The first of the mega trials

Professor Robert Tattersall

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 this installment of *Tattersall's Tales*, Robert Tattersall describes the challenges and controversies faced by the authors of the first randomised controlled trial in diabetes – the University Group Diabetes Program.

When the first randomised controlled trial in diabetes started in 1961, physicians would have been amazed to hear that 40 years later, trials in diabetes often involve 10 000 or more patients; and are often performed, for commercial reasons, in several different countries. They would also be surprised that at the beginning of the 21st century the number of authors per paper had grown so large that some journals capped the list. They would hardly be able to comprehend that sometimes the authors are not even named in the byline, but are referred to by acronyms such as the UKPDS Group or the ADVANCE Trial Investigators and in other cases it is only the writing committee that is named, with the 100 or more other contributors listed in small print at the end. This is in total contrast to the 1960s when virtually all research was done in single hospital departments and written up by less than four authors, one of whom was usually, whether he deserved it or not, the departmental head. A trial such as I am about to describe involving 12 university departments was a totally new departure, as was the involvement of a statistician.

By 1960, over 500 papers had been published on oral hypoglycaemic agents, but nobody knew whether they were better than insulin or if they would prevent the occurrence of the complications of diabetes. The only way of establishing their true value was to compare them to the gold standard of insulin – this led to the University Group Diabetes Program or UGDP (Tattersall, 1994). It was funded by the National Institutes of Health and was intended to show how a properly designed, randomised controlled clinical trial could resolve differences of clinical opinion. Patients were eligible if their diabetes had been diagnosed less than a year earlier, and if they were likely to live at least 5 years (the length of the original funding). Recruitment began in 1961 with allocation to one of four regimens.

- Insulin variable. As much insulin as necessary to maintain normal blood glucose levels.
- Insulin standard. A fixed dose of lente once daily. This was to distinguish between the blood glucose lowering and other possible effects of insulin.
- Tolbutamide. A fixed dose of 1g before breakfast and 0.5g before the evening meal – the average dose used in clinical practice.
- Placebo.

In 1962 a fixed-dose phenformin group was added.

It was hoped to recruit 200 patients in each group, which proved so difficult in the 12 university clinics that outpatients were screened to find more people with diabetes. No attempt was made to exclude people with vascular disease, and it later transpired that patients in one centre were recruited *from* the cardiac clinic! It was expected that both insulin and tolbutamide would be better than placebo, but the tolbutamide arm of the study was stopped in 1969 because analysis by what the *The Lancet* called "advanced, elaborate, and novel statistical techniques" showed a significantly higher death rate in the tolbutamide group (12.7%) than in the placebo group (4.9%). Mortality in the two insulin-treated groups was nearly the same as for placebo patients. In 1970 an ad hoc committee of the American Diabetes Association (ADA) commented that, apart from the apparent toxic effect of tolbutamide:

> *"What is even more arresting is that neither of the insulin-treated groups had a lower mortality than the placebo treated patients. This finding carries the broadest implications for the treatment of non-insulin-dependent adult onset diabetes. First, if insulin – the diabetic's medicinal remedy sine qua non – does not permit patients to live longer than does a diet, would not this class of patients, in respect to longevity, be just as well off with diet alone? Secondly, if insulin can do no better with mortality than diet, is it likely that any oral hypoglycemic agent presently available, whether or not it acts by stimulating insulin secretion, can do any better than the hormone itself or even as well?"*

The conclusion of the ADA was that the only indication for tablets was a patient poorly controlled on diet who refused to take insulin.

To say that the findings of the UGDP did not go unchallenged would be a major understatement. In 1975, the *The Lancet* described "the storm of controversy aroused by these results" as being "without parallel in modern medicine" (Editorial, 1975). The Food and Drug Administration, US, endorsed the conclusions and announced that warning labels would be put on all oral antidiabetic drugs, whereupon 40 leading American diabetologists hired a lawyer to fight this.

Arguments about the study were both personal and scientific, and were fuelled by what opponents saw as the self-righteous tone of some UGDP spokesmen. An example of personal animus was the revelation by critics that the statistician, Christian Klimt, had been a paid consultant to the US Vitamin and Pharmaceutical Corporation, New York, who made phenformin. Supporters countered by claiming that their opponents were "drug company whores" paid by Upjohn Company, Michigan – the makers of tolbutamide which had been so tarnished by the study.

The most cogent criticisms were summarised by Holbrooke Seltzer of Dallas, Texas in *Diabetes* (Seltzer, 1972) and rebutted by the UGDP investigators in the same journal (Prout et al, 1972). According to Seltzer, the odds were stacked against tolbutamide from the start because cardiac risk factors such as angina and abnormal ECGs were more common in the tolbutamide group. He, and others, believed the randomisation had broken down, although the differences could easily have arisen by chance. The investigators countered that their critics seemed not to appreciate the purpose and power of randomisation – which was probably true since randomised controlled trials had not been demanded by the FDA until 1962, and the UGDP was the first in diabetes. Previously, the evidence put to the FDA in support

of a drug was often just "testimonials" from physicians who had casually tested it on their patients and been paid for doing so.

James Moss commented in 1975 that "there were 30 deaths in the tolbutamide-treated patients with 20 in each of the other groups. Never before have 10 deaths created such a controversy." He pointed out that half of the tolbutamide patients who died had autopsies, compared with only 29% of those on placebo or insulin. If only three deaths in each group had been reassigned, the significance of the increased cardiovascular deaths in the tolbutamide group would have disappeared (Moss, 1975).

Deaths were unevenly distributed between clinics – the three that enrolled the sickest patients had the most fatalities, and the three that admitted the healthiest had the least. Moss wrote, sarcastically, that "the one thing this study proves is that patients who already have heart disease die sooner than those who do not." Arnold Bloom used to say that in some centres, swallowing tolbutamide was like drinking cyanide, while in others it was as innocuous as eating sweets!

Compliance was a problem, and only 26% of participants remained on their assigned treatment for the whole study. The attitude of the investigators to medication changes and dropouts was to ignore them. It was later pointed out that the credibility of the conclusion that insulin was ineffective in reducing cardiovascular deaths was greatly weakened by the fact that almost half of those individuals assigned to the variable insulin group who died had had virtually no insulin. When the critics finally got the records under the US *Freedom of Information Act* of 1966, they found that just over half of those studied had a fasting blood glucose level under 7.2mmol/L at baseline – leading Moss to ask how one could evaluate the benefit of a drug that lowers blood glucose levels if less than half the patients had hyperglycaemia.

How much the UGDP affected clinical practice is hard to say. My impression is that American doctors were sharply polarised. In the 1970s, a friend worked at an American clinic where oral agents were banned. Patients who failed on diet were put onto insulin with the dose being increased "until the syringe had been filled". Then the patient was left, as Arnold Bloom put it, to stew in their own sugar! In contrast, Joslin Clinic doctors continued to use oral agents, and noted in 1971 that they had been used in 10 000 of their patients and were "here to stay for the foreseeable future." The UGDP findings were heavily criticised by European opinion leaders and medical journals, and sulphonylureas and biguanides continued to be used by the 30–40% of patients in an average European clinic who were on tablets.

Clearly no truce was ever going to be possible, and in 1975 the *Lancet* summed up the mess by saying.

> *"The UGDP war remains in the balance, and the combatants are now obscured by increasingly heavy clouds of clinical, statistical and philosophical smoke. Further discussion of the results cannot now be helpful (Keen et al, 1975)."*

It was not completely the last word because, in a broadside against their critics, in 1979 the UGDP investigators claimed that "the main difficulty with the UGDP is not its design, execution or analysis but rather that it reached an unpopular conclusion" (Prout et al, 1979). Perhaps the recent controversy about rosiglitazone would have given the 1960s physicians a sense of déjà vu?

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