Research and serendipity

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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 this installment of *Tattersall's Tales*, Robert Tattersall explores the often beneficial occurence of chance in diabetes research, recounting some personal experiences that have led to a variety of important scientific discoveries over the years.

I retired in 1998, and thereafter, whenever I met my former colleagues, they invariably said "you were lucky to get out when you did". When pressed for specifics, they usually cited managerial control over their outpatient activities and the impossibility of doing research "the way you used to". I didn't really understand the latter until 2004 when I read a paper in the *British Medical Journal* in which the author explained that getting ethical approval for a relatively simple project had taken 44.5 hours, £850 and much angst (Wald, 2004). It may be that in this era of mega clinical trials there is no place for the part-time clinical researcher but such bureaucracy would probably put aspirants off for good. This would be a pity because I found research exciting and a respite from the grind of clinical medicine. The present excessively prescriptive system rules out the possibility that, like the Three Princes of Serendip, one might make fortunate discoveries by accident.

I can think of at least three occasions when I discovered things by having the freedom to "vary the protocol".

Maturity onset diabetes of the young (MODY)

The first came when I was employed at King's College Hospital as research fellow on David Pyke's study of twins with diabetes. The newly retired Wilfrid Oakley decided to look at all the patients in the clinic records with diabetes for 40 years or more (Oakley et al, 1974). They were seen at a special leisurely clinic on Tuesday mornings where Wilfrid and I (sometimes assisted by the much busier David Pyke and Peter Watkins) took a history and examined them.

One patient who chance allocated to me was a 67-year-old woman whose diabetes had been diagnosed in 1928 during her first pregnancy. Insulin had been started at once and continued for the next 42 years in a daily dose of 20–30 units. As she had never had ketonuria or been ketoacidotic, she was changed to sulphonylureas in 1970 and remained well controlled. What was striking was that after 45 years of diabetes, her fundi were normal and she had no proteinuria. She also had a strong family history of diabetes. When I mentioned her to David Pyke, he said "She sounds like Mrs Mason".

Jacqueline Mason developed diabetes in 1943 aged 12 years and was initially treated with twice-daily soluble insulin. In 1948 she discontinued this of her own accord, remaining without insulin until 1951 when she came back to King's complaining of thirst. She had not lost any weight but her blood glucose level was 25.5 mmol/L. She was "given a rocket" and restarted on insulin. In 1970, in the face of strenuous opposition from David Pyke, she insisted on being changed to sulphonylureas and, to everyone's surprise, remained well controlled. When I asked her why she had been so sure she could manage without insulin, she told me that her aunt and cousin, diagnosed respectively at 23 and 17 years of age, had both been able to stop insulin after being on it for 30 years.

Thinking that if I could find another case of this peculiar form of diabetes, I would have a series, I searched the clinic card index and found the notes of a 62-year-old woman who had developed diabetes in 1926 at age 14. She took insulin until 1970 when she was changed to sulphonylureas because of frequent hypoglycaemia on 16 units of protamine zinc insulin. What was striking about these women was that in spite of their long durations of diabetes they had no or minimal microvascular complications. Their 20 living relatives had a phenotypically identical condition and only one was still on insulin. Their pedigrees, to my inexperienced eye, suggested autosomal dominant inheritance but to be on the safe side David Pyke arranged for me to meet a professional geneticist, Harry Harris, who agreed. I wrote them up under the title "Mild familial diabetes with dominant inheritance" (Tattersall, 1974). David Pyke declined my offer of co-authorship, "because I've hardly done anything" – an important principle, which I tried to stick to thereafter. These were the first families with MODY, a term that Steve Fajans and I coined when I went to work with him in Michigan.

Nocturnal hypoglycaemia

When I went to Nottingham as a consultant in 1975, I had the good fortune to find that my registrar was Edwin Gale. I persuaded him that diabetes research would be fun and we applied to the British Diabetic Association (BDA, now Diabetes UK) for an RD Lawrence fellowship, which paid Edwin's salary for 2 years. I no longer have a copy of the application but I remember that one part was about the genetics of diabetes and involved lots of glucose tolerance tests. Another was about brittle diabetes and its resemblance to parasuicide. These projects were never done but the BDA got their money's worth in Edwin's overnight studies of poorly controlled people with type 1, which showed that:

1. Hypoglycaemia, often amazingly prolonged, was quite common even in those whose fasting or mid-morning blood glucose levels were high (Gale and Tattersall, 1979).
2. High glucose levels in the morning were not due to rebound caused by excessive secretion of counter-regulatory hormones (the Somogyi effect) but due to the pharmacokinetics of injected insulin (Gale et al, 1980).

One other important discovery that Edwin and I made off protocol was that phenformin could cause fatal lactic acidosis even in those without the classic contraindications to biguanides such as renal or heart failure (Gale and Tattersall, 1976).

As far as I remember there were no site visits or progress reports, but the powers that were in the BDA were clearly satisfied that we had spent their money wisely because further grants were forthcoming.

Hypoadrenia

In 1991 I became, against my better judgement, Clinical Director of Medicine at Nottingham University Hospital. This was a bad move but salvation came 18 months later when I saw an advertisement placed by the Wellcome Trust Centre for the History of Medicine offering clinicians a 4-month sabbatical. I wrote a rather sketchy proposal to research the introduction of insulin treatment in the East Midlands in 1923–4. I had an idea that "proper medical historians" preferred circumscribed projects like this rather than, say, a history of insulin. Whether or not this was right, I got the fellowship.

It turned out that my project was a non-starter because medical journals and the press were full of articles about insulin so it was adopted almost instantly. My tutor was not at all discomfited when I told him this. He simply said "well, do something else then". The Wellcome Library is a treasure trove of long forgotten books and journals and during my browsing I came across the grandly named Charles Eucharist de Medici Sajous (1852–1929). He entered the nascent field of endocrinology in 1903 with an 800-page book on internal secretions, which went through 10 editions up to 1922. He also popularised a new disease, "hypoadrenia", a forme fruste of Addison's disease, which developed, according to Sajous, when the adrenals were exhausted by the strains of modern living (Tattersall, 1999). The main symptoms were fatigue and increased susceptibility to infection but it also caused common and non-specific symptoms ranging from backache to sexual impotence. Physiologists poured scorn on hypoadrenia but it was popular with clinicians and Sajous was elected first president of the Endocrine Association in 1917. The final verdict of the physiologist Roy Hoskins (1880–1964) was that, "A host of sick people swallowed dried adrenal gland substance and recovered from a host of diseases. Post hoc, propter hoc – the adrenal material cured the disease and hypoadrenia was vindicated" (Hoskins, 1931).

Postscript

My experiences reminded me of the story of the discovery of nylon. In 1928 the DuPont chemical company set up a research laboratory to make artificial materials. They headhunted a Harvard protein chemist Wallace Carothers (1896–1937) at double his academic salary and gave him complete freedom to do what he wanted. No progress reports were required. This faith was richly rewarded when in 1931 Carothers discovered neoprene, a rubber substitute, and even more in 1935 with nylon or synthetic silk, which made DuPont's fortune. The moral is to back your man and let him get on with it.

We must all hope that the new proposals for the regulation and governance of clinical research by the Academy of Medical Sciences (2011) are implemented as soon as possible.

Academy of Medical Sciences (2011) *A New Pathway for the Regulation and Governance of Health Research*. AMS, London. Available at: http://bit.ly/eVgxlC (accessed 07.02.11)

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