Diabetes: learning from the past 25 years and looking to the future

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In August 2018, the National Institute of Diabetes and Digestive and Kidney Diseases of the US National Institutes of Health published the third update of *Diabetes in America*. The report provides a comprehensive picture of epidemiological, public health, clinical and trial data on diabetes and its complications provided by leading researchers and clinicians [1]. A decade of preparation, writing, editing, and reviewing makes *Diabetes in America* an authoritative reference work. That said, the rapid pace of new information in diabetes in recent years renders some of the contents somewhat out-of-date at publication; this necessitates supplementation of information with the latest data from other sources.

It is nearly a quarter of a century since the second edition of *Diabetes in America* appeared in 1995. Since then, diabetes has continued to explode in the USA and indeed around the world. A more reassuring picture is presented by declining rates of some complications of diabetes and cardiovascular mortality rates, the latter reflecting trends in the general population. Among the new elements in the 3rd edition of *Diabetes in America* are chapters on the genetics of type 1 diabetes, type 2 diabetes, and monogenic diabetes. These sit alongside discussions of the associations between diabetes and cognitive impairment, sleep disturbance, liver disease, cancer, and the skeleton. The prevention of type 1 and type 2 diabetes – more successful to date in the case of the latter – is also covered. However, discussion of the recently demonstrated cardioprotective properties of certain sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists is incomplete in some details. The paucity of data on the expanding role of continuous glucose monitoring and other new technologies has also attracted criticism from some commentators and diabetes advocacy groups. The editors acknowledge that *Diabetes in America* is not intended to provide a review of current clinical care guidelines.

In the UK, the Oxford Diabetes Symposium, supported from its inception by an unrestricted educational grant from Novo Nordisk, celebrated a milestone of its own – its 25th anniversary – almost simultaneously with the publication of *Diabetes in America*. The symposium has become an essential annual fixture on the calendar for senior diabetes clinicians and scientists who gather to share updates and discuss issues in an open and collegial environment. For most of its history, the Oxford Diabetes Symposium was hosted by Exeter College which counted Professor Sir Roger Bannister (neurologist and the first man to officially run a mile in under 4 min) among its alumni. In recent years the venue has moved to Keble College at which Professor Sir David Spiegelhalter was an undergraduate; Spiegelhalter is credited with advancing aspects of clinical trial design and interpretation during his time at the UK Medical Research Council Biostatistics Unit. Certainly, clinical trial data were very much in evidence at the 2018 Oxford Diabetes symposium. The Diabetes Control and Complications Trial was published in 1993 [2] and the UK Prospective Diabetes Study (led from the University of Oxford) followed in 1998 [3,4]. These studies set frameworks for the management of type 1 diabetes and type 2 diabetes, respectively, including the prevention of cardiovascular disease [5,6]. Clinical trials have also been center-stage in the rapid advancement of therapeutics for diabetes more recently. Some of these – cardiovascular outcome trials in type 2 diabetes – have been mandated by regulators over the past decade. Others, for example, for new or biosimilar insulins, are also strictly regulated by the Food and Drug Administration and European Medicines Agency. The design of diabetes cardiovascular outcome trials has been the subject of debate with calls for trials that, rather than being focused on cardiovascular safety in selected high-risk groups of patients, are designed to be more relevant to broader patient populations. In parallel, there has been a surge in interest in so-called real-world data which does not always mirror the results from clinical trials.

Topics covered in the 2018 Oxford Diabetes Symposium, which was a review of the last 25 years along with a look to future prospects, that have been usefully informed by recent clinical trials included: hypoglycemia (Professor Simon Heller, University of Sheffield, UK); reversal of type 2 diabetes through very-low calorie diets (Professor Roy Taylor, University of Newcastle, UK); and novel insulins (Professor Chantal Mathieu, Katholieke Universiteit Leuven, Belgium) [7].

While wide-ranging, the symposium proceeded logically from reviews of relevant basic science to leading-edge translational drug development. Professor Heller summarized data linking hypoglycemia with adverse clinical

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outcomes, including noncardiovascular events, in major trials focusing on ACCORD, VADT, and ADVANCE. He reminded delegates that cardiac events are uncommon in clinical studies making the study of adverse clinical outcomes associated with hypoglycemia problematic. Absence of universally agreed definitions of hypoglycemia hinder comparisons between clinical studies. When experimental hypoglycemia studies are considered, there is a lower limit to the degree of hypoglycemia that can be achieved using the hypoglycemia clamp technique since cerebral dysfunction is encountered when plasma glucose levels fall to ~2.5 mmol/l. or less. As for the so-called 'dead-in-bed' syndrome, initially reported in the early 1990s in the context of otherwise apparently healthy patients with type 1 diabetes [8], Professor Heller pointed to nocturnal hypoglycemia-associated acquired long QT interval as a putative promotor of potentially fatal cardiac arrhythmias. Another piece of information with important clinical implications, that is, a U-shaped curve for the relationship between cognitive function and glucose levels in children with type 1 diabetes, perhaps deserves wider appreciation [9]. Readers can find more information on the topic of hypoglycemia in diabetes at the International Hypoglycemia Study Group (*http://ihsgonline.com*). Noteworthy during Q&A was the comment that certain basal insulin analogs can be 'transformational' for some patients.

A recurring theme throughout the symposium was the heterogeneity of what is currently labeled type 2 diabetes [10]. Heterogeneity is also evident in the variable responses to medications, even those as well-established as metformin. Professor Ewan Pearson (University of Dundee, UK) looked ahead to near-future prospects for patient-level desktop pharmacogenomics to help inform individual treatment decisions based on probabilities of response and likelihood of side-effects.

Professor Roy Taylor gave a masterful presentation on a most impressive recent example of clinical science which succeeding in (a) elucidating relevant basic scientific knowledge (b) testing a clear hypothesis rigorously through detailed metabolic studies, and (c) successfully translating the results into real-world clinical practice [11,12]. The practical choice for many patients with newly diagnosed obesity-associated type 2 diabetes is now as follows: engage in an intensive 3-month very-low calorie diet that carries a good prospect of effectively reversing the disorder – or face decades of diabetes with an escalating pharmacotherapy burden. Of course, pharmacotherapy will still be required by many patients – longer-term data on sustained remission rates when patients transition to a weight-maintenance calorie intake are awaited. Nonetheless, this marks a dramatic shift in the management of type 2 diabetes.

Professor Leigh Perreault (University of Colorado, USA) provided a stimulating and wide-ranging US perspective on public health efforts in the UK to prevent or delay the onset of type 2 diabetes in high-risk individuals and provided a review of interventional clinical trial data. Time was then dedicated to a panel discussion between the National Clinical Director for Obesity and Diabetes for England (Professor Jonathan Valabhji), the Assistant Director of Improvement Support and Innovation at the main national diabetes advocacy organization (David Jones of Diabetes UK) and a Member of Parliament who brings the perspective of a senior NHS biochemist to the All-Party Parliamentary Group for Diabetes (Liz McInnes, MP). Professor Valabhji pointed to the successful roll-out of the NHS Diabetes Prevention Programme across England – a commendable national first (although issues of low take-up by some target groups has been identified).

Inevitably, this selective review cannot do full justice to the contents of the symposium, many aspects of which were of relevance to clinical practice. As reliable as ever, Professor David Matthews wrapped up the proceedings in a memorable – and at times self-knowingly irreverent – keynote lecture spanning the last 25 years and the next 25 years taking in diabetes treatment algorithms, ('improper dichotomies'), phenotyping, genotyping, big data, small data, telemedicine, novel therapies and more.

Congratulations and thanks are due to Dr Garry Tan, Dr Rustam Rea and Dr Alistair Lumb for assembling a stellar array of lecturers for this anniversary symposium. The last quarter century has witnessed considerable advances (a) in the collective understanding of the pathophysiology of diabetes and (b) the development and implementation of novel devices and pharmacotherapies. As a consequence of these advances (some of which, it should be acknowledged, were not anticipated), the risk-to-benefit equation of treatment is moving in a favorable direction (albeit with higher acquisition costs for new therapies and technologies). Clearly, much remains to be done in terms of optimizing management to improve quality of life and clinical outcomes. The range of academic expertise allied to a sound appreciation of the burden of diabetes for individuals and society that was so eloquently displayed at the 25th Oxford Diabetes Symposium bodes well for continued progress.

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ProSciento undertakes early-phase clinical development of new therapies and devices for diabetes for companies that include Eli Lilly, Novo Nordisk, Sanofi and others.

Conflicts of interest

There are no conflicts of interest.

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