This Week's Citation Classic®
CC/NUMBER 37
SEPTEMBER 14, 1987

O'Malley K, Crooks J, Duke E & Stevenson I H. Effect of age and sex on human drug metabolism. *Brit. Med. J.* 3:607-9, 1971.
[Department of Pharmacology and Therapeutics, University of Dundee, Scotland]

The capacity of geriatric inpatients to metabolise drugs was assessed by measuring the rate of elimination of two test drugs, antipyrine and phenylbutazone, and the results were compared with those of a young control group. In a number of the elderly patients the half-lives for the two drugs were markedly prolonged. These patients may be particularly at risk with regard to adverse drug reactions. [The *SCI*® indicates that this paper has been cited in over 315 publications.]

Kevin O'Malley
Department of Clinical Pharmacology
Royal College of Surgeons
Dublin 2
Ireland

June 9, 1987

On my arrival in 1970 as a research fellow in the Department of Pharmacology at the University of Dundee, I had completed two years of postgraduate medical studies and one year in pharmacology. In addition to this background, my interest in clinical pharmacology was also due to the favourable prognostications for the specialty at the time. The late James Crooks, who had recently been appointed professor and chairman of the department, had perceived with characteristic foresight that there were very considerable academic rewards to be won in this area.

I worked under the direct supervision of Ian Stevenson, who was then a lecturer (and is now a professor) in pharmacology. We sought to examine the effect of a number of variables on drug metabolism in humans and in the rat. In a variety of human studies we used antipyrine as a model drug and initially attempted to ascertain the effect of various "likely" drugs on the elimination of antipyrine. In the previous summer, a medical student, Eileen Duke, had started a study of antipyrine elimination in humans that included a number of elderly people. Stevenson and I thought it important to continue this work with the specific objective of ascertaining if old age had an effect on the elimination of antipyrine and phenylbutazone. Certainly, some evidence from animal studies indicated that this might be the case.

The study was a simple one in which subjects were given antipyrine or phenylbutazone; we then measured plasma concentration of the two drugs at intervals thereafter. For the *British Medical Journal* paper we presented only the plasma elimination half-life data. The antipyrine results were of the greatest interest for two reasons. First, there was considerable intersubject variability. Second, despite the large variability, we demonstrated a significant difference between young and old, with the mean half-life in the elderly being approximately 50 percent longer than for the young.

It was gratifying when our results were subsequently confirmed in 1975 in a much larger study from Baltimore[1] carried out by Bob Vestal and colleagues. Furthermore, we, as well as others, were able to show that not only was plasma half-life longer in the elderly, but clearance was diminished as well. We perhaps naively ascribed the differences between young and old to age alone. Vestal showed that, while one could demonstrate marked differences between old and young, much of the difference was ascribable to environmental (and perhaps other) factors, notably cigarette smoking (enzyme induction), while only a small fraction of the variance could be laid at the door of age *per se*.

The composition of the team that carried out the work is of interest. Crooks was in the process of setting up clinical pharmacology as a major section in his new department. Duke was an interested medical student hoping to gain experience in research. As a recent medical graduate with relatively little scientific background, I wished to become a scientist and had Stevenson as my mentor. This foursome represented many of the important elements in a medical school—professor/chairman, medical student, medical graduate/research fellow, and scientist, each playing an important role in the venture.

Ours was the first systematic examination of age as a determinant of drug metabolising capacity. It heralded—but did not cause!—an explosion of interest in therapeutic problems in the elderly; in particular, there has followed a rigorous scientific inquiry into the mechanisms that make the elderly a special group as far as medical therapeutics is concerned.[2]

1. Vestal R E, Norris A H, Tobin J D, Cohen B H, Shock N W & Andres R. Antipyrine metabolism in man: influence of age, alcohol, caffeine, and smoking. *Clin. Pharmacol. Ther.* 18:425-32, 1975. (Cited 225 times.)
2. O'Malley K & Waddington J L, eds. *Therapeutics in the elderly: scientific foundations and clinical practice.* Amsterdam: Excerpta Medica, 1985. 223 p.

CC/CM 1-16