Letter to the editor

Epidemiological and ethical considerations on trials with immunotherapy in pre-Type 1 (insulin-dependent) diabetes mellitus

Dear Sir,

In a previous issue of *Diabetologia* six representatives of the International Immunotherapy group in a letter [1] proposed the setting of standards for trials with immunotherapy in pre-Type 1 (insulin-dependent) diabetic subjects. The authors stated that such trials should be undertaken with informed consent and be carefully controlled and supervised as "the sensitivity, specificity, and precision of the predictive values are still not properly established".

There are reasons to be even more precise regarding the restrictiveness of such trials. For both epidemiological and ethical reasons such trials should not only be carefully controlled but strictly limited to high risk-group individuals i.e. first-degree relatives of Type 1 diabetic patients and participants should be adults or at least more than 14 years of age. The basis for this statement is:

1. The follow-up studies that have yielded predictive values of the immunological markers of Type 1 diabetes are exclusively performed in first-degree relatives of Type 1 diabetic patients i.e. a high-risk population in which the prevalence of Type 1 diabetes would be 5–10%. The predictive value of a marker is inherently dependent on the prevalence of the disease in the population under study i.e.

$$p_v = \frac{\text{prev} \times \text{sens}}{(\text{prev} \times \text{sens}) + (1 - \text{prev}) \times (1 - \text{spec})} \quad [2].$$

Using the sensitivity (0.81) and the specificity (0.99) of complement fixing islet cell antibody (CF-ICA) as markers for Type 1 diabetes given in the elegant family study by Tarn et al. [3] for the calculation of the predictive value of this marker in a general population of e.g. Swedish children 0–15 years among whom the prevalence of Type 1 diabetes is around 0.15% the positive predictive value would be 11%. This means that if an immunotherapeutic trial was conducted after CF-ICA screening in that population 9 out of 10 children who screened positive would never become diabetic regardless of any treatment given. To screen the general population for a low prevalence disease such as Type 1 diabetes the sensitivity and specificity of the marker must be very close to 1.0 and the therapy effective and harmless to be scientifically and ethically acceptable.

2. As Type 1 diabetes is most prevalent among younger people and as diabetes occurring before the age of 15 is very rarely Type 2 (non-insulin-dependent) diabetes, immunotherapeutic treatment programmes have been performed almost exclusively in recent-onset diabetic children. It is, however, clearly stated in The Council for International Organizations of Medical Science (CIOMS) Guidelines for Biomedical Research Involving Human Subjects [4] that "Children should never be involved as subjects in research that could be appropriately undertaken in adults". In fact it is possible, though somewhat less convenient, to study adult Type 1 diabetes. Another important reason is that there are reasons to believe that the side effects of immunotherapy would be more serious in a growing, than in

an adult, individuals. The quoted CIOMS' statement on research with children is, of course, based on the fundamental ethical principle of the Declaration of Helsinki that informed consent is the prerequisite for research in human subjects. When it comes to potentially hazardous immunotherapy in healthy, and only perhaps pre-Type 1 diabetic subjects (almost half CF-ICA positive first-degree relatives [3] did not become diabetic during the observation time), informed consent should be sought from the study subject as well as from the parents [5]. Even if the individual child's development and competence in understanding rather than the chronological age should determine a child's ability to give informed consent, there is evidence that until the age of 14 children do not have the understanding to give a meaningful informed consent [5].

There are thus strong scientific and ethical reasons to limit immunotherapeutic trials of pre-Type 1 diabetes to first-degree relatives of Type 1 diabetic subjects who are adult or at least older than 14 years.

It is also worth considering that more than 90% of the incident cases of Type 1 diabetes have no first-degree relatives with the disease. Thus, the possibility of arresting the increasing trend of Type 1 diabetes occurring in many countries using secondary intervention programmes such as immunotherapy seems to be very limited.

Yours sincerely,
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References

1. Bach JF, Dupré J, Eisenbarth GS, Harrison LS, MacLaren NK, Nerup J, Pozzilli P (1990) Immunotherapy in pre-Type-I diabetes mellitus. *Diabetologia* 33: 741 (Letter)
2. Ahlbom A, Norell S (1984) Introduction to modern epidemiology. Epidemiology Resources Inc, USA
3. Tarn A, Thomas JC, Dean BM, Infram D, Schwartz G, Bottazzo GF, Gale EA-Ch (1988) Predicting insulin dependent diabetes. *Lancet* i: 845–850
4. Council for International Organizations of Medical Science (1982) Proposed International Guidelines for Biomedical Research Involving Human Subjects. WHO, Geneva
5. Nicholson RH (1986) Medical research with children: ethics, law, and practice. Oxford University Press, Oxford

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Erratum

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K. Nørgaard et al.: Lack of familial predisposition to cardiovascular disease in Type 1 (insulin-dependent) diabetic patients with nephropathy

On page 371 the two columns have been reversed.