

THE INVENTION OF PROPRANOLOL

Rachel Hajar, MD, FACC*

Propranolol was “conceived in excitement and thrilled us at its birth”, recalls Sir James Black (1). His landmark invention of propranolol in 1964 and the H₂-receptor antagonist, cimetidine, in 1972 earned him the Nobel Prize in Medicine in 1988. In the past, development of drugs consisted in chemically modifying natural products but the introduction of selective beta-adrenergic blockade ushered in a new era of “designer drugs” based on the understanding of basic and physiological processes. Propranolol was the first cardiac designer drug.



Sir James Black

Digitalis, morphine, and nitroglycerine were the main cardiac drugs available to physicians as recently as 40 years ago. Rest was a mainstay of therapy for heart failure and angina. The introduction of propranolol revolutionized the pharmacologic management of coronary heart disease. Black was the first to realize that the development of a clinically useful beta-receptor blocking drug might introduce a new pharmacotherapeutic principle in the treatment of angina pectoris. Claude Bernard, the 19th century physiologist remarked that “the innovator’s skill lies in seeing what everybody has seen and thinking what nobody has thought” and this is certainly true of James Black. Previously used drugs acted by increasing oxygen transport to the heart through coronary vasodilatation. In contrast Black’s idea was to decrease the oxygen demand of the heart by blocking the beta-receptors and thereby the workload of the heart. Using the isoprenaline molecule as a basis, Black and coworkers succeeded in developing the first clinically useful beta-receptor antagonist, propranolol, in 1964.

James Black grew up in Scotland studying music as a child under the influence of his father, a mining engineer and whose love of singing gave music a central place in the life of his family. Later,

under the influence of his elder brother James who was a physician, he studied medicine but he chose to pursue research after receiving his MB degree from St. Andrew’s University in Scotland. His initial research work involved studies on Na iodoacetate. He successfully developed a technology to show that, in rats, iodoacetate rapidly and irreversibly reduced the blood pressure to 40mmHg. He says: “I was faced with the question which has influenced my thinking ever since: when and to what extent does local blood flow act as a metabolic throttle?” (2)

He started his career as a lecturer of Physiology in Singapore in 1947 and made some progress relating mucosal blood flow to rates of mucosal absorption. He had more ambitious goals however, and he quit his post as Lecturer, realizing that “experimenting in Physiology was too difficult if the inspiration was no more than wishful thinking.” He returned to London in 1950: “I had no home, no income of any kind and no prospects whatsoever. I knocked on the doors of Physiology departments all over London.” The University of Glasgow Veterinary School gave him the opportunity to start a new Physiology Department (2).

While working on gastric acid secretion and the pharmacology of histamine-stimulated acid secretion, he collaborated with George Smith, a surgeon who was concerned with finding ways to increase the supply of oxygen to the heart in patients with narrowed coronary arteries. The latter work made him wonder whether reducing myocardial demand for oxygen by annulling cardiac sympathetic drive might be equally effective in controlling angina. In 1956, he formulated a plan to find a specific adrenaline receptor antagonist, approached Imperial Chemical Industries Pharmaceuticals for help, and ended up being employed by the company (2).

Certain well known clinical, therapeutic and physiological observations (1) led Black to hypothesize that decreasing myocardial oxygen

*Director, Non-Invasive Cardiac Laboratory, Cardiology and Cardiovascular Surgery Dept., Hamad Medical Corporation, P.O. Box 3050, Doha, Qatar. E-mail:rachel@hmc.org.qa

demand through noradrenaline and adrenaline blockade might be therapeutically useful in patients with coronary artery disease:

? Exercise, anxiety, and emotion precipitate angina pectoris. The injection of adrenaline to initiate pain had been used as a diagnostic test for angina and partial thyroidectomy had been found to relieve severe angina whether or not associated with hyperthyroidism. Black noted that tachycardia seemed to be the connecting link in these disorders.

? Although nitroglycerine could quickly relieve angina through coronary vasodilatation, side effects such as flushing and headache were unpleasant. Moreover, synthetic coronary vasodilators such as dipyridamole were ineffective. Therefore, he questioned the value of seeking drugs to increase coronary blood flow in angina.

? Hyperbaric oxygen at 2 atmospheres reduced the incidence of ventricular fibrillation associated with occlusion of a coronary artery even though the oxygen-carrying capacity of the blood had increased by only 25%. Black wondered whether an equivalent small decrease in myocardial oxygen demand would be just as effective.

? Myocardial oxygen consumption is a function of arterial blood pressure and heart rate. Lowering blood pressure through systemic vasodilatation might dangerously reduce perfusion pressure and blood flow in coronary artery disease. Heart rate, which is largely determined by the cardiac autonomic nervous system, could be reduced by cardiac sympathetic blockade.

? For a long time it remained unclear how the signal substances epinephrine and norepinephrine could exhibit a contractile as well as a relaxing effect on smooth muscle. The late American scientist Raymond Ahlqvist suggested in 1948 that these apparently opposite effects of catecholamines were mediated by different receptors in the target organs, which he called alpha- and beta-receptors. Substances that selectively stimulate these receptors (agonists) were previously known as well as drugs that inhibit the effects mediated by alpha-receptors (antagonists).

Black was strongly affected by Ahlqvist's theory and credits him with jump-starting his own work on beta-blockers. He says: "There is no doubt that my own work begun in 1958, to find a way of reducing myocardial demand for oxygen in hearts whose oxygen supply was restricted by arterial disease, would not have started but for Ahlqvist's

theory" (3). In collaboration with the medicinal chemist, John Stephenson, Black began creating and testing possible compounds at Imperial Chemical Industries Pharmaceutical Division. Propranolol was officially launched in 1964 under the trade name Inderal™.

The clinical trials of propranolol convincingly showed that Black's ideas were correct. The drug caused a dose-dependent decrease in the frequency of anginal attacks and reduced both mortality and morbidity in patients with angina. Randomized clinical trials reported in the 1980s showed that beta-blockers improve survival after myocardial infarction (4) and highlighted the life saving benefit of beta-blocker therapy. Subsequently, it was found that beta-blockers were also effective in the treatment of tachyarrhythmias, hypertension, and hypertrophic obstructive cardiomyopathy.

Recently, several clinical trials have demonstrated that beta-blockers remarkably reduced mortality in patients with moderate heart failure as well as improved the quality of life and sense of well-being by reducing hospitalizations and arrhythmias (5–8). Heart failure was considered a contraindication to beta-blocker therapy, but evidence from recent heart failure trials has convincingly demonstrated the value of beta-blockers in this group of patients. Lately, it has been shown that patients who were given beta-blockers, including those with relative contraindications, had a mortality rate that was approximately 40% lower than that among patients who did not receive the therapy (9), an even larger beneficial effect than has been reported in most clinical trials (4). These new studies shatter conventional wisdom and underscore the continuing evolution in our understanding of complex disease processes. Indeed, the invention of propranolol and the techniques developed to assess its actions has contributed much to our understanding of the mechanisms of heart diseases. In addition, current studies have shown beta-blockers to be as good as newer drugs in the market such as calcium antagonists (10) and ACE inhibitors (11).

Evidence for the therapeutic and survival benefits with beta-blocker therapy is overwhelming. It is no surprise that the Nobel Committee in 1988 called the invention of propranolol "the greatest breakthrough... against heart illness since the discovery of digitalis 200 years ago" (12). 🍌

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Of Cabbages and Emperors

“From the palace walls, Diocletian watched his garden in Salonae, where what he cultivated with his own hands gave him more satisfaction than when he ruled his huge empire. When Maximinus’ ambassador begged Diocletian to become emperor for a second time, he answered, ‘If you could show the cabbage that I planted with my own hands to your emperor, he definitely wouldn’t dare suggest that I replace the peace and happiness of this place with the storms of a never-satisfied greed.’ ”

H. Stieglitz, 1845 (German scholar)

After twenty-one stressful years as Roman Emperor, Diocletian retired to the peaceful gardens of his hometown [Salonae (Solin) on the Balkan Peninsula], to grow cabbages. Historians believe that Diocletian, Roman emperor from A.D. 284 to 305, returned to the Dalmatian coast when he retired in order, at least in part, to grow cabbages. It is also speculated that he considered cabbages especially healthy fare. (Stephen Williams, *Diocletian and the Roman Recovery*, Routledge, New York, 1997).

The wholesome cabbage is one of the oldest vegetables. According to Greek myth, the plant sprang from the perspiration of Zeus. The Greeks gave cabbage to expectant mothers in order to establish good breast production. The Romans used cabbage as an antidote, especially to alcohol, believing it countered intoxication and prevented or reduced a hangover. Wild cabbage leaves eaten raw or cooked aid digestion and the breakdown of toxins in the liver. They also used cabbage leaves to cleanse infected wounds. (Andrew Chevallier. *The Encyclopedia of Medicinal Plants*. Dorling Kindersley, London, 1996;178).