The history of hypertension: 1970–2006

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Today's diabetes world is fast-moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In previous installments of *Tattersall's Tales*, Robert Tattersall explored the history of hypertension up to 1970. This instalment details developments that took place between 1970 and the present day.

By 1975 (when I became a consultant in Nottingham) it was clear from the Framingham Heart Study that hypertension was bad for coronary and cerebral vessels, especially in people with diabetes (Kannel et al, 1970; Kannel et al, 1971). Even if hypertension was more common in diabetes, which was hotly disputed, it was unclear whether treatment would make any difference. A few studies, such as the US Veterans Administration Cooperative Study in 1970, suggested that lowering blood pressure was beneficial even when an individual's blood pressure was not inordinately high (US Veterans Administration Cooperative Study, 1970). Unfortunately, people with diabetes were excluded from such trials because it was thought they would 'contaminate' the results. People also worried that, in the long term, the hypotensive effect of thiazides might be cancelled out by their diabetogenic and lipid-raising effects.

Beta-blockers, introduced in the mid-1960s, were also thought to be inadvisable for the treatment of diabetes since they masked the warning of hypoglycaemia and were diabetogenic. Concerns about beta-blockers were also raised by the discovery that a rare side effect of practolol was sclerosing peritonitis (Brown et al, 1974).

Safety was paramount because there was no precedent for using drugs to prevent, as opposed to treating, diseases and the concept was foreign to patients and doctors. Four developments in the late 1970s laid the foundations for the modern treatment of diabetes and hypertension.

Hypertension and nephropathy

The work that made antihypertensive treatment the cornerstone of the management of pre-uraemic diabetic nephropathy was that of two Danish workers – Carl Eric Mogensen and Hans-Henrik Parving (and their mentors Knud Lundbaek in Aarhus and Torsten Deckert in Copenhagen).

Mogensen's first study was based on the observation that the rate of decline of glomerular filtration rate (GFR) was correlated to blood pressure (Mogensen, 1976). Participants were followed longitudinally before and after antihypertensive treatment and preliminary results were presented at meetings in 1976.

Longer-term results were published by Mogensen in the *British Medical Journal* (Mogensen, 1982) and Parving in the *Lancet* (Parving et al, 1983). Both showed that the rate of decline of GFR without treatment was around 10–12 ml/min/year, which could be reduced to around 2–5 ml/min/year when blood pressure was controlled. These studies were criticised because of the relatively small number of participants but also, more pertinently, because of the lack of randomisation. Neverthless, an important principle was established that has stood the test of time.

Microalbuminuria

Measuring GFR was inconvenient in research and clinical practice. Happily, a technique developed several years earlier was sitting, as it were, unused on the shelf. In 1963 Harry Keen was looking for a way to document the earliest signs of renal disease in the Bedford Survey. Clinical proteinuria was the hallmark of nephropathy but he wanted to be able to measure smaller amounts. One idea was to collect a large volume of urine and concentrate it by hanging it in a dialysis membrane and fanning away the water that came through – not very practical!

At a British Diabetic Association (now known as Diabetes UK) meeting Harry and his research fellow, Costis Chlouverakis, heard Nick Hales and Philip Randle describe a method of measuring the amount of insulin by precipitating the insulin–insulin-antibody complex with a second, anti-globulin antibody. They immunised a few guinea pigs with human albumin and within a few months had discovered microalbuminuria (Keen and Chlouverakis, 1964).

Surprisingly this had already been discovered by the Ames Company. When they introduced a tablet test for urine protein (Albutest) in the 1950s, clinicians complained that it gave 'false positives' in patients in whom the standard sulphosalicylic acid test was negative. In fact Albutest was so sensitive that it was detecting microalbuminuria, but

pressure from clinicians led to its replacement by the less sensitive, and more convenient, Albustix (also made by the Ames Company). By 1982 microalbuminuria was shown to be a marker of early nephropathy (Viberti et al, 1982) and later a more general indicator of bad blood vessels.

ACE inhibitors

It was known from the early 1960s that angiotensin-converting enzyme (ACE) produced angiotensin II, which raised blood pressure and was important in malignant hypertension. A Brazilian pharmacologist working with John Vane (1927–2004) in London discovered that a peptide in the Brazilian viper venom inhibited ACE and Vane suggested to Squibb, the pharmaceutical company for whom he worked as a consultant, that they put resources into making an ACE inhibitor. This was a brave idea since most experts did not believe that ACE had anything to do with ordinary hypertension. Squibb chemist Miguel Ondetti managed to synthesise a nonapeptide (teprotide), which was effective but of no commercial interest since it had to be injected and cost a million dollars per kilogram to synthesise (Smith and Vane, 2003). The project had effectively been scrapped but in 1974 biochemist David Cushman, who had worked with Ondetti, read a paper on the synthesis of an inhibitor of carboxypeptidase, an enzyme which he thought was very similar to ACE. They were both given a great deal of flexibility by Squibb and just went back to the ACE inhibitor project without asking permission (Cushman and Ondetti, 1991). Within 18 months they had made captopril, which was launched in 1981 and became Squibb's first 'billion-dollar drug'. ACE inhibitors have improved the prognosis of type 2 diabetes beyond anyone's wildest dreams (Heart Outcomes Prevention Evaluation Study Investigators, 2000).

The UKPDS

The report from the University Group Diabetes Program in 1969–1970 threw the management of diabetes into confusion by suggesting that the control of glucose levels had no effect in preventing complications and that sulphonylureas were toxic (Tattersall, 1994). Most European diabetologists did not believe it but there was little will and even less money to do a new long-term study. In retrospect it is extraordinary that almost single-handedly Robert Turner (1938–1999) managed to start the United Kingdom Prospective Diabetes Study (UKPDS) in 1977. Finance was a constant problem and the amount he originally asked the then British Diabetic Association for was, though minute by American standards, half the annual research budget. It was the votes of the elder statesmen (John Nabarro, Arnold Bloom and Harry Keen) which secured the funding against the self-interest and scepticism of younger members of the research committee – I was one but will draw a veil over the names of the others! The original aim of the UKPDS was to find out if blood glucose control would prevent related complications but, after it transpired that nearly half the patients had hypertension, a blood pressure study was included in 1987 (1148 participants). Tight blood pressure control (to a target of 144/82 mmHg) reduced the risk of any diabetes-related end point by 24 %, microvascular end points by 37 % and strokes by 44 % (UKPDS Group, 1998). The best epitaph to Robert Turner is that he ended 100 years of controversy about whether hypertension was more common in diabetes and whether it was worth treating.

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