SIR JAMES WHYTE BLACK OM
14 June 1924 — 22 March 2010
James Whyte Black was a Scottish pharmacologist who trained in medicine at St Andrews University and had a career in drug invention and academic pharmacology, moving several times between universities and the pharmaceutical industry. He was awarded the 1988 Nobel Prize in Physiology or Medicine for his drug invention method, which was to build molecules around the structure of a natural chemical activator of a pathway involved in the aetiology of a disease. This produced two extremely useful drug categories, beta-blockers and histamine H2-antagonists, with huge impact on the previously intractable diseases of angina, hypertension and stomach ulcers. In 2000 he was awarded the UK’s highest honour, the Order of Merit (OM). His ideas on analytical pharmacology had a significant effect on the development of the discipline in the late twentieth century.

Early life and influences

James Whyte Black was born in Uddingston, Lanarkshire, the fourth of five sons of Walter Black, a mining engineer, and Catherine Whyte, a seamstress. All five sons became university graduates: a Church of Scotland minister; a psychiatrist; an engineer; a director of physical education; and of course James, a pharmacologist. The family moved back and forth between the Lanarkshire and Fife coalfields and he was educated in local authority (state) schools, mainly in Fife, ending at Cowdenbeath Secondary School, later called Beath Academy. He liked to tell a story of this time in school, about an assignment a teacher gave him to reconcile the following two statements: ‘out of sight, out of mind’ and ‘absence makes the heart grow fonder’. Black said he found the answer in the writings of Roger de Rabutin, Comte de Bussy,
who wrote: ‘absence is to love what wind is to fire; it extinguishes the small, it kindles the great’ (Ratcliffe 2016). Little doubt Black would become a pharmacologist, as even then he recognized ‘dose’ was important! The family were Baptist Christians, but religion did not play a large part in Black’s life after childhood, until late in life, with his second wife Rona MacKie, when he attended St Columba’s Church of Scotland church in Knightsbridge, London—where his funeral was held. Even then the pragmatist side prevailed as he confessed that he attended church for the ‘here and now, not the hereafter’.

Black said that his outstanding interests as a child were music and mathematics. One seminal memory was of his mathematics teacher confirming to him that an error Black found in a textbook was indeed an error. The teacher’s confidence against what appeared to be the authority of the textbook took him aback. There would seem to be echoes here of both Black’s intense interest in elevating pharmacological issues to the mathematical level (analytical pharmacology) and his confidence in resisting a prevailing view if it did not correspond to his own. The teacher, Dr Waterston, spotted his ability and persuaded him to apply for a competitive residential scholarship at St Andrews University (the Patrick Hamilton Scholarship, which allowed him to choose his subject of study). He won the scholarship, which was fortunate since his family could not otherwise have afforded to send him, and entered St Andrews aged 16 in 1941. Nevertheless, the medical course was longer and more expensive than the scholarship would cover, so that by the time he graduated he had accumulated debts, which he took a job overseas to clear.

He chose to study medicine because he had seen an older brother’s medical text books and thought it was a subject ‘rich with possibilities’ (20)*. This lack of a vocational aspect may have simplified his decision not to follow a medical career on graduation. He attributed this to disliking the impersonal relationship between doctor and patient, a view formed during his clinical training years.

He certainly took advantage of absorbing medicine’s ‘rich possibilities’, winning several medals for his undergraduate studies, and this provided the canvas for his subsequent work, in which he maintained that one of the necessary prerequisites for his method of drug invention was laying out the basis of a medical problem to be addressed.

He had a highly successful undergraduate career, but was unfortunate, part way through, to self-diagnose osteoclastoma, a rare bone tumour. Radiotherapy left him with a degree of discomfort and disability for the rest of his life, which he generally concealed well, although he also required dual knee replacement surgeries.

While an undergraduate, Black met his first wife, Hilary Vaughan, a fellow student at St Andrews. They were married when Black graduated, and she had her final year to complete. At this time, he took a job as an assistant to the professor of physiology at St Andrews, Robert Campbell Garry. This gave him teaching experience and an exposure to physiological research. At that time Garry was interested in absorption of substances from the gastrointestinal tract. Black was somewhat sceptical of Garry’s approach, but it gave him ideas for alternative experiments and embedded his lifelong interest in the gut.

**Career progression**

Black trained in medicine, started his professional life in physiology and applied these early influences to the invention of drugs.

* Numbers in this form refer to the bibliography at the end of the text.
He had an interesting career trajectory. With some overlap, Black’s career can be divided into three periods: his early research career (1947–1958); his highly successful period inventing drugs (1959–1973); and the final period spent alternating between academia and industry that was to continue until the end of his life (1973–2010).

Each period is discussed in more detail below, but, briefly, during his early period (1947–1958) he developed his technical skills and ideas in experimental physiology in two rather isolated environments: first in Singapore (1947–1949) and then in the Glasgow Veterinary College (1950–1958). So, he twice set up a physiological laboratory in a teaching college independent of a surrounding research environment. This was an exceptional way for a scientist to develop his thinking and skills between the ages of 23 and 36, before embarking on a career in the drug invention industry and subsequent oscillation between academia and industry. It also seems to have been a good way to hone an independent streak and prefigure success.

In his inventive period in the pharmaceutical industry (1959–1973) he developed his ideas about pharmacology and its reliance on synthetic chemistry, which led to the discovery of commercially successful beta-blockers and H2-antagonists.

In his last period (1973–2010), he worked in several different locations, oscillating between universities and industrial research, but essentially in an academic research and teaching environment, where he continued to pursue the invention of new drugs (particularly for gastrin receptors), contributed to the development of the field that he termed ‘analytical pharmacology’ and exerted a strong influence on the development of thinking in pharmacology generally.

**EARLY PERIOD**

*Medical college teaching in Singapore*

Black claimed that he went to Singapore purely to clear his student debts, but judging from his life, there must also have been a search for adventure and doing good. His plan was to go to Makere University in Uganda, but, when he applied for such a posting in 1946, he was sent instead to Singapore to the King Edward VII Medical College, which subsequently became part of the University of Malaya and ultimately the National University of Singapore. There he seems to have been rather isolated professionally, but he had the resources, time and opportunity to develop technical skills in building equipment for his self-generated physiology projects on intestinal blood flow and absorption. He said that in this period he ‘learned how not to do experiments’.

*Glasgow University Veterinary School*

On Black’s return to the UK in 1950, Garry, who had by then moved to the Regius Chair of Physiology in Glasgow, gave him an introduction to William Weipers. Weipers was leading the development of a rather rudimentary Glasgow Veterinary School into a new veterinary college that was soon to become part of the University of Glasgow. Black was given the remit of setting up a Department of Veterinary Physiology in a quite unsuitable building in a then run-down part of the inner city, at Garnethill, a few blocks from the C. R. Mackintosh-designed Glasgow School of Art.
Garry was already developing quite a substantial physiology department in the West Medical Building located in the relatively splendid surroundings of the Gilmourhill Campus, one-and-a-half miles away. In the 1960s, after Black left Glasgow, most of the Vet School moved to purpose-built facilities on the fringe of the city at Garscube Estate and the Department of Veterinary Physiology moved to the West Medical Building, which housed Garry’s physiology department. The veterinary physiology teaching there was run from the 1960s to the 1990s by Ken Hosie, whose supervision as a post-graduate vet student Black had inherited when he arrived (and therefore they were the sole founding members of the department). In the intervening years, Hosie developed his career in the United States. On 23 November 2018, the West Medical Building was renamed The Sir James Black Building. Sadly, Ken Hosie died earlier in 2018. He had a wry sense of humour and would have enjoyed the irony.

While in Glasgow, from 1950 to 1958, Black not only developed a teaching department but continued to develop his scientific ideas and carried out experimental work. He had access to a mechanical workshop and was able to build his own equipment both for experimental teaching and for research. He continued his interest in the gut and developed an interest in cardiac physiology, both strands figuring in his subsequent inventions of drugs in the pharmaceutical industry. In each case he was inspired by collaborators from clinical departments in Glasgow teaching hospitals, who were interested in experimental investigation of clinical issues in their respective specialisms and found in Black a willing collaborator with excellent laboratory facilities.

Adam Smith was a gastro-intestinal surgeon, who was interested in agents that stimulated gastric secretions. Their collaboration on the actions of small amines on gastric secretion in dogs provided the breakthrough publications for Black, being published in *Nature* and *The Journal of Physiology* (1, 2). For Black, this followed directly from his early work with Garry and some unsuccessful work that he carried out in Singapore. It also remained in Black’s mind while he took his next foray, into cardiac physiology, and was resurrected in his invention of drugs to block gastric acid secretion.

With George Smith, a cardiologist, his work took a new direction. Smith was interested in how the damaged heart could receive an adequate blood supply, a major focus at the time. The vasodilator effect of nitro-glycerine could achieve this temporarily, but better strategies were sought. For example, Smith was interested in whether elevated oxygen concentrations (such as in hyperbaric conditions) could increase oxygen delivery.

Calculating that even if oxygen delivery could be improved it would be a modest increase, Black wondered whether an alternative strategy would be to reduce oxygen demand in the compromised heart. He thought that a way to achieve this could be by reducing the stimulation of the heart by the sympathetic nervous system (the ‘stress’ response). His father had died of a heart attack following a car accident, and this had made him think that the so-called ‘fight or flight’ response of the sympathetic system, working through the recently identified catecholamine mediators adrenalin and noradrenalin, might be deleterious rather than helpful in the compromised heart. Furthermore, he hypothesized that the cardiac sympathetic response might be blocked selectively (i.e. without blocking the other sympathetic responses) if a drug could be found that blocked only the cardiac receptors upon which catecholamines worked to mediate excitation of the cardiac muscle.

Importantly, he had come across, in a pharmacology textbook, a then largely ignored, and 10-year old, paper by R. P. Ahlquist (Ahlquist 1948). Ahlquist suggested that there
were two types of receptor for catecholamines, which he termed alpha and beta adrenotropic receptors, on the basis that different catecholamines had different potencies of activation at each receptor. Ahlquist postulated that those in the heart and bronchi were beta. If activators could select between tissues, Black thought, then perhaps blockers could also be selective; he was encouraged in this by an observation that a commercial extract of heart muscle, Recosen, which he was testing for cardio-protective effects (3), could block the effects of adrenalin in the teaching laboratory preparation of spontaneously beating frog heart.

In retrospect this reads like a simple algorithm to invent a beta-blocker, but it is a remarkable series of thoughts. Black’s enthusiasm for Ahlquist’s ideas was not dampened by the prevailing established thoughts in pharmacology, which regarded Ahlquist’s theory as somewhat heretical.

After Black had set up and staffed his Department of Veterinary Physiology, and had developed his idea of a blocker of adrenalin in the heart as a potential alleviator of cardiac stress, he realized that he could not carry out the necessary experiments to prove his hypothesis on his own in his Glasgow laboratory. He was ready to move on. Coincidentally, he was able to present his ideas to representatives of ICI, a conglomerate chemical company with a developing pharmaceutical section, who had long-established links with the University of Glasgow. They had recently built new laboratories in Cheshire, England, and were looking to extend their portfolio in cardiovascular research. They offered him a post, which he accepted immediately and moved in 1958.

**INVENTIVE PERIOD AND APPRECIATION OF CHEMISTS**

His unique and novel approach to inventing drugs was to build molecules around the structure of a natural chemical activator of a pathway involved in the aetiology of a disease. The activator’s chemical structure would be modified to produce a synthetic compound that would retain affinity for the target but block activation of it (a receptor). He described this as creating ‘drugs crafted round a natural template’. He achieved this three times and the first two, beta-blockers (4, 5, 6) and histamine (H2) antagonists (7, 8, 9, 19), had a huge impact on the previously intractable diseases of angina, hypertension and stomach ulcers. Measured commercially, they were the first two billion-dollar (US) drugs without abuse potential (the benzodiazepines had also reached the billion-dollar mark). The third, gastrin antagonists, produced potential drugs, but remained a work in progress after his death (see (16); Barrett et al. 2012; Boyce et al. 2016, 2017).

**Invention of beta-blockers at ICI**

At ICI a team was formed, led by Black, of pharmacologists and chemists, notably J. S. Stephenson. Black said later that he had learned about both pharmacology and chemistry while at ICI, almost from scratch. This period is very well described in Quirke (2006).

They worked on the principle of starting with the selective activator, isoprenaline, and altering it so that it retained the ability to bind but not activate the beta-receptor, by joining two isoprenaline molecules at the amine end. This strategy had been used in the 1930s to block many of the excitatory actions of adrenalin (Fourneau & Bovet 1933; Bovet & Bovet-Nitti 1948), making what we now know as alpha-blockers. This idea of altering the natural activator was central to Black’s successes in drug invention. It subsequently became a central tenet of
the methods for drug ‘discovery’, or ‘invention’ as Black preferred, in the quarter-century long Golden Age for Pharmacology that followed, for which he was awarded the Nobel Prize for Physiology or Medicine in 1988.

The ICI team were greatly assisted by a discovery by Powell & Slater (1958) at the Eli Lilly Laboratories in the United States: they were trying to invent a long-lasting agonist bronchodilator based on isoprenaline. They found that dichloro-isoprenaline (DCI) had little bronchodilator action but was a blocker of adrenalin’s action in bronchi. Soon Moran & Perkins (1958) showed this in the heart. They were familiar with Ahlquist’s work, recognized this as an action at beta-receptors and coined the phrase ‘beta-adrenergic blocking drug’. Indeed Moran & Perkins fixed on the idea of beta-receptors by the coincidence of hearing Powell & Slater’s work and themselves having first-hand knowledge of Ahlquist as a colleague.

This allowed Black’s team to abandon their original dual-isoprenaline concept. They switched to adding bulky substituents to one end of the molecule, as in DCI, and soon found the prototypes for what were to be numerous beta-blockers.

Things happened quickly. They made new chemicals and tested them on biological preparations such as recording contraction and relaxation of smooth or cardiac muscle strips. The key point was to start with the natural activator (the selective activator isoprenaline is already a modification of adrenalin); this would be the template for new compounds, which ideally could lose their ability to mimic, and acquire the ability to block, the activator. In current (2020) terms they wanted to turn a full agonist (activator) into a silent antagonist (a blocker with no other action) at the same receptor site, but at that time the concept of a receptor was just beginning to be accepted, so this practical application of drug invention was pioneering work also in the field of theoretical pharmacology.

A complication was that, even at a particular receptor, some of the compounds synthesized could both activate and block (partial agonist, Stephenson 1956; Ariens et al. 1957). The activating property was ‘tissue-specific’ in that it could be detected in some tissues but was absent in others. Thus, a key problem when testing new compounds on biological assays was how to test the blocking properties of compounds that behaved as partial agonists in some systems. It was easy to miss a good blocker that had agonist properties in the bioassay being used. Black’s group solved this by using tissues that were less susceptible to activation by partial agonists and allowed the blocking action to be revealed; this was also to prove useful later in the creation of H2-antagonists. (The explanation for partial agonists in terms of varying properties of the tissue rather than varying receptor type was in its infancy at that time in the 1950s to 60s, but has been steadily unravelled since then, partly thanks to the work of Black and his collaborators.)

Black’s group invented the beta-blocker pronethalol and, when that failed a toxicity test, replaced it with propranolol, which went on to be one of the most successful drugs of all time and, scientifically as the archetypal beta-blocker, became used clinically for numerous conditions. Propranolol also became the highest grossing drug invented up to that point (4, 5, 6).

A rapid move into human and clinical applications was facilitated by a new member of their team, Robin Shanks, who had worked with Ahlquist in Georgia, heard Moran describe his work and had carried out the first demonstrations of beta blockade in man with DCI (Glover et al. 1962; Shanks 1984). Although it was not Black’s aim, a clinical collaborator, B. N. C. Prichard, quickly showed that propranolol lowered blood pressure in the clinic,
and so it was as anti-hypertensive agents that beta-blockers found their greatest utility and commercial success (see Cruickshank & Prichard 1994).

The fruit of Black’s ICI period can be summed up as ‘the major contribution of Black was to appreciate the possible clinical value of developing compounds to inhibit the sympathetic nerves to the heart, and then to persuade, and lead a team of scientists at ICI to translate the idea into reality’ (Cruickshank & Prichard 1994).

By the time that pronethalol and propranolol had been invented, Black says that he had proved his scientific point that the adrenalin-induced responses of the heart could be selectively blocked and that that was all he had promised to ICI. Looking ahead, he did not want to be involved in the development and promotion of beta-blocker drugs, but rather to invent more new drugs based on the same principles but with different targets. In particular he wanted to tackle the role of histamine on gastro-intestinal acid secretion, a topic emerging from his earlier interests. When he was informed that ICI did not wish to follow this line, he was again ready to move on to pursue his objective.

**Invention of H2-antagonists at SK**

A colleague, George Edward Paget, head of toxicology at ICI, had moved to a senior post with the American drug company Smith, Kline and French (SKF), who had laboratories in Hertfordshire in South East England. When consulted about a head of pharmacology for SKF, Black volunteered himself, and moved in 1964. There, with a new team—some taken with him from ICI, notably W. A. M. (Bill) Duncan—he set about testing the idea that histamine, like adrenalin, might act on two different receptors. This hypothesis was based on earlier observations that the existing histamine blockers did not suppress gastric acid secretion and Black wondered if this was because a second histamine ‘beta’ receptor was resistant to them. An important parallel issue was that the roles of gastrin and histamine in physiological acid secretion were unclear, so, again, Black’s hypothesis would clarify that. He sought to invent a histamine beta-blocker. To Black’s regret, by the time his team had established the new subtype, Ash & Schild (1966) had already defined a sub-set of histamine receptors as H1, so he had to go along with this precedent and name his newly defined sub-set as H2. (At the time of writing this memoir, there were four histamine receptor subtypes.)

This time the invention process took longer (very nicely described in Nayak & Ketteringham 1986). Black’s group started with histamine, since they did not have a selective agonist along the lines of isoprenaline. They had some early success in finding a selective agonist (4-Me-histamine) for the gastric H2 receptors (and a selective agonist for H1 receptors, 2-Me-histamine), but it took four more years before they invented a commercially viable H2-blocker. Again, the concept of partial agonists arose, and so eventually they made their breakthrough by finding how to design-out the agonism and find a clinically effective selective H2-blocker, cimetidine (7, 8, 9, 19). With this project completed, Black was again ready to seek a new challenge. By this time, with two extremely important drug inventions to his name, his stature was appreciated, and he was approached to take up the chair of pharmacology at University College London (UCL).

**TAKING ACADEMIA TO INDUSTRY OR VICE-VERSA**

*Chair of pharmacology at UCL*

Black accepted the UCL position in 1973 with great enthusiasm because he had very clear objectives in teaching and research that he believed could be realized in a university
context. He wanted to create a medicinal chemistry degree and a multidisciplinary research environment where he would be able to carry on his work of drug invention free from commercial restraints. He also wanted to create a purpose-built degree combining pharmacology with chemistry that would provide an excellent background for future drug inventors. He believed in teaching pharmacology as a scientific discipline rather than related to medicine.

On arrival he was disappointed to find resistance from his colleagues to modification of the curriculum and was, perhaps, unlucky that his re-entry to academia coincided with the general modularization of degrees, which was inimical to a dedicated integrated medicinal chemistry degree. He did initiate a medicinal chemistry degree, which continues to be popular (as of 2019), but he did not believe that it met his objectives.

In research he did not find it easy to obtain adequate grants for the type of work that he wished to pursue. In particular, he sought a drug discovery unit staffed by chemists and pharmacologists that would have required outside funds plus internal funds from the university that were not forthcoming. So, he concluded that the university environment was not suitable for realizing commerce-free drug invention.

Wellcome Research Laboratories
Black was consulting for the Wellcome Foundation in Beckenham, Kent, when in 1978 their head of research, John Vane FRS, offered him the post of director of therapeutic research at the Wellcome Research Laboratories. He thus returned to industry after his brief academic sojourn.

Black considered that he had a scientifically successful period at Wellcome, taking three candidate drugs through to development. He also had a fruitful collaboration with Paul Leff, a mathematician, which led to seminal papers on analytical pharmacology (10, 11). However, there were increasing disagreements with John Vane over their different approaches to drug discovery. Black’s approach was, as for adrenalin beta-receptors and H2, to focus on a concept and pursue this till the question was answered. Vane preferred the more academic approach, as exemplified by the work of Sir Henry Dale FRS, of following what was interesting. This took a great toll on both men. When Vane was awarded the Nobel Prize in Physiology or Medicine in 1982, Black decided that it would be best for him to move on. Wellcome granted him resources to set up his own laboratory in a university context and, after considering a return to UCL, in 1984 Black settled on an offer from King’s College London (KCL). He became professor of analytical pharmacology at the Rayne Institute of KCL Medical School.

Nobel Prize
This was a difficult period for Black. His wife died after a period of serious illness, and finding the additional resources to fund an independent laboratory proved complex. However, things fell into place around the time that he was awarded the Nobel Prize in Physiology or Medicine in 1988 with Gertrude Elion (ForMemRS 1995) and George Hitchings ForMemRS ‘for their discoveries of important principles for drug treatment’; it was a matter of personal regret to him that his wife did not live to see this.

Although the 1988 prize acknowledged the contribution of all three recipients to establishing ‘important principles for drug treatment’, the principles involved for Black’s co-recipients were quite different. Gertrude Elion and George Hitchings ‘demonstrated differences in nucleic acid metabolism between normal human cells, cancer cells, protozoa, bacteria and virus. On the basis of such differences a series of drugs were developed that block
nucleic acid synthesis in cancer cells and noxious organisms without damaging the normal human cells’ (The Nobel Assembly at the Karolinska Institute 1988). The key similarity with Black’s method was that they moved away from making drugs by modifying natural products and, instead, made fundamental biological discoveries that produced new targets for drugs or new ways in which the drugs interacted with the targets (13).

James Black Foundation and KCL

He established the James Black Foundation in 1988 with funding from the American drug company Johnson and Johnson (J&J) and led a team of 25 scientists in drug research, including work on gastrin. The Foundation was based at the King’s College Plant Science building on Half Moon Lane in Dulwich, London, from 1988 to 2006; an excellent example of the repurposing of buildings that universities became adept at in the late twentieth century. However, funding came to an end in 2006; in Black’s view J&J did not give them enough time to achieve their objectives.

Then Black’s group returned to the campus of KCL and continued their research on gastrin. Black’s interest in gastrin was piqued when years after introduction of the histamine H2-blockers they were shown to cause a secondary increase in gastrin in the bloodstream, reducing the H2-blockers’ ability to suppress gastric acid production. During subsequent years, the group invented several gastrin blockers with the aim of preventing the effect of the gastrin increase. However, in the 1980s a new class of medicines, the proton pump inhibitors (PPIs), became available that are more effective than H2-blockers at suppressing gastric acid, and PPIs became the preferred choice to treat acid-related conditions.

Meanwhile, there was increasing evidence that gastrin not only controls acid production by the stomach, but also controls growth of cells in the lining of the stomach and in other organs, such as the pancreas. So, Black sponsored clinical trials of one of his gastrin blockers, JB95008, in patients with cancer of the pancreas. Although it prolonged life significantly compared with placebo (16), it was not effective enough when taken orally and had to be administered by continuous intravenous infusion, which stopped development.

Black joined a start-up company called Trio Medicines in order to license and develop YF476 (now called netazepide), a gastrin blocker that he had always regarded as the gold standard among its class. He said the project gave him a new lease of life. Despite needing regular blood transfusions for his own terminal cancer, and often being in much pain, he was very stoic and unstinting in his commitment to the netazepide project. Development of netazepide has continued since his death (Boyce et al. 2017), and an international, multicentre trial in patients with stomach tumours that are gastrin-driven begins in 2020. Furthermore, there are many other clinical indications for a gastrin blocker.

Not only was Black active with the gastrin antagonist project, but he even returned to beta-blockers. This time Black’s hypothesis was to develop a preferential beta2-receptor blocker to test in heart failure. Again, this was against the prevailing dogma that suggests it is the beta1-receptor that mediates the negative effects of the excess catecholamine drive to the failing heart.

During this period, Black was chancellor of the University of Dundee (1992–2006). This was a period of great expansion and success for life sciences in Dundee, and Black took a keen interest in developments. In 2007 a new interdisciplinary research centre was created and named The Sir James Black Centre in his honour.
ANALYTICAL PHARMACOLOGY AND NOMENCLATURE

Black’s career spanned an important period in the development of the discipline of pharmacology when receptors for chemical messengers moved from being abstract concepts to being chemical entities whose operation was understood, at least partly, at the chemical level.

His contribution to analytical pharmacology was of great importance to the development of late twentieth-century pharmacological theory and practice. One of his seminal papers, [the] ‘Operational models of pharmacological agonism’, has recently (2019) been revived and is instrumental in quantifying ‘ligand bias’, the latest major modification in receptor theory (10, 11, 15). However, Black’s greatest contribution to analytical pharmacology was how he repeatedly demonstrated that rigorous and thorough analysis of every aspect of quantitative pharmacology—the shape and Hill slope of concentration–response curves, the effect produced by antagonists, the difference in a compound’s potency relative to its affinity—all of these would tell a very compelling story about how the drug interacted with the receptor to produce its (patho)physiological effect, and, as importantly, in drug discovery how a chemical modification of the ligand altered these properties. He found a complex, detailed and richly told story, where most saw dose–response curves.

When he started in the 1950s, the concept of ‘receptors’ was beginning to be accepted but the method of assaying drug or hormone action was by bioassay, and only the most mathematically bent of pharmacologists held the concept of ‘receptors’. This provided his discovery/inventive process with both opportunity and obstruction, respectively, in his two great discoveries of drug classes. This proved to be the start of our current twenty-first-century understanding of multiple properties of receptors.

He enjoyed toying with nomenclature. Black based his terminology on the concept pioneered by A. J. Clark FRS that receptors responded in a similar way to a chemical substance no matter what its biological origin, regarding the chemical agent as a hormone whether it be a neurotransmitter, a traditionally understood ‘blood-borne hormone’ or a locally released cytokine, that is to say ‘a reversible monomolecular reaction occurs between the drug and some substance either in the cell or on its surface’ (Clark 1926). So, he regarded the receptors for all intercellular communication as ‘hormone receptors’, based on ‘hormone’ being a simple derivation from the Greek for ‘messenger’. In his particular field this also avoided the head-scratching of whether the beta-receptor should be named for its partner adrenalin (endocrine hormone) or its other partner noradrenalin (neurotransmitter). This also allowed him to avoid what he regarded as the incorrect and confusing term ‘drug receptors’ (as they evolved for natural hormones, not drugs). He also studiously kept out of the ludicrous American/British nomenclature disagreement between adrenergic receptor/adrenoceptor, which describe the same thing; neither conforms to the universal convention on naming receptors after the natural mediator—‘adrenalin-receptor’ would be better. Black’s solution was to refer to ‘beta-receptors’ and ‘beta-blockers’, which is, indeed, what almost everyone has done ever since in real speech (Vanhoutte et al. 1996; McGrath 2015).

In the title and theme of his Nobel Prize Lecture, Black coined the phrase ‘syntopic antagonism’ to describe the phenomenon by which a blocking drug (antagonist) would occupy the same place on the receptor as the activator (agonist) that it was blocking (13). However, no one else seems to have taken it up. In other areas of biology this term would mean ‘having the ability to coexist without interference with the other species’. This could actually have
been quite a nice way to develop a distinctly pharmacological term referring to interaction at receptors as distinct from adopting the term ‘orthosteric’, which was used for compounds acting at the active sites of enzymes. Interestingly, in Alquist’s seminal paper on alpha- and beta-receptors he used the term adrenotropic, which was a misnomer and no one else picked it up.

Black was also keen to avoid what he regarded as the absurd term ‘drug discoverer’ (as if drugs had been hidden somewhere), choosing instead ‘drug inventor’ as his main calling. This precision in the use of language is the mark of the man and illustrates his clarity of thought. Indeed, he said from time to time that his aim in inventing drugs was to provide tools to answer questions on physiological control and that the clinical benefits were fortunate consequences; it is doubtful whether his industrial sponsors supported this view. However, in considering all his writings it seems that he was a little playful in emphasizing ‘science’ or ‘medicine’ whenever it suited his argument better (see various autobiographies, e.g. (10), (12), (14), (17), (18), (20)). Thus, it was particularly apt that his Nobel Prize was for ‘Physiology or Medicine’ (13).

PERSONAL NOTES AND STORIES

Black had an unusual appreciation for the opinion of non-experts; one might even go as far as to say he valued input from the naive (figure 1). This view is expressed in a letter Black wrote to one of us: ‘I find it interesting that many of our great, revolutionary scientists, such as Newton, Darwin, Mendel, Einstein and Faraday, were inappropriately trained. They had no intellectual baggage to shed.’ Another more direct example was his desire for input from students, because they had yet to learn the prevailing dogma. A specific example of his fondness for input from students can be found in an anecdote written in a memorial issue of British Journal of Pharmacology for him: ‘In the mid 1990s I was walking with Sir James at a scientific congress in San Diego. A very distinguished scientist approached us and said, “Jim, I need 30 minutes of your time to discuss some things with you”. To which Black politely replied, “of course, please have your secretary contact my office and we will schedule it”. We walked along for another ten steps or so, and a frightened and awestruck student approached us and quietly mumbled, “Sir James, would it be possible to have 5 minutes of your time to show you my data?” Black simply put his arm around the student and said, “Why don’t we have lunch?” That story has forever affected my attitude about how important students are’ (Bond 2010).

On a personal level, the last period of his life was very happy. In 1994 he married Professor Rona Mackie, a distinguished dermatologist and renowned expert in malignant melanoma. She also played a role as scientific mentor and foil throughout their marriage. Even when his health was declining, Black never seemed to lose his humour and modesty. During a visit to Black while he was at St Christopher’s Hospice in East Dulwich, we noticed on his personal locker a very nicely stencilled, ‘Sir James’. However, someone had taken a pen and scratched out ‘Sir James’ and simply printed ‘Jim’ in its place (for more anecdotes see British Journal of Pharmacology, 2010, vol. 160, Supp. 1). Jim and Rona never stopped enjoying life and travelling the world. This was made clear in her uplifting eulogy at his funeral.

Nobel Laureate for inventing two of the most successful drugs in history, tremendous success in both industry and academia, chancellor of a major university and beloved husband
and family man, Sir James Whyte Black truly had a remarkable life. He is survived by Lady Rona Black, Stephanie, his daughter from his first marriage to Hilary, and stepchildren Alison and Douglas.

**HONOURS**

1976  Fellow, Royal Society  
      Lasker Award  
1978  Mullard Award, Royal Society  
1980  UMIST Hon. Fellowship  
      Japanese US Congress Plenary Lecture  
      Mayo Graduate School Distinguished Lecturer  
      Dali Award, Barcelona  
1981  Hon. Fellow, Royal College of Physicians and Surgeons of Glasgow  
      City of Philadelphia John Scott Medal  
      Knight Bachelor  
1982  Wolf Foundation Award  
1986  Hon. Fellow, Royal Society of Edinburgh  
1988  Nobel Prize for Physiology or Medicine  
1989  Hon. Member, The Physiological Society
Sir James Whyte Black

1990  Hon. Associate, Royal College of Veterinary Surgeons
1991  Hon. Fellow, Royal Belgian Academy of Medicine
1993  Hon. Fellow, Royal College of Surgeons of Edinburgh
1994  Active Member, New York Academy of Sciences
1995  Hon. Fellowship, Royal Society of Medicine
1996  Fellow, Royal College of Physicians of Edinburgh
       Lee Kwan Yu Visitor and Medal, Singapore
1997  Harry Gold Medal, American Society of Pharmacology and Experimental Therapeutics
       Wellcome Gold Medal, British Pharmacological Society
1998  Hon. Fellow, British Medical Association
1999  Gold Medal, European Society of Cardiology
2000  Order of Merit
2004  Hon. Fellow, British Pharmacological Society
       Royal Medal from the Royal Society
Date not known: Hon. Member, American College of Physicians

In addition to the James Black Foundation, Black was to have another three buildings named in his honour: At KCL, the James Black Centre was built; at the University of Dundee, the Centre for Interdisciplinary Research was renamed the James Black Centre; and Glasgow’s West Medical Building was renamed as the Sir James Black Building. This building is also the centre of teaching activity for physiology and pharmacology at the University of Glasgow, and Black made one of his famous visits there in which he was interested only in talking to the students.

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The portrait photograph was taken by Rex Coleman in 1977 and is © Godfrey Argent Studio.

AUTHOR PROFILES

John Christie McGrath BSc PhD FRSB HonFBPhS HonMPS

During a long career at the University of Glasgow, John McGrath held the Regius Chair of Physiology 1991–2012, in succession to J. W. Black’s mentor R. C. Garry; was chair of The Physiological Society 2006–2008; and was editor-in-chief of the British Journal of Pharmacology 2009–2015. In collaboration with clinicians and the pharmaceutical industry, his research investigates fundamental autonomic mechanisms, receptor pharmacology, including adrenergic mechanisms, and their application to therapeutics. Like Black, he came from a working-class background in west central Scotland and, in a small world, a best friend’s father was Black’s brother-in-law. He is currently (2020) an honorary professor at the University of Sydney and emeritus regius professor at the University of Glasgow.
Richard Bond earned a pharmacy PhD degree at the University of Houston. He received his PhD in pharmacology with Dr David E. Clarke, and did his postdoctoral training with Dr Paul M. Vanhoutte at Baylor College of Medicine. His early work provided functional evidence for a β-adrenoceptor. Then, in collaboration with Robert J. Lefkowitz and others, he undertook studies on the spontaneous activity of G-protein-coupled receptors (GPCRs). Most recently, he became interested in the paradigm shift that occurred with regard to the use of β-blockers in the treatment of congestive heart failure and speculated the reversal of dogma may be indicative of a more general pattern that is applicable to other diseases. Among the honours he has received is being appointed Honorary Fellow of the British Pharmacological Society. Bond is currently professor of pharmacology at the University of Houston in Texas.

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