Obituary

Stephen Edward Smith

Clinical Pharmacologist
1929–2007

Michael D. Rawlins and Shirley A. Smith

Stephen Smith – along with Desmond Laurence, Andrew Herxheimer, Colin Dollery and Paul Turner – was one of the pioneers of British clinical pharmacology. Like them, he trained as a physician; but he decided to pursue an academic career in pharmacology with an emphasis that was largely about the clinical aspects of the discipline.

His medical training was at Oxford and St Thomas's Hospital. After the traditional pre- and post- registration house officer posts, he was called up for his national service in the army. He had intended to become an anaesthetist, and his army experience was designed to give him a solid grounding in the specialty.

During his time in the army May and Baker introduced a new, allegedly shorter acting, anaesthetic (buthalitone). Smith undertook a study comparing the duration of effect of buthalitone, with that of thiopentone, and found they were virtually the same [1]. He had become fascinated by the possibilities that pharmacology offered.

He might still have become an anaesthetist had he not displayed uncharacteristic belligerence during the anatomy viva voce part of the (then) FFA examination. When asked, for the third time, whether a particular bone was membranous or cartilaginous he replied: *"I don't know. I don't care. And I don't see what possible importance it could be to an anaesthetist"*. And he walked out.

Smith spent the next 36 years of his life in the pharmacology department of St. Thomas's Hospital Medical School successively as lecturer, senior lecturer, reader and finally professor of clinical pharmacology. When St. Thomas's and Guys merged, he became the chairman of the Division of Clinical Pharmacology of the United Medical and Dental Schools. On his retirement, in 1993, he became Senior Research Fellow in Neuro-Ophthalmology at the National Hospital for Nervous Diseases where he continued to carry out research, and see patients, until a few weeks before his death.

Although eclectic in his interests, Smith made three massive contributions to clinical pharmacology. He was one of the very earliest pharmacogeneticists; he was a founder of the sub-discipline of ocular pharmacology; and he was a wonderfully memorable – and effective – teacher.

Smith was fascinated by interindividual differences in the response to drug therapy. In the late 1960s a few studies had examined the extent to which genetic factors might explain differences in the rates of drug metabolism. Smith, however, was more interested in the heritability of pharmacodynamic differences. With the late Åke Bertler, he undertook twin studies, using volunteers from the Swedish twin registry, to examine the contribution of genetic factors to the effects of intravenous hyoscine *N*-butylbromide (on heart rate) and of topical phenylephrine (on pupillary size).

He and Bertler [2] showed that monovular, but not binovular, twins showed significant concordance in responses to both drugs. They also demonstrated, however, that the responses were dependent on the concordance of peripheral sympathetic and parasympathetic tone within each twin. They did not fall into the trap of suggesting that there was some genetic trait, at the receptor level, that mediated these differences in response. Rather, they attributed them to genetically determined influences on the resting tone of the autonomic nervous system.

Around this time, Smith also investigated the heritability of taste thresholds [3]. During the late 1960s there had been emerging evidence [4] that associations might exist between the sensitivities of receptors in taste buds and those which determined responses in the central and peripheral nervous systems. Indeed, the hope had been expressed that the measurement of taste sensitivity might have value in predicting the intensity of systemic drug response. The notion of "personalised medicine" was alive 35 years ago!

Smith's work on taste thresholds [3] showed that, at least to quinine, twin and parent-offspring showed very marked heritability (0.85 and 0.55 respectively). Yet, good scientist that he was, he went to great pains to describe the limitations of these studies. How, for example, might shared environmental factors contribute to the apparent similarities between twins and parent-offspring relationships? He discussed whether this might be as a result of parental resemblance during development; or the result of imitative behaviour through dietary control.

Smith's second great achievement was in ocular pharmacology. At around the same time as he was studying the pharmacogenetics of mydriatic agents he began to become intrigued by ocular pharmacology in general. His first, and very important, contribution was to compare the effectiveness of mydriatics for routine fundal inspection. He demonstrated, beyond doubt, that the short acting tropicamide was much more comfortable and practical for this purpose than others in common use at that time (e.g. cyclopentolate, homatropine, eucatropine) [5,6]. Patients the world over have benefited from these findings. The combination of tropicamide and phenylephrine is still the routine regime for mydriasis in many ophthalmology clinics [7].

Most of Smith's subsequent research was concerned with ocular pharmacology and physiology in health and disease. He explored the effects of a variety of drugs, and diseases, on intraocular pressure and pulsatile ocular blood flow. He studied, in depth, pupillary abnormalities in diseases such as Horner's, Holmes-Adie's syndromes and systemic autonomic neuropathies such as that associated with diabetes mellitus. And he undertook a careful investigation into the after effects of eximer laser photorefractive keratectomy.

The final stage in Smith's career at Queen's Square extended his clinical practice and research into the diagnosis of autonomic failure either confined to the eye or as part of more a widespread neuropathy. An important technique he employed was that of dynamic pupillometry in which abnormalities in the rate of change in pupil size, in response to light stimuli or drugs, can be used to reveal the pathology of the autonomic innervation.

Smith was also a gifted and popular teacher. One of us (MDR) should know because he taught me pharmacology as an undergraduate. When I had become a lecturer in medicine (and Smith was, by that stage, a senior lecturer in clinical pharmacology) we both became concerned about the limited teaching of therapeutics to undergraduate medical students. We decided to offer therapeutics ward rounds to final year students. In those heady days, where notions of curricula were almost non-existent, we just announced that – from a particular afternoon – we would be conducting teaching rounds in the subject.

The sessions involved my presenting, in outline, three patients. I would explain the rationale for the treatments that were being given. Smith would then harangue me –

and the students – about the reasons, the evidence, and what problems that might be expected. The students enjoyed, and seemed to learn, from our very public encounters. About 10 appeared for the first ward round but – within a month – over 50 wanted to come. But it was Smith's teaching skills that persuaded such large numbers of devotees to come along and not mine. I was his foil. I did not let him criticize, unreasonably, the treatments my patients were receiving. But, when he had a good point (as he often did) I would demur. And, of course, the students loved it!

On one of the last occasions that we met he described to me – in exquisite detail – how to prepare opium in a form that was suitable for smoking in a pipe. It was something he had learned – and enjoyed – during the two years he spent in Burma. I tried to explain that this was information overload for the chairman of the Home Office's Advisory Council on the Misuse of Drugs. He said it was part of my education!

REFERENCES

- 1 Kane PO, Smith SE. Thiopentone and buthalitone: the relationship between depth of anaesthesia, plasma concentration and plasma protein binding. *Br J Clin Pharmacol* 1959; 14: 261–4.
- 2 Bertler Å, Smith SE. Genetic influences in drug responses of the eye and the heart. *Clin Sci* 1971; 40: 403–10.
- 3 Smith SE, Davies PDO. Quinine taste thresholds: a family study and a twin study. *Ann Hum Genet* 1973; 37: 227–32.
- 4 Knopp W, Fischer R, Beck J, Teitalbaum A. Clinical implications of the relationship between taste sensitivity and the appearance of extrapyramidal side effects. *Dis Nerv Syst* 1966; 27: 729–35.
- 5 Smith SE. Mydriatic drugs for routine fundal inspection. *Lancet* 1971; October 16: 837–9.
- 6 Smith SE. Dose-response relationships in tropicamide-induced mydriasis and cycloplegia. *Br J Clin Pharmacol* 1974; 1: 37–40.
- 7 Smith SE, Smith SA. Dilate the pupil and see the fundus. *Br Med J* 1984; 289: 111–2.