Diabetologia (1999) 42: 1–2

Diabetologia

Editorial

The world of Diabetologia in 1999

Diabetologia's first year in Vienna has been an exciting experience. Submissions came from all over the world and were almost evenly distributed between European (60%) and other countries (40%) led by Japan (14%). The influx of new manuscripts rose by 20% surpassing 900 submissions but the available space for publication remained constant. This resulted in considerable competition for space, more hard work both for the reviewers and the editorial staff. Naturally, with this, editorial decisions as to acceptance or rejection of papers have become increasingly more difficult. To alleviate the limitation on space the Editorial Board has decided to add *Short communications* to the Journal's list of staples. Subheadings have been introduced to help our time-pressed readers to immediately locate papers of particular interest to them. Abstracts will also be structured in future to make it easier to spot important information. To provide for quick, in depth, dissemination of hot novel research the category of Rapid communications is to be opened up to important Full-length papers. These will be subject to rapid but most rigorous review of both scientific standard and relevance for our readers dedicated to diabetes research and care. We hope these changes will further *Diabetologia's* service to the academic and medical community beyond that offered to date and would truly welcome your suggestions for more improvements. Finally as it is of utmost importance for the editing process to receive reviews by our deadlines we ask for your active support in this regard. Likewise it is very helpful when authors use the opportunity to provide a list of potential reviewers when submitting a manuscript.

The world of *Diabetologia* is, however, not dominated by technical editorial detail but by diabetes research, which is a fascinating blend of basic and clinical science. Major clinical strides in the last year have included the proposal of new more stringent diagnostic criteria by the American Diabetes Association [1] – still expected to evoke considerable debate – and the final reports of the therapeutic United Kingdom Prospective Diabetes Study (UKPDS) [2–5].

The UKPDS was a mammoth task and analysed prospectively 3867 newly diagnosed patients with Type II (non-insulin-dependent) diabetes mellitus. The main message of this study was that an improvement in metabolic control with a fall in HbA_{1c} from 7.9% to 7.0% substantially reduces the risk of microvascular complications (by 25%) and of any diabetes-related death (by 10%) [2]. This outcome was independent of the mode of treatment. This is, however, not to say treatment with insulin at the onset of Type II diabetes – when diet would suffice – is to be recommended as it promotes polyphagia, weight gain and also insulin resistance. Thus it is frequently counter-productive. The data obtained by the UKPDS are in line with that reported by the Diabetes Control and Complications Trial (DCCT) for patients with Type I (insulin-dependent) diabetes mellitus [6] and convincingly confirm Dr. Pirart's landmark study on 'Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients obtained between 1947 and 1973' [7]. This report showed conclusively, with the methods of its time, that good metabolic control delays the onset of late diabetes-associated complications. It is amazing that this extremely important study was not cited in either of the final reports of the more recent studies [2–6].

The important observation that lowering blood pressure, regardless if by captopril or atenolol [3], has the same effect in reducing the sequelae of hypertension as to fatal and non-fatal diabetic complications will reconcile the internist with clinical diabetology, up until now had been a tendency to reinvent the rules of internal medicin of treating nephropathy and hypertension whenever it does occur. Some puzzle, however, is raised by the finding that conventional (non-intensive) treatment of Type II diabetic patients is associated, among single endpoints, with fewer deaths from renal disease than intensive treatment with more improved HbA_{1c} [2]. The recommendation of UKPDS no. 34 [3] that 'glucose control with metformin could be the first line pharmacological therapy of choice' in overweight diabetic patients is – at considerable expense – in line with what has been described as 'rational treatment of NIDDM' based on clinical and physiological knowledge in the past [8]. Of some concern is, however, the observation that drug interaction between sulphonylurea and metformin could be detrimental and add to dia-

betes-related death when both drugs are combined after long-term pretreatment with sulphonylurea [3].

The clinical impact of such large prospective intervention studies is manifold and is not to be underestimated. They provide lots of news but also plenty of confirmatory and lateral observation. Thereby, helpful self-regulation and correction of previous findings and preconceived therapeutic ideas can be mediated. This applies in particular to the finding of the University Group Diabetes Program (UGDP) study (which analysed 1027 newly diagnosed diabetic patients), that the oral antidiabetic agents, tolbutamide and phenformin, but not insulin contribute to diabetes-associated cardiovascular mortality [9]. The validity of the study and its conclusion have been debated extensively and emotionally for years. What though is the answer to the problem of different antidiabetic drugs being analysed in the two large unrepeatable UKPDS and UGDP studies when they stand against each other (unless class action is claimed)? One message of the UKPDS is that even tremendously costly prospective studies will give us only partial answers, some news and hints as to new risks which include potential detrimental drug interaction when the biguanide metformin is added after 10 years of sulphonylurea treatment. Thus, in the absence of absolute truth, some insecurity will unavoidably remain and clinical judgement will retain its domain.

Some major news with potentially great impact on prevention of Type II diabetes has been provided by basic research on modes of controlling fuel stores and energy supply. Both seem to become more accessible not only via the feedback loop between leptin, a polypeptide hormone produced by adipose tissue, and the hypothalamus [10] but also by the discovery of orexins in the lateral hypothalamus and of their ability to increase food intake [11]. It is noteworthy that leptin, given intravenously, is able to increase glucose turnover and uptake in mice or to decrease their hepatic glycogen content [12]. Both discoveries not only further our understanding of the causes of excess calorie ingestion but also open new strategies for its avoidance. Thus, appropriate therapeutic manipulation of these appetite hormones will help to reduce the risk of developing obesity and associated insulin insensitivity, instrumental in the untimely and premature manifestation of genetically predisposed Type II diabetes.

Besides quantitative control of energy/calorie intake, better qualitative definition of ingested fat might be of considerable additional importance because lipotoxicity, mediated by fatty acids, has a strong impact on insulin sensitivity and secretion [13]. As the composition of fat stores in adipose tissues reflects qualitatively that of ingested fat, any fat mediated insulinotropic lipotoxicity will be perpetuated until fat stores are either depleted or have otherwise changed their composition. The sheer size of the fat deposit of an obese person could thus well guarantee that stored saturated fat and the like can be provided long-term and thereby prolong its detrimental action. Thus, any nutritional mistakes made over the years could contribute long-term to carbohydrate intolerance. Against this background diabetes research needs to develop a stronger nutritional interest and analyse in even more detail the sequelae of fat quality on all aspects of insulin sensitivity.

Clearly we have lots of work to do in 1999 and beyond to try even harder to solve the riddles of diabetes and its rational treatment. I look forward to the fruits of your labour in the form of fine manuscripts submitted to *Diabetologia*. The Editorial Board, the staff of the Editorial Office and myself will do our best to help you in the publication of your endeavours.

Happy New Year.

Werner Waldhäusl

References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997) Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 20: 1183–1197
2. UK Prospective Diabetes Study Group (1998) Intensive blood glucose control with sulphonylurea of insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352: 837–853
3. UK Prospective Diabetes Study Group (1998) Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352: 854–865
4. UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317: 703–713
5. UK Prospective Diabetes Study Group (1998) Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 317: 713–720
6. The Diabetes Control and Complications Trial Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 329: 977–986
7. Pirart J (1978) Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. Diabetes Care 1: 168–188
8. Waldhäusl W (1990) Rational treatment of non-insulin-dependent diabetes mellitus: does it exist? Diabetes Nutr Metab 4: 259–265
9. University Group Diabetes Program (1976) A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 19 [Suppl 2] 785–930
10. Friedmann JM, Halaas JL (1998) Leptin and the regulation of body weight in mammals. Nature 395: 763–770
11. Sakurai T, Yanagisawa M (1998) Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein coupled receptors that regulate feeding behaviour. Cell 92: 573–585
12. Kamohara S, Burcelin R, Halaas JC, Friedman JM, Charron MJ (1997) Acute stimulation of glucose metabolism in mice by leptin treatment. Nature 389: 374–377
13. McGarry JD, Dobbings RL (1999) Fatty acids, lipotoxicity and insulin secretion. Diabetologia 42 (in press)