chromosome specific gene probes, but to the availability of families with more than one member being affected. The need for a databank of families with diabetes mellitus and of immortalized cell lines and/or DNA to be made available to researchers not only within the field of diabetes, but in any scientific discipline was voiced at the Second International Conference of Diabetes held in Monaco in the spring of 1988. The scientists' recommendation at this meeting was that such cell lines should be made available for research aimed at understanding the complex pattern of inheritance of Type 1 as well as Type 2 diabetes. The National Diabetes Advisory Board has made a similar recommendation. Recently interest has also been focussed on the fact that not all individuals with diabetes develop diabetic complications. For example, diabetic nephropathy only develops in 40–50% of affected individuals. There is data indicating that if the affected individual has a diabetic sibling or parent with this complication, the risk of developing the same complication is increased. Diabetic complications have been associated with alterations in blood pressure or blood lipids and there is increasing interest in uncovering genetic linkage or association to complications.

The National Disease Research Interchange (NDRI) is a Philadelphia-based non-profit organization which supplies researchers with tissues and organs. An initiative has been taken by NDRI to form the Human Biological Data Interchange (HBDI) to create a databank of families affected by diabetes. This endeavour of HBDI has recently become successful through an effective partnership with the Juvenile Diabetes Foundation International. This organization has used its mailing list to approach their membership with questionnaires to obtain useful pedigrees for investigative purposes. As of May 1990, more than 10,000 questionnaires have been screened and a family assessment committee of the HBDI has evaluated the pedigrees to recommend Epstein-Bar virus transformations to prepare cell lines. The first catalogue of immortalized cell lines is now available in collaboration with Coriell Institute in Camden, New Jersey, USA.

The human cell lines available from the Coriell Institute are certified to be mycoplasma-free. The cells are available as liquid nitrogen frozen stock cultures. The HBDI and the Coriell Institute also plan to make DNA available.

Each family in the catalogue has been verified by HLA typing. HLA typing and clinical information will be available through HBDI. The families will remain anonymous but have agreed to be approached for additional questions. HBDI will be the medium to pass on information from the families to investigators. Since Type 1 diabetes is a disease which may develop at any age, the families will be continually followed to record if any additional member develops the disease. This information will also be made available from HBDI.

The success in preparing this first HBDI catalogue was only possible because of the generosity of NDRI, a special grant from the Juvenile Diabetes Foundation International (JDFI) and the volunteer contributions from Dr. P. Rubinstein, The New York Blood Bank Center, New York who HLA-typed the families, and M. Sheehy who shared several multiplex families.

The HBDI catalogue of diabetic families will continue to grow dependent on available funds and user interest. It is planned to base the growth on questionnaires to be sent to families in 120 JDFI chapters in the USA, Canada and at least 12 other countries. HBDI welcomes proposals to initiate projects in obtaining cell lines from twins, families with both Type 1 and Type 2 diabetes, siblings with diabetes, three generation families, families with Type 1 diabetes in addition to other autoimmune diseases, families with several diabetic members both with and without complications, etc. Based on project proposals, HBDI will select and contact families for bleeding and subsequent EBV transformations.

We believe that the availability of these diabetes families will be of great interest to the scientific community in the promotion of studies on the genetic susceptibility to Type 1 and Type 2 diabetes and its complications. In times of reduced funding from NIH, these cell lines offer an inexpensive resource to study genetic aspects of diabetes mellitus. The bank of diabetic families is a public domain and made available to the scientific community for as a low price as possible.

Scientists interested in obtaining these cell lines for research can contact the HBDI program, National Disease Research Interchange, 2401 Walnut Street, Suite 408, Philadelphia, Pennsylvania, 19103 USA. Telephone: 215-557-7361, Fax: 215-557-7154.

Yours sincerely,
On behalf of the Human Biological Data Interchange,
Å. Lernmark, Chairman, L. Ducat, President, G. Eisenbarth, J. Ott, M. A. Permutt, P. Rubinstein, R. Spielman

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