OBITUARY

James Black (1924–2010)

Pharmacologist who changed the face of medicine.

James Black, Jim to his many friends and colleagues, shared the Nobel Prize in Physiology or Medicine in 1988 for pioneering research that led to two new classes of drug. Adrenergic β -blockers and histamine H_2 -receptor antagonists have benefited millions of patients and often saved lives. By his example, Black made a massive contribution to the concept that pharmacological receptors offer fertile ground for drug discovery. His work opened up research on biogenic amines — chemical messengers that have subsequently provided the foundation for establishing new types of drug action.

This is all the more impressive because Black never received formal research training. Indeed, as a physiologist, he had to teach himself what he has termed ‘analytical pharmacology’.

Black, who died on 22 March, graduated in medicine from the University of St Andrews, UK, in 1946, but decided against a career as a medical practitioner. He found that “the way patients were treated was unacceptably insensitive”, and instead chose a career in physiology. In 1950, he created a physiology department at the University of Glasgow Veterinary School, and over the next eight years built a research laboratory that housed advanced cardiovascular technology.

At Glasgow, Black became interested in the clinical problem of angina pectoris, severe chest pain caused by a shortage of oxygen to the heart. The heart responds to the body's demand for blood circulation, and when oxygen levels are low, hormones instruct it to beat faster. If the circulation is unable to keep up, the heart can become starved of oxygen and produces pain. Black argued that reducing the effects of the hormones adrenaline and noradrenaline on the heart would break the cycle by preventing the increase in heart rate.

Anti-adrenaline drugs were a well-recognized group in the late 1950s, and Raymond Ahlquist had already proposed in 1948 that the widespread effects of adrenaline were mediated by two classes of receptor, α and β . Black wanted to find a β -receptor antagonist to block the effects of adrenaline. He approached ICI Pharmaceuticals Division for a grant and they persuaded him to join them in 1958. However, Black was careful not to guarantee a new drug: “All I ever promised was that I was sure that I could develop a new pharmacological agent which might answer a physiological question. Any utility would be implicit in that answer.”

At ICI, Black was introduced to chemistry.

Without an antagonist as a chemical lead, he had to start cold, using the selective ‘agonist’ isoprenaline. This activates the β -receptors, triggering a response that mimics the natural one induced by adrenaline. None of Black's isoprenaline analogues blocked the β -receptors. Then, in 1958, a publication appeared describing dichloroisoprenaline (DCI) as lowering heart rate.

Strangely, in Black's bioassays DCI was as powerful a stimulant as isoprenaline. He set up other assays and was astonished to find that, depending on the tissue preparation, DCI could be a full agonist, activating the β -receptors, or an antagonist that bound to the receptors but failed to activate them. As Black stated later, “as analytical pharmacologists, what we see of the properties of a new molecule is totally dependent on the bioassay we use”.

A simple analogue of DCI soon led to the first β -blocker, pronethalol. This proved to be only a prototype drug, and Black and his team mounted a chemistry programme to yield the drug propranolol in 1964. Today, propranolol and related drugs are widely used to control blood pressure. Yet the considerable effort required to develop such a compound and bring it to market was not intellectually challenging enough for Black, and by 1963 he was thinking about other physiological problems.

Black had worked on gastric-acid secretion at Glasgow and now there was a fresh puzzle to solve — namely, the role of the hormone gastrin and histamine in stimulating gastric-acid production. If the stimulants driving

gastric-acid secretion could be blocked, he postulated, then the corresponding reduction in acidity would allow patients' peptic ulcers to heal. But at this stage, it wasn't clear whether histamine was even involved as a natural stimulant.

In the early 1960s, gastroenterologists were convinced that gastrin was the direct driver of gastric-acid secretion, and the pharmaceutical industry, including ICI, were set on finding a gastrin antagonist. Black had other ideas. He could see a strong analogy between histamine and adrenaline, and had no doubt that a histamine antagonist that blocked secretion could be found. In 1964, he accepted an invitation to join Smith Kline & French Laboratories to pursue this project.

As before, Black started collaborating with medicinal chemists. After nearly four years of failure, he decided to reinvestigate a particular class of compound using a refined assay design. The sixth compound synthesized, N^a -guanylhistamine, on retesting, was found to have a slight inhibitory effect on gastric-acid secretion. Here at last was a lead for the medicinal chemists. Refined into burimamide, the prototype drug proved the existence of histamine H_2 receptors and was verified as a histamine blocker in human volunteers. The chemists ultimately designed the anti-ulcer drug cimetidine, which very quickly became the world's first drug to make sales of more than US\$1 billion a year.

Black identified his own criteria for successful drug research: well-recognized clinical problems that could be related to physiological processes; a defined chemical starting point; and an easy way of proving that the drug would work in humans. Black's genius was to analyse pathways without resorting to wishful thinking.

Jim Black was a formidable teacher. All who worked with him benefited from his enquiring mind and ability to make you question what you were trying to achieve. No scientist from a pharmaceutical-industry background has been so widely recognized. His achievements were acknowledged by his Nobel prize, his election to the Royal Society and membership of the Order of Merit. He was truly a giant.

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