Historical Perspectives

Sir James Black and Propranolol

The Role of the Basic Sciences in the History of Cardiovascular Pharmacology

Melanie P. Stapleton

The history of cardiology encompasses some of the most revered names in medical history, many belonging to physicians who have advanced knowledge beyond their time. However, there have been countless others whose work in the basic sciences has paid large dividends to clinical cardiology. The original example of such an individual is William Harvey, whose reasoned experimentation led to the understanding of the circulation of blood.

Another such man, Sir James Black, has contributed to basic scientific and clinical knowledge in cardiology, both as a physician and as a basic scientist. His invention of propranolol, the beta adrenergic receptor antagonist that revolutionized the medical management of angina pectoris, is considered to be one of the most important contributions to clinical medicine and pharmacology of the 20th century. His method of research, his discoveries about adrenergic pharmacology, and his clarification of the mechanisms of cardiac action are all strengths of his work. In 1988, he was awarded the Nobel Prize in Medicine.

Sir James's conclusions and method of research have continued to influence work in clinical pharmacology and cardiovascular medicine. Thus, the development of propranolol runs parallel to most other great achievements in medicine: the genius of a few builds on the accomplishments of many, and the discovery influences thinking long after the breakthrough has occurred. ***(Tex Heart Inst J 1997;24:336-42)***

Within the infant rind of this weak flower
Poison hath residence and medicine power.

– William Shakespeare,
Romeo and Juliet

Melanie Patricia Stapleton is the 1997 winner of the Texas Heart Institute Award for Undergraduate Writing in the History of Cardiovascular Medicine and Surgery. This is her winning paper.

Key words: *Angina pectoris/drug therapy; Black J; history of medicine, 18th cent.; history of medicine, 19th cent.; history of medicine, 20th cent.; history of medicine, modern; propranolol*

From: *Faculty of Medicine, University of Calgary, Calgary, AB, Canada*

Address for reprints: *Melanie P. Stapleton, 2938 Unwin Rd NW, Calgary, AB, Canada T2N 4C9*

Humanity has long sought to harness the power of medicine to cure illness and to prolong life, yet it is only in the last half century that substantial progress has been made towards that goal. These recent achievements have not emerged from a vacuum, but have built upon the many small discoveries that preceded them. In cardiovascular medicine, countless physicians have worked to clarify the clinical mysteries of the heart and circulation. However, workers in the basic sciences have also made discoveries important to cardiology. John A. Callahan of the Mayo Clinic has written, "some of the outstanding contributors to cardiology would be surprised to hear themselves described as cardiologists."[1] The quintessential example of such an individual is William Harvey, the "grandfather of cardiology," because of his work on the physiology of the circulation. Similarly, the invention* of propranolol in the 1960s by Sir James Black (Fig. 1), an academic and industrial pharmacologist, revolutionized the medical treatment of angina pectoris, clarified the mechanisms of cardiac action, and influenced industrial approaches to future medical research. Sir James perceived links between clinical medicine and academic pharmacology and approached the clinical problem not from the bedside, but from the laboratory. "The innovator's skill, as Claude Bernard remarked, is in 'seeing what everybody has seen, and

*Sir James defines a discovery as the elucidation of something that exists with or without human understanding of it (e.g., the structure of DNA). An invention, on the other hand, does not exist until the researcher has created it (e.g., a drug such as propranolol). The words discovery and invention will be used according to these definitions.

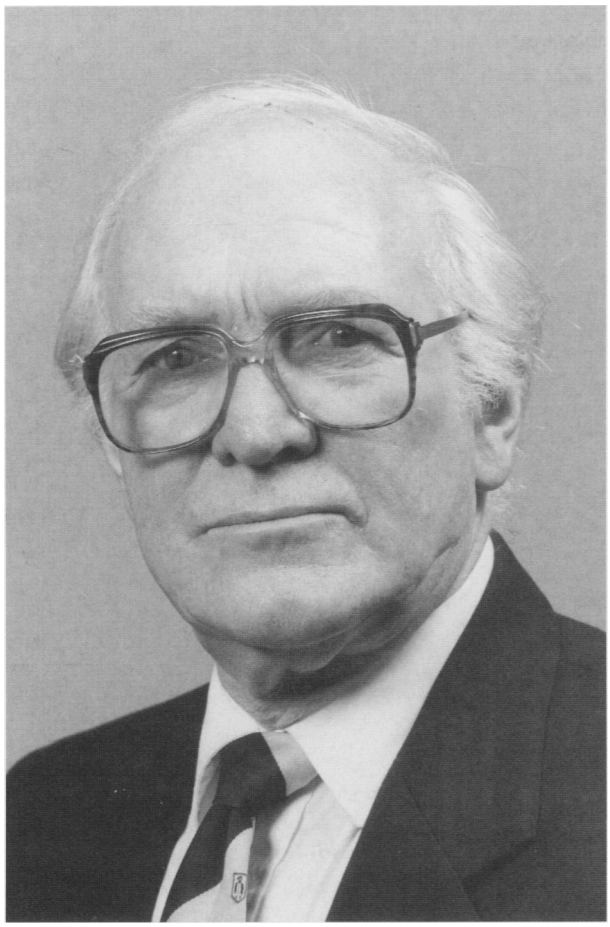

Fig. 1 *Sir James Black, the pharmacologist who invented propranolol, the beta adrenergic receptor antagonist that revolutionized the medical management of ischemic heart disease. (Reproduced by permission.)*

thinking what nobody has thought.'"[2] This is precisely what Sir James did.

Until the invention of propranolol, nitrates were the only pharmacologic tools that physicians could use against angina, and these proved inadequate in the treatment of the condition. Propranolol reduced both morbidity and mortality in ischemic heart disease, and eventually proved useful in other areas of cardiology. Sir James's accomplishment, however, was not limited to the clinical impact of the drug. His research in cardiovascular pharmacology contributed to the clinical understanding of the etiology of angina pectoris and fostered a deeper knowledge of the basic pharmacology of the autonomic nervous system. His own work has continued to the present day, and his research still influences work in clinical pharmacology and cardiovascular medicine. Thus, the development of propranolol runs parallel to most other great achievements in medicine: the genius of a few builds on the accomplishments of many, and the discovery influences thinking long after the breakthrough has occurred.

The History of Angina Pectoris

The historical foundation for the invention of propranolol began in 1768, with the 1st recorded clinical description of angina pectoris.

> They who are afflicted with it are seized while they are walking (more especially if it be uphill and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all uneasiness vanishes.[3]

This description, by William Heberden, is as accurate as any modern description of the symptoms of angina. However, the pathophysiology of angina eluded clinicians for more than 2 centuries after Heberden's description. It would be many years before the overlapping roles of atherosclerosis, vasospasm, and ischemia were known; in the meanwhile, research and other scholarly activity generated much debate and confusion, but little useful clinical knowledge. Even Heberden's original observations became obscure with time, for later authorities attributed a vast array of incorrect statements to him. Laennec, for example, quoted Heberden to support the idea that angina was an innocuous nervous disorder, when Heberden had actually published the observation that angina was associated with sudden death.[4]

Atherosclerosis, now known to be intimately associated with angina pectoris, was observed after Heberden's work, but was misunderstood. Caleb Hillier Parry, in his *Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris, Illustrated by Dissections* (1799), recounts the classical anecdote in which, during the course of an autopsy, he discovered something hard and gritty in the coronary arteries and ". . . well remember[ed] looking up to the ceiling, which was old and crumbling, conceiving that some plaister (sic) had fallen down."[5] He discovered, however, that the vessels had hardened, or ossified, and later in the same book he states that, ". . . a principle cause of the syncope anginosa is to be looked for in disordered coronary arteries."[5] Parry's error was in presuming that the hardened arteries restricted movement of the heart, thus causing the pain of angina.

Although we can see with hindsight that Parry was on the verge of understanding the ischemic nature of the pain of angina, this point was missed for many more years. Ironically, the delay in understanding angina was a result of the development of new diagnostic methods in cardiology. With the discovery of auscultation, cardiology quickly became the study of heart sounds. The murmurs associated with valvular disease were amenable to diagnosis by

Laennec's auscultatory system, but coronary artery disease was silent. Even as late as 1872, it was said that, ". . . such prominence is still given to the subject of valvular disease that many persons have come to regard the term as synonymous with all heart disease."[6] This "golden era" in cardiovascular diagnosis was a bleak time for coronary artery disease.

The next significant insight into angina came from Sir Richard Quain. In his 1852 paper "On Fatty Diseases of the Heart," he records his observation of the deposition of fatty material in the blood vessels, which he attributes to, ". . . local modification of nutrition."[7] He linked the fatty heart to a number of effects, including, "languid and feeble circulation, a sense of uneasiness and oppression in the chest, embarrassment and distress in breathing, coma, syncope, angina pectoris, sudden death. . . ."[7] Quain was also the 1st to propose that angina could occur in variant vascular conditions: 1) in ossified coronary arteries; 2) in vessels with fatty accumulation; and 3) in the absence of any apparent disease.

The sophistication of Quain's theories in the 1850s is impressive. It is therefore unfortunate that neither he nor his contemporaries pursued this train of thought. Quain appears to have abandoned his work on fatty disease of the arteries, and to have concentrated, in his later work, on the heart itself. Stokes, a contemporary of Quain's, summed up the common thinking of the time when, in 1854, he wrote that, ". . . obstruction of the coronary arteries may or may not be present, and is probably not infrequent, but as a cause of angina its actions are remote, and its existence unnecessary."[8]

By 1872, Quain himself had abandoned his discussion of the blood vessels and spoke only of fatty degeneration of the heart itself. In his Lumleian Lectures, he spoke of both fatty hypertrophy and fatty degeneration of the heart. Fatty degeneration of the heart was described as a situation in which the heart tissue is paler than usual, spotted, and mottled; this, he said, is particularly noted after coronary artery occlusion.[9] The tissue he described is likely infarcted tissue, but he failed to connect fatty degeneration of the heart with fatty degeneration of the vessels. Quain also made no distinction between ischemia and infarction. Inconsistencies between observation in the clinic and at autopsy confounded the issue even more: some people with coronary ossification at death had no angina in life, while some without ossification at death did have angina in life. William Stokes eventually argued that, ". . . ossification of both the coronary arteries may exist, and yet the muscular structure be found not only without atrophy, but red, firm, and in all respects healthy."[10]

The inability to distinguish between ischemia and infarction also plagued Sir Clifford Allbutt, who in 1915 stated that angina was caused by disease of the aorta. This was inferred from his observation of angina in the sufferers of syphilitic aortitis. In his opinion, ". . . the coronary hypothesis was dead and buried."[4] While his work contributed to the general confusion surrounding the causes of angina, several of his clinical observations were important contributions to the pool of general knowledge. Allbutt observed that angina was brought on by exercise, but not caused by it; citing the example of the lack of angina in heavy laborers, he established that effort or heavy strain played no causative role in the condition.[11] When discussing therapy, he notes that another physician recommended oxygen inhalations 2 to 3 times a day to ward off attacks, and that diet, moderate exercise, and rest were key components of therapy.[11] Even without an understanding of the mechanism of the disease, Allbutt was able to recommend rational and effective methods for alleviation of symptoms.

This was the information available to clinicians at the start of the 1900s. In a short time, however, several papers, which became the foundation for Sir James's work, were published. In 1912, James B. Herrick[12] established that thrombosis and occlusion were not necessarily fatal, thus enabling a clinical distinction between ischemia and infarction. A comprehensive explanation of angina followed in 1928, when C.S. Keefer and W.H. Resnik published their landmark paper "Angina Pectoris: A Syndrome Caused by Anoxemia of the Myocardium."[13] Here they confirmed that anoxemia was the underlying cause of angina, but could itself be caused by such diverse conditions as coronary artery disease, vasospasm, and decreased oxygen saturation of the blood. Acute myocardial infarction was linked to coronary artery obstruction and angina, which underscored the danger of sudden death in patients with angina.[13] The paper provided a clear explanation of the clinical and anatomical findings of previous authorities. This understanding of the role of ischemia was the foundation for Sir James's work.

Autonomic Pharmacology and the Sympathin Theory

Sir James's genius lay in the fact that he considered not only clinical work, but work done in the field of autonomic pharmacology.* By the 1930s, when Keefer and Resnik's paper began to influence clinical medicine, autonomic pharmacology was a science hampered both by limited basic scientific knowledge and by the lack of appropriate experimental models. Epinephrine (also known as adrenaline) had been known since 1894, and the in vivo effects were quickly discovered. John Jacob Abel,

*Sir James received his MB from St. Andrews University in Scotland, but he chose to pursue research because he was interested in understanding what he called the "generalities" of medicine.[14]

the 1st professor of pharmacology in the western hemisphere, was central in isolating the substance for future research. Jokichi Takamine applied for and received a United States patent on the substance, and went on to make a fortune with his marketing of Adrenalin™; ironically, the product that he marketed was not pure epinephrine, but a mixture of the hormone and its sibling compound, norepinephrine (or noradrenaline).[15] Both in vivo and in vitro effects of these substances were known, but explanations for them were lacking. Injected epinephrine caused tachycardia and an increase in blood pressure. The "anti-epinephrine" drugs of the day, such as phenoxybenzamine, could reverse the rise in blood pressure, but did not affect the tachycardia. The sympathin theory emerged in 1939 as an attempt to explain these findings. Walter B. Cannon and Arturo Rosenblueth proposed that certain unidentified molecules, named sympathins E and I, combined with the adrenergic transmitters to produce an active substance in the cells: sympathin E caused excitatory actions, and sympathin I caused inhibitory ones.[16] There were numerous problems with this elaborate theory, not the least of which was the fact that neither E nor I could be shown to exist—nor was any explanation offered as to the nature of these compounds. Despite this, the sympathin theory became popular and was well-entrenched in the literature within a few years.

Raymond Ahlquist and the Alpha and Beta Receptors

In 1948, Raymond Ahlquist published his paper on adrenergic nervous transmission. Ahlquist proposed that different receptors, not different molecular modifiers, caused different tissue responses. These specific receptors for epinephrine and norepinephrine, which he localized to different tissues, were generically named alpha and beta receptors.[17] Although this concept is now recognized in pharmacology as basic, Ahlquist found it difficult to publish his carefully reasoned and thoroughly researched paper. As he himself later commented,

> The original paper was rejected by the *Journal of Pharmacology and Experimental Therapeutics*, was loser in the Abel Award competition, and finally was published in the *American Journal of Physiology* due to my personal friendship with a great physiologist, W.F. Hamilton.[18]

It is curious that Ahlquist had so much trouble finding acceptance for his theory, because it had the benefit of simplicity, supporting evidence, and, as history would show, accuracy. His paper was largely ignored, perhaps due to the fact that he had a different approach to pharmacology and used mathematical modeling to explain medicine. The research scientists who read it and agreed with his conclusions started working with his theories, but they were few in number.

Good science and good luck finally met in the form of Drill's *Pharmacology in Medicine* textbook, 1st published in 1954. Ahlquist had been invited to write the chapter on adrenergic pharmacology, and seized the opportunity to write his theory of alpha and beta receptors. This text was the one chosen by Sir James Black, when he was preparing to lecture medical students on the topic. Instead of reading about sympathins, he encountered—in Ahlquist—beta receptors in the heart, general receptor theory, and mathematics. Instead of merely transmitting accepted information from a book to his students, Sir James himself became intrigued by the potential for pharmacologic intervention offered by Ahlquist's system. So profound was the effect of Ahlquist's writing that even today an edition of Drill's book sits in Sir James's office bookcase, and in an article about Ahlquist's role in the development of the beta antagonists, he wrote:

> Now there is no doubt that this theory of two receptors had a powerful influence in directing the studies of clinical investigators once suitable agents, such as propranolol, became available. There is equally 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 Ahlquist's theory.[19]

Reducing the Myocardial Oxygen Demand: Pronethalol and Propranolol

The direction of research that Sir James pursued was not the track chosen by many at that time. Mainstream research in cardiovascular pharmacology focused on vasodilators, since the effects of nitroglycerin were well-known. Because nitrates dilated peripheral vessels, researchers and clinicians alike assumed that they dilated the vessels of the heart and increased oxygen delivery to the myocardium. The calcium channel blockers were originally developed as vasodilators, and only later was it discovered that they blocked calcium channels—thus proving that eventually the right drug could be found for the wrong reasons. Sir James, however, did not seek to increase myocardial oxygen delivery; instead, he approached the problem from the opposite direction: Could the myocardial need for oxygen be reduced?

Sir James's rationale for this approach arose from a number of observations. The therapy available in

the form of nitroglycerin was inadequate, because patients exchanged chest pain for facial flushing and headaches. Other coronary vasodilators under development, such as dipyridamole, were proving to be clinically ineffective. He was aware that myocardial oxygen consumption was determined by both systemic arterial pressure and heart rate, but reducing systemic arterial pressure was dangerous and could lead to myocardial infarction. Therefore, heart rate, which was determined largely by autonomic nervous input, became his target.[20]

In Sir James's own words, "These clinical, therapeutic, and physiological features of hearts coping with coronary artery disease all seemed to point to the potential advantage of annulling the actions of the sympathetic hormones, noradrenaline and adrenaline, on the heart."[20] Ahlquist's 2-receptor system gave him the starting point: He wanted to find a beta-receptor antagonist. In collaboration with the medicinal chemist John Stephenson, Sir James began creating and testing possible compounds at Imperial Chemical Industries' Pharmaceutical Division.

They were assisted by the work of C.E. Powell and I.H. Slater, who published a report in 1958 about dichloroisoprenaline (DCI), an analog of isoprenaline developed by Eli Lilly as a possible long-acting bronchodilator. Instead of acting like isoprenaline, however, DCI had the opposite effect: that is, antagonism.[21] Stephenson quickly prepared DCI for testing, and Sir James applied it to a number of bioassays. Dichloroisoprenaline is now classified as a partial agonist, and its properties as such soon became apparent, with very tissue-specific effects in vitro. Although the 2 scientists concluded that DCI was not the compound they were seeking, it inspired them to synthesize a compound based on it—Imperial Chemicals Industries' compound ICI 38,174, later known both as nethalide and pronethalol. This was not simply another compound to be synthesized and screened; instead, Sir James says that it, ". . . was conceived in excitement and thrilled us at its birth."[20]

Pronethalol did not disappoint. In the laboratory, it antagonized the myocardial beta adrenergic receptors, but not the peripheral alpha receptors.[22] Simultaneous clinical investigation yielded the same results in human beings, and demonstrated that pronethalol decreased heart rate and increased exercise tolerance in people with angina.[23]

Pronethalol itself never came into widespread clinical use; it was found to produce thymic tumors in mice, and was discarded in favor of a similar, safer compound, ICI 45,520. Imperial Chemicals Industries' compound ICI 45,520 would later be called propranolol. Propranolol was officially "launched" in 1964 under the trade name Inderal, and changed the face of cardiovascular medicine. Evidence quickly mounted to show that the drug reduced both morbidity and mortality in angina sufferers. The drug caused a dose-dependent decrease in the frequency of anginal attacks[24] and, after 3 years, patients treated with beta blockers had a death rate from myocardial infarction 4 times less than those who had not received the drug.[25] Later, evidence mounted to show propranolol's usefulness in the treatment of arrhythmias and hypertension. Finally, both the drug itself and the techniques developed to assess its actions contributed to the understanding of the mechanisms of cardiac diseases. More than 10 years after the introduction of beta blockers, it was concluded that, ". . . beta antagonists, and propranolol in particular, have clarified mechanisms in angina pectoris, cardiac arrhythmias and some aspects of essential hypertension as well as hypertrophic obstructive cardiomyopathy."[26]

Academia, Industry, and the James Black Foundation

Quite apart from its effects on clinical medicine, propranolol added momentum to the wave of drug discovery that changed the role of the pharmaceutical industry in medicine. Propranolol also served to highlight the difficulties in obtaining international approval of new drugs. By World War II, the British pharmaceutical industry was seen as lagging behind other industrialized nations in drug development and manufacture, particularly as a consequence of the country's inability to manufacture the quantities of penicillin the nation needed during the war. Therefore, the British industry turned for inspiration to foreign models for drug development, such as those provided by salvarsan in Germany, by insulin in Canada, and by the work on sulfonamides in France.[27] Once discoveries such as propranolol had revived the British industry, problems in the international delivery of new drugs emerged. Although introduced in 1964, propranolol was not approved in the United States for the treatment of angina until 1973, much later than in most other countries. By the late 1970s, the conservatism of the Food and Drug Administration had delayed the approval of many drugs developed outside the United States, particularly cardiovascular drugs.[28] This need to get marketing approval country by country was the worst of the problems that industry would face in manufacturing and promoting drugs in the new world market.

Sir James was relatively new in the world of industrial pharmacology at the time of his discovery, and his experiences in academic and industrial settings since that time have shaped his current approach to research. His method of research may be one of his most profound contributions to medicine. When he became interested in the possibility of finding a beta receptor antagonist, he was working

as an academic pharmacologist. In 1958, he approached Imperial Chemical Industries' pharmaceutical division for a grant to support his project; instead, Imperial Chemical offered the 34-year-old St. Andrew's graduate his own laboratory. When he left academic pharmacology in 1958, he worked 1st on propranolol, then invented the H2-receptor antagonist cimetidine on the basis of the same principles. It was on the strength of these 2 discoveries that he received the Nobel Prize for Physiology or Medicine in 1988, which he shared with Gertrude B. Elion and George Hitchings.

He accepted posts at University College London (1973 to 1977), the Wellcome Foundation (1977 to 1984), and King's College London (1984 to present).[29] In 1988, however, he established the James Black Foundation in Dulwich, England, to promote his vision of pharmacologic research and to discover prototypic drugs for development elsewhere.[30] The Foundation that grew out of Sir James's own experiences in academics and industry is based on the concept that

> . . . the majority of significant research discoveries result from the concentrated efforts of small, well-resourced teams of talented and highly-focused scientists, who are unencumbered by the organizational distractions, decision time lags, and lack of direction frequently encountered in large public and industrial institutions.[30]

This goal is achieved by keeping the number of scientists at the Foundation small: currently, there are 20. This is because Sir James believes that, ". . . scientists are inherently inflationary;" that is, science and its practice are constantly increasing in size, and decreased efficiency is inherent in that growth.[30] The numbers of scientists are kept low by contracting out any service possible. The only service that cannot be bought, according to Sir James, is the way that he thinks and approaches a problem.[14] That method of thinking and working has resulted in research success in drug invention; drug development is left to other, larger organizations. The 3-step process used by the Foundation is the same that proved so successful in the search for a beta receptor antagonist: 1) start with a clinical problem; 2) identify the controlling chemicals or hormones in the system; and 3) start at the most basic molecular level, and test similar molecules for in vitro activity.[30]

Sir James's own goals with the Foundation include promoting scientific achievement, enhancing productivity, and creating an atmosphere in which scientific achievement and productivity can flourish.[14] There can be no doubt of the magnitude of the Foundation's achievements: the work accomplished in areas as diverse as research on cholecystokinin, 5-hydroxytryptamine, and other transmitters has expanded knowledge of homeostatic systems and pharmacologic intervention. In regard to keeping the number of research scientists small, Sir James says, ". . . it is easier to keep our research focused, and we need only a small table to sit around and talk, explore, argue, daydream and then head home on a high of intellectual excitement."[29] Similarly, in a recent article describing the research problems tackled by the group, he says that the article ". . . is meant to be a family album, not a work of reference."[29] It is easy to draw parallels between the Black Foundation and organizations such as Birmingham's Lunar Society in the late 1700s, which were small, intimate groups of learned individuals brought together by a strong interest in scientific knowledge. Perhaps, then, Sir James's Foundation is a modern version of these past societies, but one that incorporates specific goals and organized research into a scholarly collective.

Sir Clifford Allbutt, mentioned earlier in this discussion, wrote in 1915 that

> A physician can have no greater reward than the knowledge that he has been the means of bringing relief in a cruel disease, especially when this relief prevails over an agonizing symptom.[11]

Clearly, progress in bringing relief to the sufferers of cardiac disease does not depend solely on cardiologists and other clinicians. Researchers in the basic medical sciences, such as Sir James Black in pharmacology, have been instrumental in many breakthroughs in cardiovascular medicine. Sir James's invention of propranolol has enabled physicians to achieve Allbutt's noble goals. Directly, propranolol has brought relief and increased longevity to patients afflicted with angina pectoris. Indirectly, Sir James's method of research, his contributions to cardiovascular knowledge, and his ongoing work in promoting research through the Black Foundation have left a legacy that will enable future clinicians and scientists to make further progress in medicine.

Acknowledgments

I would like to extend my sincere thanks to Sir James Black and the James Black Foundation for their generosity in granting me an interview when I researched this paper at the Wellcome Library.

I would also like to thank the Alberta Medical Foundation for its encouragement and financial support, which made the research work in London possible.

References

1. Callahan JA. Medical history and the cardiologist. Int J Cardiol 1988;19:1-4.
2. Vlietstra RE. The history of cardiology—is it important today? Clin Cardiol 1995;18:367-9.
3. Heberden W. Pectoris Dolor. In: Willius FA, Keys TE, editors. Cardiac classics: a collection of classic works on the heart and circulation with comprehensive biographical accounts of the authors. St. Louis: C.V. Mosby Company, 1941: 222-4.
4. Snellen HA. Coronary heart disease. In: Snellen HA, editor, History of cardiology: a brief outline of the 350 years' prelude to an explosive growth. Rotterdam: Donker Academic Publications, 1984:154-70.
5. Parry CH. An inquiry into the symptoms and causes of the syncope anginosa, commonly called angina pectoris, illustrated by dissections. London: R. Cruttwell, 1799:1-167.
6. Quain R. Abstract of the Lumleian Lectures on diseases of the muscular walls of the heart, lecture I. Lancet 1872;1:391-2.
7. Quain R. On fatty diseases of the heart. Edinburgh Med Surg J 1852;77:120-52.
8. Stokes W. Deranged action of the heart. In: The diseases of the heart and the aorta. Philadelphia: Lindsay and Blakiston, 1854:481-92.
9. Quain R. Abstract of the Lumleian Lectures on diseases of the muscular walls of the heart, lecture III. Lancet 1872;1: 459-60.
10. Stokes W. On fatty degeneration of the heart. In: The diseases of the heart and the aorta. Philadelphia: Lindsay and Blakiston, 1854;302-20.
11. Allbutt C. Diseases of the arteries including angina pectoris, Vol. 2. London; Macmillan and Co., 1915;56-148.
12. Herrick JB. Clinical features of sudden obstruction of the coronary arteries. JAMA 1912;59:2015-20.
13. Keefer CS, Resnik WH. Angina pectoris: a syndrome caused by anoxemia of the myocardium. Arch Int Med 1928;41:769-807.
14. Personal interview with Sir James Black, 24 June 1997, Dulwich (London), England.
15. Acierno LJ. Pharmacologic modalities. In: Acierno AJ, editor. The history of cardiology. New York: Parthenon Publishing Group, 1994:699-734.
16. Cannon WB, Rosenblueth A. Autonomic neuro-effector systems. New York: The Macmillan Co., 1937:133-87.
17. Ahlquist RP. A study of the adrenotropic receptors. Am J Physiol 1948;153:586-600.
18. Ahlquist RP. Adrenergic receptors: a personal and practical view. Perspect Biol Med 1973;17:119-22.
19. Black JW. Ahlquist and the development of beta-adrenoceptor antagonists. Postgrad Med J 1976;52(Suppl 4):11-3.
20. Black J. Drugs from emasculated hormones: the principle of syntopic antagonism. Science 1989;245:486-93.
21. Powell CE, Slater IH. Blocking of inhibitory adrenergic receptors by a dichloro analog of isoproterenol. J Pharmacol and Exp Ther 1958;122:480-8.
22. Black JW, Stephenson JS. Pharmacology of a new adrenergic beta-receptor-blocking compound (nethalide). Lancet 1962(2):311-4.
23. Dornhorst AC, Robinson BF. Clinical pharmacology of a beta-adrenergic-blocking agent (nethalide). Lancet 1962(2): 314-6.
24. Prichard BN. Propranolol in the treatment of angina: a review. Postgrad Med J 1976;52(Suppl 4):35-41.
25. Lambert DM. Effect of propranolol on mortality in patients with angina. Postgrad Med J 1976;52(Suppl 4):57-60.
26. Fitzgerald JD. Beta-blockade and mechanisms of disease. Postgrad Med J 1976;52(Suppl 4):184-90.
27. Liebenau J. The twentieth century British pharmaceutical industry in international context. In: Liebenau J, Higby GJ, Stroud EC, eds. Pill pedlars: essays on the history of the pharmaceutical industry. London: Wellcome Institute, 1994: 123-33.
28. Schwartzman D. The life of drug patients. In: Schwartzman D. Innovation in the pharmaceutical industry. Baltimore: Johns Hopkins University Press, 1976:162-81.
29. Black J. A personal view of pharmacology. Annu Rev Pharmacol Toxicol 1996;36:1-33.
30. James Black Foundation promotional materials. Published by the James Black Foundation, King's College School of Medicine and Dentistry, 68 Half Moon Lane, Dulwich (London), England.