James W. Black was born in Lanarkshire, a coal mining district of Scotland, on June 14, 1924 and died in London on March 22, 2010. He was the fourth of five sons of a mining engineer and a housewife. His family could not afford to send him to university, but at the age of 15, on the advice of his high school mathematics teacher, he applied for and won a scholarship to nearby St Andrew’s University, where, under the influence of an older brother, he attended its medical school. His clinical training in medical school was at University College, which subsequently became the University of Dundee. (Black served as Chancellor of his alma mater later, vide infra.)

He decided not to practice medicine because of what he perceived to be “insensitive” treatment of patients that he had observed. Instead, on graduation, he joined the Physiology Department of St Andrews as an Assistant Lecturer and began his research career in Professor R. C. Garry’s laboratory, where he studied the intestinal absorption of carbohydrates. In 1947, Black and his new wife, the former Hilary Vaughan whom he had met at St Andrews, moved to Singapore, where he served for 3 years as a Lecturer in Physiology at the King Edward VII College of Medicine, University of Malaya. That move was necessitated, subsequently described by Black, as: “an inevitable result of marriage, debts accumulated to pay for the completion of my medical studies, and pitiful academic prospects.” On returning to Scotland in 1950, he became Senior Lecturer and Head of the Department of Physiology at the new Glasgow Veterinary School, where he built a state-of-the-art physiology teaching laboratory. He conducted research and published his first article on the effects of 5-hydroxytryptamine on gastric acid secretions. This early work stimulated his lifelong interest in the control of gastric acid secretion.

While in Glasgow, Black also collaborated with a surgeon, George Smith, in developing methods to increase oxygen supply to the hearts of patients with coronary artery disease. Given the primitive state of cardiac surgery at the time, he concluded that the imbalance between oxygen supply and demand in this condition could be corrected more easily by reducing the latter pharmacologically. To pursue this work, in 1958, he took up a position as Senior Pharmacologist at the Imperial Chemical Industries (ICI) Corporation in Cheshire, England. This led to his development of pronethalol, the first β-adrenergic blocker.

In 1964, Black wanted to develop a blocker of acid secretion by the stomach; this interest fit the needs of the Smith, Kline and French Research Laboratories, where he became head of biological research and led the team that developed the first histamine 2 (H2) blockers.

On completion of these two programs as an employee of industry, Black felt that his further research could be pursued with greater freedom in academia and, in 1973, he accepted the Chair in Pharmacology at University College, London. Here, he developed a model course in medicinal chemistry and, as stated in his autobiography, he “made progress in modeling and analyzing pharmacological activity at the tissue levels, my new passion. But after fours years, I was suffering from withdrawal symptoms from lack of a chemical collaboration. Thus, I eagerly accepted (Sir) John Vane’s [Nobel Laureate, 1982] invitation to join the Wellcome Foundation.”

Here Black focused on analytic pharmacology, which he developed as a distinct discipline. Indeed, in 1984, he moved to King’s College London Medical School, where he became Professor of Analytic Pharmacology, a position he occupied until 1992, when he assumed Emeritus status and became Chancellor of his alma mater, the University of Dundee. However, he maintained a laboratory at King’s until 2002. In 1988, he established the James Black Foundation in London, sponsored by Johnson and Johnson, where he led a team of 25 scientists in the study of receptor pharmacology. They characterized adenosine receptors and studied atrial strips from transgenic mice that overexpressed human β2-adrenergic receptors. They were successful in finding receptor blockers to cholecystokinin.

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(CCK1 and CCK2) and to histamine (H3). They discovered four compounds that went into humans (S. Kalindjian, personal communication, 2010).

Professor Black’s enormous scientific contributions were amply recognized. In 1976, he was elected a Fellow of the Royal Society and received the Lasker Award. He was knighted in 1981. In 1988, along with George H. Hitchings and Gertrude B. Elion, Sir James received the Nobel Prize for Physiology or Medicine for his development of the first β and histamine 2 receptor blockers. In 2000, he was appointed to the Order of Merit by Queen Elizabeth II and, in 2004, received the Royal Medal. These two honors are the most distinguished awards presented by Queen Elizabeth II to British citizens. In 2006, on his retirement as Chancellor, the University of Dundee opened the Sir James Black Center, a state-of-the-art research facility, in which 250 scientists and staff are conducting research on diabetes, cancer, and tropical diseases. At the time of his death, Black was hailed as one of the greatest Scottish scientists of the last century.

Black, whom I met in 1985 at the time that he received an honorary doctorate from Harvard University, was modest and shy, with a wry sense of humor. When told that he had won an Nobel prize, he became quite excited and said that he wished he “had my β-blocker handy.” At the presentation of the Nobel Prize to Black, Professor Folke Sjöqvist of the Karolinska Institute in Stockholm stated:

“In a letter to a close friend, written a few months before his death in 1896, Alfred Nobel (who developed nitroglycerine as the key component of dynamite) wrote: ‘My heart trouble will keep me here in Paris. . . . Isn’t it the irony of fate that I have been prescribed nitroglycerin to be taken internally!’ Nitroglycerin reduces the pain of angina pectoris by dilating the cardiac blood vessels and thereby increasing the supply of oxygen to the heart. Sir James Black was the first to recognize that an alternative therapeutic strategy for angina would be to use a drug which decreases the heart’s requirement for oxygen. He therefore focused his attention on the specialized binding sites, the so-called β-receptors, on heart-muscle cells to which the stress hormones adrenaline and noradrenaline bind and thereby increase the workload and oxygen demand of the heart . . .”

In his Nobel Lecture, Black described his research as follows:

“The work that is the theme of this lecture began in the early summer of 1958 when I joined Imperial Chemical Industries’ Pharmaceuticals Division. I had gone there to pursue a very clear project that had been developing in my mind for several years. The idea had clinical, therapeutic, physiological and pharmacological elements . . . Sjöqvist (had) proposed that the widespread physiological effects of adrenaline were mediated by two classes of receptors, α and β. In this new classification, the antiadrenaline drugs of the day were α-receptor antagonists, and isoprenaline was a selective stimulant of β-receptors . . . Compound ICI 38 174 was conceived in excitement and thrilled us at its birth. Pronethalol was an antagonist without any sign of agonist activity in both atrial and ventricular tissues. In anesthetized animals, pronethalol reduced the resting heart rate and depressed the increments from isoprenaline or stimulation of cardiac sympathetic nerves . . . The potential benefit of β-adrenoceptor blockade for people with embarrassed hearts was seen in the first patient with angina of effort. After pronethalol he was able to do more work before the onset of pain forced him to stop when his heart rate had eventually reached the same level as in the control run.

“In 1964 I went to Smith, Kline and French Laboratories Ltd to pursue another project that I had been thinking about for some time . . . The clinical problem was gastric and duodenal ulcers. The immediate cause of ulceration was recognized to be hypersecretion of acid, but the nature of the driving stimulus was unknown. The one clear fact was that patients with duodenal ulcers gave an exaggerated secretory response to histamine, the basis of a diagnostic test . . . The histamine project was started by analogy with my experience with the adrenaline project . . . Both started from well-recognized clinical problems at a time when they could be illuminated by specific hypothetical modeling at the laboratory level.”

Comment

Since Black’s discovery, β-adrenergic blockers have been the cornerstone of the treatment for a number of cardiovascular disorders: not only for angina pectoris but also acute myocardial infarction, congestive heart failure, and a variety of atrial and ventricular arrhythmias, as well as hypertension. A half-century after their discovery, β-adrenergic blockers remain among the most important cardiovascular drugs in the pharmacopoeia; they have prolonged and improved the quality of life of tens, perhaps hundreds of millions of patients worldwide. Because several β-blockers have become generic, they are now used even more commonly than in the past and because of their effectiveness and low cost they are especially popular in developing nations.

When Black turned his attention from β-adrenergic to H2 receptor blockers, available antihistamines inhibited histamine-induced smooth muscle contraction but did not inhibit histamine-induced gastric acid secretion or uterine relaxation. Black and his colleagues synthesized analogues and derivatives of histamine. Burimamide represented a big step forward because it was the first selective H2 blocker but had low potency and poor oral availability. Minor modifications led to the synthesis of the related compound cimetidine, an orally active potent agent that has been an effective suppressant of histamine and of gastrin-stimulated gastric acid secretion. This agent has been used widely and successfully in the treatment of peptic ulcer.

In the early 1980s, Black collaborated with Leff in developing pharmacological models of agonism activity and a new framework for analyzing and systematically classifying drug actions. Among the numerous insights derived from this approach was strong support of the hypothesis that gastrin stimulates gastric acid secretion by the stomach via the release of
endogenous histamine.\textsuperscript{10} They used their model to deduce how the shape and slope of dose–response curves were affected by functional antagonism, indirect competitive antagonism, mixed agonist/antagonist, and dual receptor systems.

In looking back on Black’s dazzlingly successful professional life, several points stand out. First, Black was an MD who had no postgraduate clinical training and never practiced medicine. However, his contributions were designed to control two diseases: angina pectoris and duodenal ulcer. Undoubtedly, his medical training inspired him to solve these very common and important clinical problems. He worked systematically to find drugs to treat and prevent these conditions, collaborating closely with chemists.

Second, Black carried out his most important, and enduring, research as a full-time employee of pharmaceutical companies that provided him with the freedom, resources, and collaborators necessary to succeed. As a consequence, the public received the benefit of two important classes of drugs, the fields moved forward, the companies prospered, and Black was rewarded for these two “grand slams” with fame and honor: a win-win-win-win situation if there ever was one. However, personally Black did not prosper much financially directly from his discoveries.

Black appreciated that his discovery of $\beta$-blocking drugs and subsequently H2 blockers rested on the “nontarget oriented” discovery of adrenergic receptors by Ahlqvist, an academic pharmacologist at the University of Georgia, with whom Black shared the Lasker Award.\textsuperscript{11}

Finally, after Black’s election to the Royal Society and his receipt of the Lasker Award in 1976, he did not rest on his laurels. He continued to conduct important research, developed a new field (Analytic Pharmacology) and for several years, simultaneously headed two active research laboratories, while serving as a University Chancellor. Days before his death, and 22 years after he received the Nobel Prize, an article that he coauthored with colleagues at Yale was e-published ahead of print.\textsuperscript{12} James Black was a true scientist, who saw research as an end in itself, not a means to an end.

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Sir James W. Black, MD, FRS: 1924–2010
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