Celebrating a Decade of *Dialogues*  
**The Tree of Cardiovascular Knowledge**

*Celebrating a Decade of Dialogues in Cardiovascular Medicine*

*D. J. Hearse, R. Ferrari*

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**The Tree of Cardiovascular Knowledge**

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The tree represents the evolution of knowledge, starting from the roots, passing through the trunk, boughs, branches, twigs, and leaves, and culminating in the fruit—the product of human investigative endeavors.

In its first 10 years of publication, *Dialogues* has explored the fruits of humankind’s research and ingenuity in many areas of cardiovascular medicine. To date, 40 issues have been devoted to major cardiovascular issues ranging from the origins and management of ischemic heart disease to the challenge of using cellular implants to rebuild the damaged heart.

As Editors, we take great pride in the success of *Dialogues*—this is undoubtedly due to the outstanding caliber of our distinguished faculty of authors, aided by the innovative format of the Journal, which devotes each issue to a single topic of cardiovascular interest, each representing a fruit of the cardiovascular tree of knowledge. The success of the Journal also owes much to Servier, our sponsor and publisher, who has provided, through Dr David Mason and his colleagues, outstanding technical support and publishing skills.

Like Ramon Llull’s disciple, staring in admiration at the Tree of Knowledge his master is pointing at, the Editors of this Journal have viewed with amazement the remarkable advances that have been made in understanding the functioning of the cardiovascular system and the evolution, treatment, and prevention of cardiac disease.
To celebrate the first ten years of Dialogues, we decided to explore some of the outstanding successes that have revolutionized the understanding and management of heart disease. However, whereas Ramon Llull’s tree is heavily laden with all the fruits of knowledge, we had to prune ours to a symbolic ten, one for each year of Dialogues. Selecting these from the cardiological cornucopia was not easy, but with the help of our Consulting Editors a consensus was reached on which we should retain for their particularly far-reaching implications for our time.

To truly do justice to this special issue, we felt that we needed some very expert help in the form of a Guest Editor who could guide us through the project and recruit an outstanding faculty of authors. One name came immediately to mind: in Arnold Katz, not only do we find a remarkable researcher and a distinguished physician, but also an individual with a lifelong passion for the history of medicine and matters philosophical. We were genuinely delighted when Arnold accepted the challenge and we wish to express here our sincere thanks and immense admiration for the task that he has so successfully undertaken. Indeed it was Arnold who suggested that each article should be modeled on the Tree of Knowledge—asking our authors to identify the seminal discoveries that became the roots and trunk rich in rising sap, and to chart the evolution of various pathways of scientific exploration that formed the branches, which after decades or sometimes centuries of investigation, were to bear the fruits that advanced our understanding and saved many lives. After leading us on this fascinating tour of the major landmarks that have shaped the development of cardiology, we then asked Arnold to undertake the difficult and risky task of predicting what the tree might look like ten years from now, which he has done in a thought-provoking paper (Outlook) that most appositely concludes this anniversary issue.

We hope our readers enjoy this tribute to the medical quest for knowledge.
The study of the cardiovascular system dates back to the anatomic descriptions and speculations of Antiquity. Little progress was made during the Middle Ages and early Renaissance, until the birth of hemodynamics with William Harvey’s groundbreaking discovery of the circulation in 1628, based on experimentation and, to some extent, shrewd hypothesis, as without the microscope he had no proof of the existence of the capillary system. The mercury manometer was invented in 1828 by Jean-Louis Poiseuille. The pioneering work of 19th-century physiologists such as Karl Ludwig, Otto Frank, and Ernest Starling was followed by that of 20th-century clinicians like Helen Taussig, Alfred Blalock, Maude Abbott, and André Courmand. More recent milestones include the advent of investigational catheterization, culminating in percutaneous catheter-based methods for the treatment of certain forms of heart disease.

**Keywords:** hemodynamics; physiology; Frank-Starling law; catheterization; angioplasty; angiography; balloon catheter; stent; molecular intervention

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The tree of hemodynamic knowledge and practice begins with a single trunk whose roots reach 2500 years into the speculations of Antiquity. Anatomical observations account for the compact core of inner rings. Physiological knowledge as such did not really exist, except as a largely speculative superstructure, and this was to remain the case for the first 2000 years, during which growth was slow and the trunk spindly. Intellectual relationships between successive enquirers were often tenuous until the late Renaissance inaugurated the era of empirical and transmissible science.

**THE DAWN OF CARDIAC PHYSIOLOGY: FROM HARVEY TO HALES**

Along the way, some retrospectively promising shoots were either neglected because they were meaningless given the resources of the time (for example, the conclusion thought to have been reached by Erasistratos in Alexandria that arteries are connected to veins by capillaries), or were murderously pruned by representatives of reigning orthodoxies (as was the case of Michael Servetus, whose contention that blood mixed with air and changed color in the lungs was fated to leave no trace on succeeding medical generations, given that both writings and their author were burned at the stake in 1553 by Calvin’s followers in Geneva because of his rejection of the Trinity and the divinity of Jesus).

Only a few decades after Servetus, the exclusively scientific preoccupations of William Harvey (1578-1657), nourished under Hieronymus Fabricius (1537-1619) in Padua, revived the flagging trunk. Harvey’s masterpiece, published in 1628, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus,* signaled the end of the Renaissance and the beginning of the modern era (Figure 1). It was short—72 pages—
because to the point. Not only did it eschew theology, but it marked the cusp between the anatomy of the dissection tables of Padua and scientific physiology.

The experimental methods by which Harvey reached his conclusions were to form the basis for all future work in physiology. Cold-blooded animals (small fish, frogs, and snakes) with their much slower heart rate, in particular shrimps with their transparent shells, afforded a direct window onto the heart’s action. By combining these observations with the postmortem dissection of humans, Harvey reached the following conclusions:

- The atria contract together, followed by simultaneous contraction of the ventricles, rather than the four chambers contracting independently. The heart expels blood with each contraction and receives blood with each relaxation, the latter thanks in part to the venous valves, which as Harvey explained, allowed the blood to flow easily one way through them, toward the heart, but blocked the passage in the opposite direction.
- Contraction of the heart coincides with expansion of the arteries, which are then filled by positive pressure transmitted from the heart, as opposed to the previous belief that arteries expanded like bellows to draw in blood by negative pressure.
- Andreas Vesalius (1514-1564) was correct in maintaining, against the then established doctrine of Galen (130-200 AD), that “by Hercules!” there are no septal pores between the ventricles; similarly, Realdus Columbus (1516-1559) was correct in stating that all blood from the right ventricle passes through the lungs to the left ventricle.
- Because the volume of blood forced out of the heart in an hour far exceeds its volume in the whole animal, it is inconceivable that it can be absorbed by the body from ingested food and continually replaced by blood manufactured in the liver from chyle. Blood must be therefore in constant circulation.
- Simple experiment shows that there must be connections invisible to the naked eye between arteries and veins. If a tight ligature is applied to the arm, the distal veins appear normal. But if the ligature is loosened just enough to allow arterial blood into the arm, while con-

Jean-Louis Marie Poiseuille (1799-1869) invented the mercury manometer in 1828, and later derived his law that flow varies as the fourth power of the radius. But perhaps the supreme example of the new wave of academic physiologists was Karl Ludwig (1816-1895), whose kymograph (“wave-writer” Figure 3) was to be used for recording physiological data for the next 100 years. He built the Physiological Institute in Leipzig on a grand scale to his own design, with interconnecting wings devoted to histology and anatomy, physiological chemistry, and the physical study of physiological problems. In reaction against the diehard believers in natural philosophy and vitalism who still plagued academia, his physiological science was uncompromisingly quantitative, analytical, and physicochemical. Physiology underpinned medicine, since “every case of illness is a physiological experiment and each physiological experiment is an artificially produced illness.” Ludwig’s infantry was the animals who provided a wealth of new infor-
mation on cardiovascular and respiratory physiology. His generals were his assistants and pupils, who carried the campaign far and wide, to Britain, America, and Russia.

Other physiologists with an equal devotion to measurement succeeded in deriving laws. In Germany, Otto Frank (1865-1944) drew on Ludwig's work with the isolated frog heart to derive a law concerning the dependence of the shape of the isometric or pressure curve on the initial tension. The peaks of the isometric pressure curve rise with increasing initial tension (filling), then decline beyond a certain degree of filling (Figure 4).4 In practical terms, if end-diastolic fiber length increases due to increased filling, the heart contracts more strongly to eject the increased volume. The heart compensates for both increased pressure and volume work by dilatation within physiological limits, but can become decompensated by overdilatation.

Starling's thesis, which put together much that had already been appreciated by several late 19th century physiologists in addition to Frank, found intuitive acceptance among his contemporary clinicians, familiar with the enlarged weak hearts that improved in performance when venous pressure was lowered by venesection or tourniquets.7 It also provided the framework for the more detailed studies conducted by succeeding generations, led notably by Carl Wiggers (1883-1963) at Western Reserve University, Cleveland, Ohio, and Arthur Guyton (1919-2003) at the University of Mississippi. Author of the cardiac cycle graphic since familiar to medical students the world over—the "Wiggers diagram" displaying the interrelationships between electrocardiogram, chamber and aorta pressures, ventricular volume, heart sounds, aortic flow rate, and the venous pulse over a single cardiac cycle (Figure 5, next page)—Wiggers was directly inspired by his predecessors. In particular, he spent time in Otto Frank's laboratory in Munich (Wiggers was the son of German immigrants), and subsequently visited Starling's laboratory.
in London. Echoing Ludwig’s “Die Methode ist alles,” Wiggers’ habit was to “assess scientific reports as much by an investigator’s technical habits as by the actual data and deductions.” He personally derived most of the variables in his diagram. He was also the first to produce a precise record of the relatively small pressure changes in the pulmonary circulation with respiration. It was a modification of the Wiggers transducer that was subsequently adapted to an intracardiac catheter to measure right heart pressures in unanesthetized humans.

Guyton too had a natural affinity with a range of electronic devices from childhood, and was fond of building analog computers. His particular interest, cultivated over several college summers, was in the mathematical analysis of electronic circuits. He brought this approach to the analysis of physiologic mechanisms, whether renal, respiratory, or circulatory. One of his classic papers begins with a reference to Starling (the curve relating cardiac output to mean right atrial pressure), proceeds to a mathematical analysis of a simplified closed circuit circulatory system and its experimental verification in 47 dogs, and concludes with a formula for venous return as a determinant of cardiac output. This approach was to reach its most remarkable expression in the “Guyton diagram,” his 1972 computer model of the cardiovascular system. Resembling a modern circuit board, it was the first to integrate the multiple factors influencing the peripheral circulation, heart, endocrine systems, autonomic nervous system, kidneys, and body fluids. The distance traveled since Starling, who had performed much of his work on the isolated heart despite an all-encompassing knowledge of physiology, had become considerable.
THE FIRST CLINICAL APPLICATIONS

Hemodynamic studies such as those conducted by Wiggers and Guyton were blurring the boundaries between physiology and clinical medicine. Wiggers’ “every disease is an experiment that nature performs” echoed Ludwig’s “every case of illness is a physiological experiment”. Helen Taussig (1898-1986) encountered many such experiments in her practice as cardiologist to the children’s clinic at Johns Hopkins (Figure 6). Informed by the hemodynamics of the normal and valve-diseased heart, and by the remarkable compendium of the pathology of congenital disease produced by Maude Abbott (1869-1940) in Canada, Taussig was able to propose surgical remedies for otherwise intractable childhood disease, and assist from the head of the table at the initial implementation by Alfred Blalock (1899-1964) of her palliative shunt solution to Fallot’s tetralogy.

From the end of World War II onwards, clinical applications of the accumulated anatomic and physiologic knowledge grew in many directions. However, perhaps the single most important branch, and the one that was to support the greatest profusion of applications in subsequent years, first emerged in 1929 in Eberswalde near Berlin, when a surgical intern only one year out of medical school, Werner Forssmann (1904-1979) was looking for a rapid and safe method of getting drugs directly into the cardiac chambers rather than injecting them blindly through the chest wall. After initial experiments in cadavers, and against his chief’s instructions, Forssmann introduced a thin radiopaque urological catheter into his own left antecubital vein, and advanced it into his right atrium guided by a fluoroscopic image projected onto a mirror. He then climbed a flight of stairs to the x-ray department where the catheter’s position was documented. In reporting his experiment, he suggested that the method might be useful in physiological studies, and he went on to show, again on himself, that the right heart could be visualized radiographically by injecting iodinated contrast materials through a catheter into the right atrium.

Unfortunately, in terms of our tree, the growth of this hugely promising new branch was stunted for over a decade in the absence of immediate practical applications. The requisite transducer technology for measuring flow, pressure, and volume had yet to catch up. Forssmann lost his job and, ironically, all hope of a career in cardiology, becoming a urologist instead.

Beginning in 1941, André Cournand (1895-1988), a French-born physician and physiologist who came to the United States in 1931, carried out extensive studies with Dickinson Richards (1895-1973) at the Columbia University division of Bellevue Hospital using Forssmann’s catheterization technique. They established that the catheter could be left in place for long periods without harm, and that the tip could be advanced through the right ventricle into the pulmonary artery, the preferred site for sampling mixed venous blood (the right ventricle acting as mixer). The world’s first diagnostic cardiac catheterization laboratory was opened at Johns Hopkins hospital in 1945. Aided by the presence of Taussig and Blalock, catheterization rapidly established itself as a reliable gold standard technique of disease and preoperative assessment. A couple of years later, Lewis Dexter (1910-1995) and colleagues at the Peter Bent Brigham Hospital reported indirect measurement of mean left atrial pressure using a catheter “wedged” in the distal pulmonary artery, thus describing a variable that remains fundamental in cardiac intensive care to this day. The pioneers of cardiac catheterization, Cournand, Richards, and Forssmann, received the Nobel prize in 1956. Yet this was only the start. In his Nobel lecture, Cournand described Forssmann’s catheter as “the key in the lock”. It was to remain, in rapidly evolving forms, the mainstay instrument of hemodynamic investigation and, increasingly, therapeutic intervention. In the left ventricle, catheterization was combined with imaging to realize a project outlined by Otto Frank in 1895: it provided the data points that enabled pressure to be continuously plotted against volume through the complete cardiac cycle, thus generating the pressure-volume loop graphic of ventricular function. On the normal loop, all four phases of the cardiac cycle (isovolumic contraction, ejection, isovolumic relaxation, and filling) are clearly separate. The area of the loop measures the net external stroke work, ie, the useful work done by the myocardium on the circulation. The correla-
tion between clinical condition—valvular disease, heart failure, cardiomyopathy—and loop size and shape was so clinically relevant that pressure-volume loops became integral to the assessment, management and teaching of cardiac disease (Figure 7).

Less successful, through no fault of the catheter, was the attempt to characterize left ventricular performance in terms of "contractility" based on a high-fidelity pressure recording at a single moment in time and under a single set of loading conditions. Defined as the variable force of ventricular contraction, independent of changes in heart rate, preload, or afterload, contractility became a hemodynamic Holy Grail, pursued as a potentially easy and rapid marker. Defined as the variable force of ventricular contraction, independent of changes in heart rate, preload, or afterload, contractility became a hemodynamic Holy Grail, pursued as a potentially easy and rapid marker. Eventually, after a decade of effort and the sacrifice of forests of pulp, "contractility" was abandoned, as even in the best of cardiological hands it lacked the scientific underpinnings required to discriminate between normal and abnormal myocardium.

OPENING THE DISEASED ARTERY: THE ADVENT OF ANGIOPLASTY

In other hands, the catheter was a magic wand, sprouting specialties at a touch. In 1958, Mason Sones (1919-1985), a pediatric cardiologist at the Cleveland Clinic, was performing an aortogram in a patient with aortic valve disease when he realized that the catheter had accidentally entered the right coronary artery. Before it could be removed, 30 cc of contrast dye had been released. Expecting the heart to fibrillate, Sones prepared himself to open the chest. In fact the heart went into asystole, and restarted when he asked the patient to cough—on the third cough. If the heart could survive 30 cc of dye into a coronary artery, reasoned Sones, it would readily tolerate the much smaller amounts sufficient to visualize the coronary vasculature: "I knew that night that we finally had a tool that would define the anatomic nature of coronary artery disease." The visualization technique unleashed the diagnostic potential of coronary angiography. After being perfected by using a flexitip catheter with both end and side holes that selectively opacified the coronary arteries when introduced from the brachial artery, angiography quickly became the standard assessment procedure before any coronary intervention. Given the excitement generated by coronary angiography, it took special vision—and some serendipity—to realize, within just a few years, that diagnostics far from exhausted the potential of the endovascular catheter. Charles Dotter (1929-1985) was only 32 when he became professor and chairman of radiology at the University of Oregon medical school in Portland, Oregon. Two years later, in 1963, as he was passing a percutaneously introduced catheter retrogradely through the right iliac artery to perform an abdominal aortogram in a patient with renal artery stenosis, he realized that he had accidentally recanalized an occlusion. As with Mason Sones, accident found a mind fully prepared, in this case for the revolutionary concept of interventional radiology. Dotter immediately mapped the decades ahead, fast-forwarding to improvements such as balloons and stents. Meanwhile, with his trainee, Melvin Judkins (1922-1985), he undertook the first intentional percutaneous transluminal angioplasty in January 1964 on an elderly woman with a nonhealing ulcer and gangrenous toes referred for amputation. Minutes after he dilated her stenosed superficial femoral artery, her foot was warm and hyperemic, and the patient, already 82, was to live a further three years "walking on her own two feet."

Dotter produced a prophetic video the same year starring himself as a once-claudicating patient skipping out of sight down a hospital corridor. His message to the skeptics


was that angioplasty was vessel-friendly: reaming, drilling, plowing and blasting—each illustrated by an industrial close-up—were not involved. However, the technique did have a drawback. Stenoses were dilated with a bougie, so that operators were limited by the diameter of the cut-down artery. Several attempts to design a small-entry balloon catheter were made, including by Judkins (in itself the idea was not new: it had been attempted over 100 years previously for the urethra). But early balloon catheter designs failed either because of poor patient outcome or because the soft elastic of the balloon “dog-boned” (i.e., spread laterally) to either side of the stenosis rather than expanding against the stenosis in a forceful radial direction.

Andreas Gruentzig (1939-1985, Figure 8),21 a West German, came to Zurich in 1969 to pursue his interest in dilating arteries through a small aperture. He produced a series of prototype Dotter catheters fitted with balloons, searching for a viable material and design. Containing the expansion of the balloon was a particular problem, given the latex-like materials in common use. The breakthrough came when he crossed the road from the university hospital to the Federal Institute of Technology, and met with Heinrich Hopff, a professor emeritus of organic chemistry with a background in the polymer industry, who suggested he used polyvinylchloride instead. The prototypes with this much sturdier material were handmade by Walter Schlumpff, the husband of Gruentzig’s operating room assistant. In 1974, Gruentzig reported that he had successfully dilated peripheral arteries in 15 patients. By 1977, again with Schlumpff’s assistance, he was ready to launch a coronary version of his double-lumen balloon catheter.

The first patient was a 38-year-old man with proximal stenosis of the left anterior descending artery. Angioplasty was performed with an emergency bypass team in readiness. It was unnecessary. The patient remained symptom-free for the next 23 years, by which time the site of the original dilatation was still patent.22 Other efforts at balloon angioplasty started almost immediately, first in New York and San Francisco, and then all over as interventional cardiologists and radiologists attended Gruentzig’s courses in Zurich. In 1980 Gruentzig moved to Emory University and was able to report zero inpatient mortality in the first 1000 cases performed by himself or his associates. Safety and efficacy were continuously increased by improvements in catheter design and the introduction of digital radiography. The advance of the technique was so widespread that it soon became autonomous, being barely halted by the premature death of Gruentzig himself with his wife and dogs, one Sunday evening, as he piloted his plane back from a weekend retreat.

**Figure 8. Andreas Gruentzig (1939-1985).**


**KEEPING THE DISEASED ARTERY OPEN: THE STENT**

Dotter was a pilot too, a mountaineer, and more. He and Gruentzig were not theoreticians so much as consummate and committed technicians. Dotter invented his own interventional tools, often using unconventional materials—guitar strings, Volkswagen speedometer cables, and the like. He made some of his own catheters, extruding the Teflon tips with a blowtorch, in the same way that Gruentzig fashioned his prototypes in his kitchen with Schlumpff. Dotter was the widerranging and more provocative. “The stethoscope and electrocardiograph,” he wrote in a 1962 issue of Electrical Engineering, “are instrumental equivalents of the ear trumpet and smoked drum recorder.” His favorite logo—which he sketched himself, since that was another of his talents—showed a domestic pipe crossed with a wrench. He could see no higher calling than to be a vascular plumber. He was a catheter evangelist, pained by the pain of cardiac surgery. He was known to have conducted Grand Rounds standing next to an oscilloscope; after 20 minutes, he would roll up his sleeve and reveal that he had had a catheter in his heart from the start. He would then plug himself into the oscilloscope and continue Grand Rounds, moving the catheter between heart chambers.

On the Monday after his death, Gruentzig had been due to meet with Richard Schatz, the future designer of the Palmaz-Schatz stent. Complications of angioplasty included reocclusion and collapse of the dilated segment. Dotter and Judkins had speculated in 1964 that a temporary endovascular silastic splint might maintain an adequate lumen after creating a pathway across a
previously occluded vessel, including coronary arteries. They coined the term "stent" for vascular implants in their description of endarterial placement of tubular coiled wire grafts in the femoral and popliteal arteries of healthy dogs, but did not develop the idea further. The first applications came in Europe. Five months after Gruentzig’s death, Jacques Puel implanted the first coronary stent in a patient in Toulouse, France.

The early days of coronary stenting were not easy. Long-term success was far from predictable. Initial follow-up studies with a self-expanding stent (Wallstent), for example, showed a 24% occlusion rate and a daunting 7.6% 1-year mortality. However, following an array of technical improvements and the introduction of improved antiplatelet therapy in place of anticoagulation, stenting can be said to have come of age in 1996, with the results of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial.23 Primary angioplasty with the stent-armed balloon became the default first-line coronary intervention, including in the emergency situation. Difficulties remain, however, including restenosis and stent thrombosis, the latter all the more serious as it often results in sudden death with little or no prior warning. The recent success of devices eluting antiproliferative drugs in preventing restenosis points the way forward, and is putting an end to alternative approaches such as brachytherapy. Results to date suggest that percutaneous interventions using these devices will provide long-term results as good as with coronary artery bypass grafting, at far less invasive cost.24

**TOWARD THE ERA OF MOLECULAR INTERVENTION**

Proponents of numerous other interventions—and their patients—have been less fortunate. Ablative approaches, such as directional atherectomy, laser revascularization, and rotational ablation using a high-speed diamond coated burr, appeared as promising as stenting in principle, but produced indifferent outcomes and higher rates of peri-procedural infarction and major adverse cardiac events. Thrombolysis remains a valid alternative option in the emergency situation, especially when performed prehospital. In general, outside the emergency situation, treatment of coronary disease by percutaneous intervention appears to be moving inexorably away from the plumbing solutions introduced by Dotter and Gruentzig toward approaches grounded in molecular pharmacology and genetic modification, with each step becoming more expensive. Thus catheters are being used during angioplasty for gene transfer—vascular endothelial growth factor (VEGF) or fibroblast growth factor, either as DNA or protein—with the aim of encouraging angiogenesis, in an approach that is still too new for definitive assessment.

**Balloons and Valves**

Balloon dilatation has also been used in the treatment of valvular stenosis (whether congenital or acquired). Percutaneous balloon mitral valvuloplasty is now the treatment of choice for young patients with pliable, non-calcified rheumatic mitral stenosis and no left atrial thrombus, outperforming closed surgical commissurotomy, and producing both short and long-term results comparable to open surgical commissurotomy. Balloon dilatation of aortic stenosis in adults proved to be a failure in the majority, but paved the way for a valve composed of three bovine pericardial leaflets mounted within a balloon expandable stent. This valve can be implanted percutaneously, and early results look promising.25,26

**Conclusion**

A visitor to the stunted sapling of hemodynamic knowledge in 1600 would be dumbfounded by the strength, height, and breadth of today’s tree, dotted with the vigorous growth of leaves afforded by the new specialties. The progression has been natural, from a small core of anatomy through a massive construct of physiology to a crown of therapeutics upheld by the most powerful of bioengineering branches. In recent decades the pace of progress has been stupefying. Millions the world over are benefitting from procedures that were inconceivable only 50 years ago. Could the same rate of growth could continue for a further 50 years? This doesn’t seem unlikely if the current blossoming of genomics and proteomics is any indication!
REFERENCES

1. Servetus M.

2. Harvey W.

3. Shuster A, Shipley AE.

4. Fishman AP, Richards DW, eds.

5. Lombard WP.

6. Starling EH.

7. Webb-Peploe MM, Shepherd JT.

8. Wiggers CJ.

9. Guyton AC, Lindsey AW, Kaufmann BN.

10. Guyton AC, Coleman TG, Granger HJ.

11. Abbott M.

12. Forssmann W.
Die Sondierung des rechten Herzens [Catheterization of the right heart]. Klin Wochenschr. 1929;8:2085-2090.

Studies of congenital heart disease. II. The pressure and oxygen content of blood in the right auricle, right ventricle and pulmonary artery in control patients, with observations on the oxygen saturation and source of pulmonary capillary blood. J Clin Invest. 1947;26:554-560.

14. Cournand AF.

15. Frank O.


17. Dodge HT, Sandler H, Baxley WA, Hawley RR.

18. Harris P.


22. King SB, Meier B.


24. Serruys PW, Ong ATL, Morice MC, et al. on behalf of the ARTS Investigators.


owadays, when technology seems to reign supreme—and, like the fruit on a tree tends to monopolize our attention—it is good to remember that clinical skills can be the best diagnostic method. In particular, the history of the illness may be the only clue to a puzzling diagnosis. “Listen to the patient and he will give you the answer.” This is advice that medical students, formerly including myself, have never really accepted from their teachers, believing that a laboratory method must be the best. In other words, we overlooked the roots, without which the tree would not exist. The symbol of the tree, which serves as a leitmotiv throughout this issue of Dialogues—and which, as a dedicated botanist, is one that greatly appeals to me—is particularly relevant in the realm of diagnosis: no part of the tree is independent of the rest and, although pruning is necessary, and even mandatory, as each new stage in the growth of the tree takes place, never does a more recent stage supersede the earlier ones.

### CARDIAC EXAMINATION

Physical examination is of great value by itself, but also because it points the way to other modes of investigation. Percussion of the chest was invented in 1761 by Leopold Auenbrugger in Austria, inspired by his father, an innkeeper, who would tap his oaken casks to estimate the quantity of wine they contained. Auenbrugger first used percussion in a case of pericardial effusion, and his method was popularized by Jean Nicolas Corvisart in France in 1806. In 1828, Pierre-Adolphe Piéron invented the pleximeter—an ivory plaque placed on the chest and struck with a finger. Medical students were taught to carefully percuss the borders of the heart up to about 1950, but John Parkinson had already shown that radiology was the only reliable way of determining cardiac size. Percussion of the heart is now rarely used. By contrast, the jugular venous pulse and pressure have stood the test of time, even if some doctors now neglect to look at them. The venous pulse of tricuspid incompetence was described by Giovanni Maria Lancisi as far back as 1745, and the findings in various arrhythmias were well known 100 years ago. In 1933, Thomas Lewis introduced the standard method of assessing right heart failure by measurement of the height of the jugular venous pressure above the sternal angle.
heart with an ear applied directly to the chest, that is, almost directly, for sometimes a piece of fine cloth was interposed between the doctor's ear and the patient's chest. On September 13, 1816 René Théophile Hyacinthe Laennec, then aged 35, while on a ward round at the Hôpital Necker in Paris, decided, as he said to “avail ourselves of the use which acoustics yields to us,” and having rolled up the cahier de visite of a student, he applied that cylinder of paper to the chest. Thus was born médiate auscultation and the momentous invention of the stethoscope. Laennec soon replaced the roll of paper, and a roll of pasted cardboard, by his famous wooden cylinder, which itself soon became modified by himself and others. Others such as James Hope in England and Austin Flint in America soon adopted this method, helped by Sir John Forbes' translation in 1821 of Laennec’s 1819 book De L'Ausculation Médiate.

However, the monaural model was not ideal and indeed it was described by an American doctor as “the objectionable European instrument.” Nevertheless, its many modifications persisted for nearly one hundred years and as late as 1912 an instrument catalog showed 78 monaural types. A variety of monaural stethoscope is still used today in some countries by obstetricians and midwives.

Naturally, however, there was an early desire to produce a binaural instrument, and Charles James Blasius Williams of London made the first one in 1829 using two bent lead pipes. Progress depended on getting flexible material for the tubing and before vulcanization of rubber was achieved in 1839, there were two other plant substances available, namely, gutta-percha (from the milky juice of trees of the Palagium and Payena genera, Sapotaceae family), and untreated rubber (from the milky juice of Hevea brasiliensis and other species, Euphorbiaceae family), called caoutchouc (from the Quechua kaucho) or gum elastic. In 1841, William Stroud led the way by covering a coiled wire tube with silk impregnated with caoutchouc, and Arthur Leared of London made a molded binaural model in 1851 from gutta-percha. But the first truly practical binaural device was that of George P. Camman of New York in 1855. It had a bell-shaped chest piece joined to the two earpieces by tubes of gum elastic and even had a spring to hold the earpieces snugly together. (Figure 1). By 1912, there were 53 types of binaural models, including that of S. Scott Alison, who produced good quality recordings of sounds and murmurs (Fig-
The introduction of filtration into the amplifying system by M. B. Rappaport and Howard B. Sprague in America in 1941 made it easier to analyze sounds and murmurs and these workers delineated the physical and physiological laws governing auscultation. In the 1950s, Alfredo Luisada in Chicago was a great pioneer, as was Aubrey Leatham in London. A different look was provided in Baltimore by Victor McKusick, who invented the spectral phonocardiogram, whereby murmurs were recorded according to their frequency range and intensity. Five monographs on phonocardiography appeared in the 20th century, from 1911 to 1963. However, now, in 2005, the method is virtually obsolete and clinicians are no longer interested in checking their auscultatory findings.

**GRAPHIC REGISTRATION**

Scientific investigation of the cardiovascular system started in 1628 with the experimental work of William Harvey, but it was not until the 19th century that recording methods were developed and at first these were done, as one might expect, by animal physiologists. The invention of the rotating drum recorder, the kymograph (wave recorder) in 1846 by Karl Ludwig was an essential start, and its potential was built upon by Étienne Jules Marey in Paris, who recorded the intracardiac pressures in horses using a kymograph with pen recorders. Marey is an important figure in the history of cardiology, for by modifying his instruments so that they were applicable to humans, he was largely responsible for the introduction of investigational techniques on which modern cardiology is based. In 1859, he invented a sphygmograph (pulse recorder), which he strapped to the patient’s arm to record the arterial pulse. Recordings with various instruments were often made onto paper with a deposit of soot which was removed by a stylus giving a white line—the smoked paper recording, made permanent with a coating of varnish. This was the method used in 1882 in the sphygmograph of Robert Ellis Dudgeon. This small instrument strapped easily onto the radial artery at the wrist and it became the preferred method for recording the arterial pulse, analyzing not only the rhythm, but also waveform. And then came a decisive moment in cardiac investigation when James Mackenzie invented his clinical polygraph in 1890. He modified the Dudgeon sphygmograph by using a second stylus connected to a tambour, which allowed the jugular venous pulse, or the apex beat, to...
be recorded at the same time as the radial pulse (Figure 3). In other words, one could simultaneously record events from the right and left heart. Using this device, Mackenzie showed the essential feature of what was later proved to be atrial fibrillation (Figure 4). Smoked paper was awkward to use, and in 1906 Mackenzie invented an ink-writing polygraph, which was redesigned by Thomas Lewis in 1914. The Mackenzie-Lewis polygraph was portable and easy to use and it was widely used to elucidate arrhythmias even after the electrocardiogram had become established. For example, it recorded very well the large a waves of junctional tachycardia. The next step in recording mechanical events was with photographic recording, which was first done quite simply by placing the stylus of, say, a venous pulse tambour, in the beam of light of an electrocardiograph. From 1911 to 1915, Thomas Lewis used this method for his experimental studies on dogs with recordings from the atria and ventricles. But it is Otto Frank of Munich who has the credit for introducing precise optical recordings of pressure pulses, a method taken up in the USA by Carl Wiggers. Crighton Bramwell in Manchester used cathode-ray recording in the 1930s, but this never became popular. After the 1950s, electronic recording devices made it possible to record mechanical events with ease and precision, using the hot stylus method, which was best developed by the Sanborn Company in the USA. An ingenious method that was developed in Sweden by Carl Hellmuth Hertz and R. Elmqvist was the ink-jet recorder, which overcame the problem of friction by the stylus on the paper. It was called a Mingo-graph, from the Latin “to pass water,” literally a urinating apparatus! It was also good for phonocardiography.

**PULSE MEASUREMENT AND RECORDING**

Examination of the pulse was practiced from the very earliest times and was known to the Chinese in 2700 BC (the Huangdi Neijing, Nanjing, and Maijing canons of medicine) and to the ancient Egyptians (as recounted in the Edwin Smith papyrus of around 3000 BC). Claudius Galen, whose writings dominated medicine for centuries, wrote 18 books on the pulse around AD 180 and, for example, his pulsus captis had a double impulse like the leap of a goat, and probably was a dicrotic pulse. However, finding a method to measure the rate of the pulse proved a difficult problem, and various so-called water clocks from Egyptian and Roman times were not satisfactory. The first solution was Galilei Galilei’s invention of a pendulum-driven device called a pulsilogium, in about 1580. Although spring-driven watches were available around 1600 or earlier, they measured only hours, but in 1707 Sir John Floyer invented his pulse watch, which ran for 60 seconds only. By the 19th century, there was no problem in measuring the pulse rate and more attention was paid to pulse abnormalities and to their recording. The sphygmograph of Karl Vierordt in 1855, which preceded Marey’s work, was used by him to record pulsus paradoxus in a patient with pericarditis. Clinicians described important pulse abnormalities even if they did not record them, a notable example being the collapsing pulse of aortic incompetence of Dominic John Corrigan in Dublin in 1832. But observation was not enough for Thomas Lewis, the clinical scientist, and in 1906 he undertook experiments on the mechanism of the dicrotic pulse. In patients undergoing a venesection, he showed how volume depletion caused the pulse to become dicrotic. And in the laboratory, he had a reservoir system connected to a tambour with a sphygmograph mounted on its surface, and produced dicrotism with artificial volume changes.
APEX CARDIOGRAPHY

William Harvey had noted how the apex of the heart rises up and strikes the chest wall producing the apex beat and, in the 19th century, various investigators turned their attention to this clinical sign. Foremost was Étienne Jules Marey who made recordings of the apexcardiogram, a debate with Joseph Honoré Simon Beau about their significance led him to make the first-ever intracardiac recordings. This was carried out in horses using balloon-tipped catheters in the right and left ventricles in 1861. Pierre Carl Édouard Potain in Paris, in 1875, used apex recordings with simultaneous venous and arterial tracings and James Mackenzie, in 1902, showed that their diagnostic value has been underrecognized. For example, Peter Nixon used a linear displacement transducer to obtain precise recordings and he studied the position of the atrial beat on the left ventricular apex tracing. When there was left ventricular failure, the atrial impulse climbed the higher on the upstroke of the curve the worse the failure (Figure 5).

BALLISTOCARDIOGRAPHY

This method was a recording of the recoil of the body as a whole as a result of the ejection of blood from the heart, and the idea behind it was the attractive one of being able to record the force of contraction of the left ventricle and also the stroke volume. It was Isaac Starr in the USA who promoted this method from 1939 onwards and he was followed in the 1950s by William Dock in New York. It was said that coronary heart disease produced a special wave in the tracing. But this technique was never proven to be of value and it was discarded.

RADIOLOGY

The discovery of x-rays by Wilhelm Conrad Roentgen in 1895 created a sensation in the scientific world. Within one year, nearly 100 papers were published on this new type of radiation. Roentgen had produced an image on a photographic plate, and, as early as 1896, Francis Henry Williams in Boston, USA, wrote, 'the pulsations of the heart may be followed with the fluoroscope, not only ventricular but also auricular contractions and dilatations.' His book, The Roentgen Rays in Medicine and Surgery, was a landmark text in 1901. Fluoroscopy became the accepted method of cardiac examination, and a particular method of doing it gained favor. This was the orthodiagram, invented by Friedrich Moritz in Munich, in which a central beam of rays was moved around the cardiac margins, allowing the outline of the heart and aorta to be drawn onto the fluoroscopic screen and then traced onto a sheet of paper (Figure 6). In 1916, Kodak was able to replace the cumbersome glass plate with photographic film, which made heart x-rays easier to process. Previously it had been said that the plate might show little beyond the finger marks of the radiographer. In 1924, H. Assmann of Leipzig wrote one of the earliest books on cardiac radiology, followed in America in 1937 by Hugo Roesler's Clinical Roentgenology of the Cardiovascular System, while Charles Laubry in Paris published a large text in 1939. In many cardiac clinics it became a routine for all the patients to be examined under the fluoroscope at the end of the session, viewing the cardiac silhouette from three aspects and outlining the esophagus with barium to show the left atrium. Primitive "screening" apparatus would spit and hiss, and much radiation was scattered. This method also gave information about
the pulmonary circulation, such as the “hilar dance” pulsations seen with a left-to-right shunt in atrial septal defect. Fluoroscopy proved of great importance when Helen Taussig at Johns Hopkins Hospital used it as her prime method of examination in congenital heart disease. The oligemic underfilled lungs in tetralogy of Fallot guided her to devise the famous Blalock-Taussig operation of 1944 (Figure 7).

An interesting approach to record cardiac pulsations was the technique of kymography in which x-rays were passed through the chest to a film that moved at a constant rate behind a grid of lead strips. This produced a jagged outline to the cardiac silhouette showing movement or lack of it. This method was soon abandoned and forgotten. Improvements in x-ray generators allowed teleradiography to become a practical proposition in the 1930s after its first description in 1905. The distance from the tube to the chest had to be at least 6 feet to minimize distortion, and it is now the current standard chest radiograph. Good quality chest x-rays showed not only interesting cardiac silhouettes such as that in 1933 of coarctation of the aorta, but also the changes in the lung fields from heart failure, notably perhaps the B lines of Peter Kerley, also described in 1933.

The chest radiograph has the great merit of being readily available almost everywhere as it is easy to perform with basic x-ray equipment, and although it owes nothing to modern technology it remains a standard method of investigation.

**ECHOCARDIOGRAPHY**

Like other instrumental methods, the diagnostic use of ultrasound had a long gestation. This method is based on the piezoelectric principle, which was described in France by Jacques and Pierre Curie in 1880. The sinking of the Titanic in 1912 led E. G. Richardson in Britain to have the idea of using a beam of underwater sound to detect icebergs, and then in 1917 Paul Langevin in France made a piezoelectric generator for submarine detection. It was found that ultrasound could be transmitted through many substances and that echoes were reflected back at interfaces having different acoustic impedance. The earliest ultrasound method was the A scan, and it was used in 1929 by S. Y. Sokolov in Russia to detect flaws in metal, while his attempt to examine the cerebral ventricles was the first medical application of ultrasound. In 1941, F. A. Firestone in the USA patented an ultrasonic metal flaw detection technique and it was this method that led indirectly to the modern development of cardiac ultrasound by a German physicist, Carl Hellmuth Hertz, in Lund, Sweden, in 1953. He borrowed an ultrasonoscope from a shipyard and together with the cardiologist Inge Edler echoes were recorded from Dr Hertz’s heart. Thus was modern echocardiography born. They modified the device calling it “an ultrasound reflectoscope” and used it in 1954 to show the features of mitral stenosis, including the changes before and after mitral valvotomy (Figure 8, next page). They were also responsible for the M-mode display format, which provides a graphic display showing variations of position with time—something vital for cardiology. In Lund, in 1960, I saw a remarkably elegant study when an echocardiogram of the anterior leaflet of the mitral valve was recorded with a simultaneous left atrial pressure tracing. The latter was done by Stig Radner using his suprasternal see-
The use of cardiac ultrasound was essentially a European development. In 1957, S. Effert in Germany emphasized its value and showed masses in the left atrium. On the whole, however, its potential achieved slow recognition in spite of the fact that leading cardiologists were shown the technique.

The first clinical studies in the USA were carried out in 1963 by H. Reid and C. Joyner and it was also in 1963 that Harvey Feigenbaum started his seminal work. Employing an apparatus used by neurologists at his hospital, he was able to show pericardial effusions and it he who first used the term echocardiography. Feigenbaum trained young physicians in the method and his book *Echocardiography*, which was first published in 1972, became an essential text on the subject. Advances such as “compound B scanning” in the mid 1960s gave good results in internal medicine, but not for the heart, and a major breakthrough came in 1972 when N. Bom in Rotterdam invented the linear array scanner, which produced real-time images. Shortly afterwards, J. M. Griffith and W. L. Henry in Washington introduced the mechanical “a sector” scanner. J. Somer in Holland described a multicrystal ultrasound equivalent of the “phased array radar scanner” used for missile tracking, while F. L. Thurstone and O. T. von Ramm in the USA turned this into a reality for cardiology. Almost all cardiac scanners in use today employ this technology.

Then came a quite different use of reflected ultrasound, which relied on the fact that ultrasound that is reflected from a moving target has its frequency altered by the Doppler effect. This was first used to detect moving structures in the heart by S. Satomura in Japan in 1957, and the method was further developed by D. Baker in the USA, G. Peronneau in France, and P. Wells in the UK. In 1978, Liv Hatle and her colleagues in Norway showed how continuous-wave Doppler could quantify pressure gradients across valves. It also shows the abnormal blood flow in the turbulent jets created by valvular regurgitation and intracardiac shunts. Around 1985, Kasai in Japan developed the first real-time color scanner.

A new approach to cardiac echo was pioneered in Japan in 1977 by K. Hisanaga who introduced transesophageal echocardiography, making use of the fact that the left atrium is in close contact with the esophagus. This technique relied on the development of high-frequency phased array transducers. It has been useful in searching for causes of systemic emboli by finding a left atrial thrombus or a tumor, and by showing a patent foramen ovale. A modern echo machine provides all the modalities of echocardiography, and while continuous-wave Doppler can measure pressure gradients and the pulmonary artery pressure, it is pulsed Doppler that will estimate the size of an intracardiac shunt. The practice of pediatric cardiology has been literally transformed by echocardiography, and now, to give just one example, sick neonates can be evaluated without the need for emergency catheterization—and midnight surgery. Intrauterine echo studies of the fetus can show even complex congenital lesions at an early stage of pregnancy.

Although echocardiography has revolutionized clinical diagnosis and management across the board, it has also advanced our knowledge of cardiac physiology. D. G. Gibson used M-mode echocardiography to perform sophisticated studies of left ventricular function in health and disease, while Graham Leech and Aubrey Leatham used simultaneous phonocardiograms and echocardiograms to elucidate the mechanism of the first heart sound.

The information from echocardiography in its various modes is so comprehensive that it has led to a diminished respect for the traditional methods of cardiac diagnosis. However, these still have an important role in asking what questions the echocardiograph is required to answer. In many countries it is the highly skilled technical staff that perform most of the examinations, and the role of the cardiac ultrasonographer needs strong emphasis and applause for the excellence of their work.

**Figure 8.** A historic echocardiogram showing for the first time the movements [E to F] of the anterior cusp of the mitral valve before (left) and after (right) mitral valvotomy.

MODERN DIAGNOSTIC METHODS

Computed tomography (CT)

Computed tomography (CT) of x-ray images was the brilliant invention of Godfrey Hounsfield in Britain in 1972. The mathematics were so involved that some big organizations, having thought about the idea, decided that it was too difficult to pursue. At first, image acquisition was too slow to permit examination of the heart, but the development of multidetector CT in 1999 produced excellent results and permits the heart to be viewed in three dimensions. Currently, the main uses of cardiac CT are for coronary artery calcium scanning and CT coronary angiography. High calcium scores can predict an increased incidence of adverse coronary events, even up to a 22-fold increase. After intravenous contrast, the images of the coronary arteries are very good down to a resolution of 0.5 mm. Compared with catheter angiography, there is a sensitivity of 92% to 95% and a specificity of 86% to 93%.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) uses large magnets and radio frequency waves to produce high-quality still and moving pictures of the body’s internal structures. It was invented by Paul Lauterbur in the USA and Peter Mansfield in Britain, starting in 1973. MRI acquires information about the heart as it is beating and can display abnormalities in cardiac chamber contraction and show abnormal patterns of blood flow. After a bolus of gadolinium, it is possible to assess myocardial perfusion on a semiquantitative basis. Cardiac MRI has been widely used for perfusion studies and for the evaluation of congenital heart disease.16

Radionuclide imaging

Radionuclide imaging was first used a long time ago when H. L. Blumgart and P. Weiss in 1937 injected radium C intravenously to measure the circulation time. In 1948, S. S. Kety used radioactive sodium to determine blood flow in the myocardium. Use of radionuclide diagnosis. With thallium 201 and newer compounds, this method is widely used to detect areas of transient myocardial ischemia after exercise, among other applications.17

CONCLUSION: A BRIEF HISTORY OF DIAGNOSTIC CARDIOLOGY

The tree of cardiological diagnosis has witnessed dramatic growth since the days when diagnosis was based on a doctor’s eyes, hands, and questions. Informed cardiac diagnosis could not get under way until there was good evidence of the disease process from autopsy examination—clinico-pathological correlation started with Morgagni’s work De Sedibus in 1761. This was notably continued in France in the 19th century where clinical diagnosis was born in 1819 with the invention of the stethoscope. There was an urgent need to make recordings of the beating heart and this led to the invention of the polygraph in 1882 and, importantly, in 1901, to the birth of electrocardiography, while the discovery of x-rays in 1895 gave rise to cardiac radiology. Intracardiac pressures had long been measured in animals and the introduction of cardiac catheterization in the early 1940s enabled this to be done in humans. This was soon to be followed by contrast visualization of the heart, which gave the precise diagnosis needed for open-heart surgery in congenital heart disease. Echocardiography, invented in 1953, was especially helpful for cardiac diagnosis in showing not only cardiac anatomy, but also blood flow. Being noninvasive, it proved a wonderful tool for patients, especially for infants and young children. Recent developments in multidetector computed tomography scanning and magnetic resonance imaging are already proving very useful and hold much promise for the future. Notwithstanding the dramatic achievements of all these increasingly sophisticated diagnostic tools, to paraphrase from The Gondoliers, there is still “no probable possible shadow of doubt” that a thorough history and physical examination are the best way to commence the diagnostic process: for all the wealth of branches and foliage we should not forget the humble but firm basis on which diagnosis—be it cardiology or any other field of medicine—is rooted: listen, look, touch.

REFERENCES

1. Gibson D.

2. Hollman A.

3. Blaufox MD.
4. Fleming PR.  
A Short History of Cardiology.  Amsterdam, The Netherlands; Editions Rodopi; 1997.

5. Leatham A.  
Auscultation and phonocardiography; a personal view of the past 40 years.  
Br Heart J. 1987;57:397-403.

6. Acierno LJ.  

7. Hollman A.  

8. Mackenzie J.  

9. Bethell HJN, Nixon PGF.  
Understanding the atrial sound.  

10. Lewis T.  
Material relating to coarctation of the aorta of the adult type.  
Heart. 1933;16: 205-261.

11. Taussig H.  

12. Edler I, Gustafson A.  
Ultrasonic cardiogram in mitral stenosis.  

13. Feigenbaum H.  
Evolution of echocardiography  

14. Chambers JB.  

15. Weyman AE.  
The year in echocardiography.  

16. Muir AL.  
Cardiac imaging fifty years on.  
Br Heart J. 1987;58:1-5.

17. Ell PJ.  
In attempting to construct a “tree” describing the history of heart failure, I have concluded that this tree of knowledge is, in fact, a bush. Although both have roots and branches, the middle structure is quite different; in a tree, a single trunk supports the entire structure, whereas in a bush, many stems link the branches to the roots. Because much of what was once widely believed to be true is now known to be incorrect, and much that we now view as correct emerged suddenly and unexpectedly, this structure exemplifies the paradigm shifts described by Thomas Kuhn. The roots in heart failure research have always been nourished by the clinical syndrome, which by stimulating efforts to understand what is wrong with these patients, provided the nutrients for the many stems of pathophysiology and therapy. However, not all of these stems have remained viable; some disappeared completely, while others—including many that once seemed vibrant and strong—have withered. I wonder whether some of the stems that seem strong today will not suffer the latter fate.

HEART FAILURE AS A CLINICAL SYNDROME

Although humans have always suffered from heart failure, identification of this syndrome in early writings is difficult because the clinical findings, most of which are not diagnostic, were not understood in terms of pathophysiology. Palpation of the pulse is noted in the Edwin Smith papyrus, written in Egypt some 5000 years ago, but it was Hippocrates and other Greek physicians of the 6th to 5th centuries BCE, who made the first solid efforts to organize their clinical observations. Their writings describe a few patients with what might be heart failure, but because the heart’s function as a pump was not understood, it is difficult to relate signs and symptoms that suggest heart disease to this syndrome. Furthermore, most treatments were based on a physiology that viewed health as a balance between competing humors. The Hippocratic texts do include a few examples of what today can be viewed as rational therapy for the complications of heart failure, Most notable is drilling through a rib (to avoid eventual closure of a hole in soft tissue) to drain a pleural effusion that had been located when the physician listened for a “succussion splash” while an assistant shook the patient. Because blood spurting from a severed artery is hot, the heart came to be viewed as the source of heat. This misconception, promulgated by Galen—a 2nd-century Greek physician whose writings were to domi-
nate medicine until the 17th century\(^5\)—led to the widespread practice of bloodletting to treat fevers, and indeed most maladies. We now know, of course, that the adverse consequences of bleeding almost always exceed any benefit, which provides a classic example—indeed the classic example—of the harm caused by therapy that is based on an erroneous understanding of pathophysiology.

**HEART FAILURE AS A HEMODYNAMIC SYNDROME**

Virtually no progress could be made in treating heart failure until the heart was understood to pump blood. Credit for this discovery belongs to William Harvey, whose *De Motu Cordis*, published in 1628, marked the emergence of the most durable pathophysiological stem in the heart failure bush. That *De Motu Cordis* appeared at a time when others were beginning to describe key features of the circulation\(^3\) illustrates the general rule that discoveries occur when the time is propitious. Although lacking Harvey’s physiological thoroughness, these earlier descriptions indicate that 17th-century physiologists had begun to realize that the heart is a pump and not a furnace.

In spite of its monumental importance, *De Motu Cordis* had little immediate impact on the understanding and treatment of heart failure. Although Harvey was an accomplished physician, he wrote surprisingly little about how his discovery might explain the signs and symptoms of heart failure. In fact, almost a century was to pass before the hemodynamic cause of this syndrome was elucidated.\(^5,6\) Postmortem dissection of the human body, which provided the soil that nourished another durable stem of the heart failure bush, became increasingly common during the 17th century. Autopsies allowed the clinical investigators of that time, after they had observed and recorded the clinical findings that preceded the death of a patient, to open the body in an attempt to learn what had caused the illness. In the century that followed *De Motu Cordis*, Lazare Rivière, James Hope, John Mayow, Richard Lower, Raymond Vieussens, and Giovanni Maria Lancisi began to relate the clinical features of heart failure to the abnormal hemodynamics.\(^6,8\) Assignment of priority among these and other 17th- and 18th-century authors is impossible because their case descriptions were generally compiled in books that were often published posthumously, frequently after the observations had circulated throughout Europe. The clearest early explanation of the hemodynamic abnormalities in heart failure is that of Vieussens, whose compassionate description of a patient whose death was caused by mitral stenosis is followed by a detailed discussion of the autopsy findings that includes a drawing of the stenotic mitral valve (Figure 1)\(^9\) and a remarkably modern explanation of the pathophysiology. Unfortunately, recognition of the hemodynamic basis for the signs and symptoms of heart failure was to have almost no impact on treatment for almost 300 years.

An exception to the generalization that understanding of pathophysiology is essential to treating disease occurred in 1785, when William Withering learned of an herbalist in Shropshire who was dispensing a remedy that was effective in treating dropsy. Using his knowledge of botany (which until the late 19th century was included in the medical curriculum), he concluded that the active ingredient is the leaf of *Digitalis purpurea*, the purple foxglove. Withering, of course, had no way of knowing how digitalis helped his patients, most of whom probably had rheumatic mitral stenosis complicated by atrial fibrillation; the ability of cardiac glycosides to slow the heart in this condition may have been the basis for his observation that digitalis “has a power over the motion of the heart, to a degree yet unobserved in any other medicine.” Others thought that the benefits of this drug were due to a diuretic effect mediated by the kidneys, later to its inotropic effect, and most recently to its sympatholytic and vagomimetic effects—but this gets us ahead of our story.

**HEART FAILURE AS A CONSEQUENCE OF ARCHITECTURAL ABNORMALITIES IN THE HEART**

Emphasis on postmortem examination drew attention to changes in the size and shape of the failing heart,\(^4\) and led 18th- and 19th-century authorities to recognize two forms of hypertrophy, which today are generally called concentric and eccentric hypertrophy. Credit for this
distinction is generally assigned to Jean Nicolas Corvisart, a French clinician-pathologist who noted that the former, which he called “active hypertrophy,” has a better prognosis than “passive hypertrophy,” which came to be called dilatation. Concentric hypertrophy, or more simply hypertrophy, was for a time believed to be an adaptive response that helps the heart avoid the dire prognosis associated with dilatation. By the end of the 19th century, however, it had become clear that hypertrophy, like dilatation, is an imperfect adaptive response. This led William Osler, in 1892, to describe three phases in the response to overload (Table I).10,11 The first, development of hypertrophy, alleviates symptoms, because as the heart enlarges, it becomes better able to handle the increased load; this led to the second phase of full compensation, when symptoms improve further. The adaptive response ends in a third, maladaptive, phase of hypertrophy, which Osler called broken compensation, where degeneration and weakening of the heart muscle worsen symptoms and cause the death of the patient.

One of the more remarkable observations made during the 19th century was that obstruction of left ventricular ejection, for example, in aortic stenosis, causes concentric hypertrophy, whereas regurgitant lesions like aortic insufficiency cause the heart to dilate. In modern terms, these observations suggest that increased afterload and increased preload initiate different phenotypes of hypertrophy by activating different proliferative signaling pathways (see below). Unfortunately, until the end of the 20th century, these and other features of the architectural stem provided few clues regarding treatment, aside from “pushing” digitalis, which sometimes killed the patient, little could be done to alleviate the suffering caused when increasingly frequent and more severe episodes of pulmonary edema heralded the approach of a cruel death.

HEART FAILURE AS A HEMODYNAMIC SYNDROME (AGAIN)

The hemodynamic abnormalities in heart failure, while understood by a few highly trained physicians, were largely ignored until 1915, when Ernest Starling presented his Linacre Lecture on the “Law of the Heart.” Although the role of diastolic volume in determining cardiac output was known to physiologists during the latter half of the 19th century,12 most physicians based their views regarding the consequence of increased cavity size on the pathological finding that dilatation is associated with a poor outcome. Starling’s prestige was such that, within a decade after his lecture, dilatation had come to be viewed as a beneficial short-term hemodynamic response, rather than a deleterious long-term architectural response. This focus on hemodynamics was also stimulated by Carl Wiggers’ research on valvular heart disease, which after World War II was to provide the foundation for modern cardiac surgery.

The renewed interest in hemodynamics had little impact on patient care, except for the use of rotating tourniquets, and sometimes venesection (a rare example where Galen’s therapy was appropriate), to treat acute pulmonary edema. My father, Louis Katz, who graduated from Medical School in 1921 after having worked as a student with Wiggers, told me that during his in-

### THREE PHASES IN THE HEART’S RESPONSE TO HEMODYNAMIC OVERLOAD

<table>
<thead>
<tr>
<th>Phase 1: Osler: Development; Meerson: Transient breakdown.</th>
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<tbody>
<tr>
<td><strong>Clinical:</strong> Symptomatic left ventricular dysfunction after mild overload acute left ventricular failure and cardiogenic shock after severe overload.</td>
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<tr>
<td><strong>Pathophysiology:</strong> Left ventricular dilatation, pulmonary congestion, low cardiac output, early hypertrophy.</td>
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<th>Phase 2: Osler: Full compensation; Meerson: Stable hyperfunction.</th>
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<tr>
<td><strong>Clinical:</strong> Class I-II heart failure.</td>
</tr>
<tr>
<td><strong>Pathophysiology:</strong> Improved symptoms, resolved pulmonary congestion, increased cardiac output, established myocardial hypertrophy.</td>
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<tr>
<th>Phase 3: Osler: Broken compensation; Meerson: Progressive cardiosclerosis.</th>
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<tbody>
<tr>
<td><strong>Clinical:</strong> Class III-IV heart failure.</td>
</tr>
<tr>
<td><strong>Pathophysiology:</strong> Worsening congestion, hemodynamic deterioration, continued hypertrophy with progressive ventricular dilatation, myocardial cell death, fibrosis.</td>
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*Table I.*
ternship he could do little for most cardiac patients except to try to determine what was wrong, after which he would wait until the patient died to see if he was correct—as he did not find this at all satisfying, he returned to research. An even more telling anecdote was published by Sir George Pickering:

... very few clinicians knew [anything] of the venous pressure. I remember vividly being an intern in 1930 to one of the best physicians whom it was my privilege to know, whose specialty was heart disease, and who was not acquainted with the message contained in the veins of the neck. This struck me most forcibly when I was asked to transfuse a patient with mitral stenosis and severe anemia, whose jugular veins were intensely distended... It struck me at the time as very odd that a patient who presented a sign indicating the desirability of venesection should be transfused. I was thus, in a way, scarcely surprised when the patient developed acute pulmonary edema as a result of transfusion and died.\(^{13}\)

**HEART FAILURE AS A DISORDER OF THE KIDNEYS**

The discovery of the diuretic effect of organic mercurials had an enormous impact on the treatment of heart failure. Although fluid retention had been proposed as a cause of dropsy in the 16th century, there was no safe way to get rid of it. The diuretic effect of inorganic mercurials was well known, but their toxic/therapeutic ratio is so low that they usually did more harm than good. All this changed in 1920, when Paul Saxl and R. Heilig injected an organic mercurial to kill the spirochetes in a patient with syphilitic heart disease and, to their surprise, observed a massive diuresis\(^{14}\) that was subsequently found to be caused by inhibition of sodium resorption by the renal tubules. However, because these drugs cease to be effective when given more than 2 to 3 times each week, they are of little benefit in severely ill patients. The search for powerful diuretics that could be given orally shifted the focus of heart failure research to renal physiology, and ended successfully in the late 1950s and early 1960s with the discovery of the diuretics, and then of loop diuretics. This solid and durable stem of the heart failure bush illustrates how a chance discovery, along with an understanding of pathophysiology, came to alleviate human suffering.

The attention paid to the kidneys had an impact on my own training when, as an intern applicant in 1956, I attended a Medical Grand Rounds on heart failure at a prominent New York hospital that I had selected to be my first choice. After listening to an hour-long discussion dealing only with the kidneys, I could not resist asking: “Does the heart have anything to do with heart failure?” Not surprisingly, I went on to intern at my second choice in Boston.

**ENERGETICS OF HEART FAILURE**

Between the 1930s and 1950s, most experimental studies of heart failure used animal models whose hemodynamics resembled those seen clinically, but where the pathophysiology was entirely different. These included deteriorating heart-lung preparations, where the heart fails largely because particulates in the perfusates occluded the coronary microcirculation, and a model of acute right heart dilatation created by constricting the pulmonary artery and avulsing the tricuspid valve. While useful in studying the renal response, these models have little relevance to clinical heart failure. It is not surprising that these studies led to the erroneous view that energetics in the failing heart are normal; a conclusion that was reinforced by data that for technical reasons were flawed, suggesting that heart failure is caused by a change in the molecular weight of cardiac myosin.\(^{15}\) The erroneous view that energy-starvation does not play an important role in heart failure was one reason that many failed to predict the detrimental effects of inotropic therapy and the potential benefits of \(\beta\)-adrenergic blockers (see below).

**CARDIAC CATHETERIZATION AND CARDIAC SURGERY**

Cardiac catheterization, which in the late 1940s brought more than a half century of basic research to the bedside, provided the accurate clinical diagnoses needed for cardiac surgery and so helped revolutionize the treatment of rheumatic and congenital heart disease—then the most common causes of heart failure. These advances, which are described elsewhere in this issue, are mentioned here because they are among the clearest examples of how basic science research improves clinical therapy.\(^{16}\)

**HEART FAILURE AS IMPAIRED MYOCARDIAL CONTRACTILITY**

Between the 1920s and the 1960s, students were commonly taught that the failing heart operates on the descending limb of the Starling curve. This is surprising because Starling had made it clear in his Linacre Lecture that the heart cannot achieve a steady state when increasing chamber volume decreases its ability to eject. This confusion ended in 1955, when Stanley Samoff demonstrated that the heart can operate on different Starling curves,
shifting to a “lower” curve when contractility is depressed (Figure 2). This discovery came at a time when rapid progress in muscle biochemistry had shown that calcium delivery to the cytosol and its binding to troponin, a regulatory protein in the myofilaments, are major determinants of myocardial contractility. Together, these discoveries shifted the focus of heart failure research to the depressed contractility.

Efforts to apply this new knowledge to patients were hampered by difficulties in defining myocardial contractility and the fact that, although most investigators had some idea as to what contractility was, no one knew how to measure it. Research in this field during the 1960s and 1970s was based on concepts developed by A. V. Hill, whose classic work on the frog sartorius—where curves relating muscle load to shortening velocity are hyperbolic—had dominated skeletal muscle physiology for almost half a century. However, efforts to measure \( V_{\text{max}} \), the maximal shortening velocity of a muscle contracting with zero load, not being stabilized, made it impossible to determine \( V_{\text{max}} \), which many viewed as the gold standard in quantifying contractility. After almost two decades of heated controversy, it became clear that myocardial contractility cannot be measured accurately in patients.

**VASODILATOR AND INOTROPIC THERAPY**

At the end of the 1970s, in spite of the successful development of oral diuretics and use of digitalis, patients with heart failure continued to suffer and die. However, the causes of this syndrome were changing; rheumatic fever was disappearing and most patients with valvular and congenital heart disease were improved by the cardiac surgeon, who could also alleviate angina pectoris in patients with ischemic heart disease, which in developed countries was emerging as the major cause of cardiovascular death. At the same time, more precise diagnostic tools were identifying an increasing number of patients in whom heart failure is caused by a cardiomyopathy. For these reasons, heart failure came to be viewed as a hemodynamic disorder caused when depressed left ventricular contractility reduces the ability of the diseased heart to eject. This view, along with recognition of the harm caused by increased afterload, one of the body’s responses to low cardiac output, provided the rationale for two new stems in the heart failure bush—afterload reduction and inotropic therapy.

The short-term benefits of afterload reduction, which by unloading the failing heart causes obvious hemodynamic improvement, led Jay Cohn to organize VHeFT I (Veterans Administration Heart Failure Trial I), a long-term clinical trial that examined the effects of several vasodilators on long-term prognosis. This randomized double-blind trial, published in 1986, was the first of the large heart failure trials that now represent the “gold standard” in evaluating therapy. The major findings were that a long-acting nitrate in combination with hydralazine prolongs survival, whereas prazosin, an \( \alpha \)-adrenergic blocker, has no benefit (Figure 3A, next page). This pioneering study, which also highlighted the poor prognosis in heart failure, led to additional trials that sought to document a survival benefit for other vasodilators. However, the results were generally disappointing because, in spite of the ability of all vasodilators to cause short-term hemodynamic improvement, most worsen long-term prognosis. A major exception was CONSENSUS (COoperative North
Scandinavian ENalapril SUrvival Study), which, by documenting a remarkable benefit in patients given an angiotensin II converting-enzyme (ACE) inhibitor (Figure 3B),22 opened a new area of research.

Efforts during the 1970s and 1980s to develop new inotropic agents were aided by further clarification of the role of calcium in contraction, excitation-contraction coupling, and relaxation, and by the discovery that cyclic AMP mediates the positive inotropic response to sympathetic stimulation. The widely held belief that increasing contractility would benefit patients with heart failure was reinforced by observations that norepinephrine and other β-agonists, which increase cellular cyclic AMP levels, cause short-term hemodynamic improvement in patients with acute heart failure. However, evidence that the failing heart is energy-starved led a minority to believe that the energy cost of the inotropic and chronotropic responses to cyclic AMP could harm patients with chronic heart failure. This provoked a sharp controversy that ended when several clinical trials showed that long-term inotropic therapy with β-agonists and phosphodiesterase inhibitors does more harm than good. At the same time, a long-awaited clinical trial showed that cardiac glycosides, which had come to be viewed as inotropes, do not improve survival in patients with heart failure who remain in sinus rhythm.

REMODELING, ACE INHIBITORS, AND MOLECULAR BIOLOGY

A new era of heart failure research began in 1985, when a landmark paper by Janis Pfeffer, Mark Pfeffer, and Eugene Braunwald23 showed that it is possible to inhibit deterioration of the failing heart. The key observation was that an ACE inhibitor slows the progressive dilatation that follows experimental myocardial infarction (Figure 4).23 To describe the cavity enlargement, which the investigators viewed as "a compensatory remodeling (dilation) of the left ventricle [that allows] preservation of forward output at any filling pressure," they chose the term remodeling, which highlights the beneficial short-term hemodynamic response to dilatation described by Starling, rather than the deleterious long-term architectural effect noted in the 19th century.

The clinical importance of this discovery became apparent the following year when, at a meeting held in Oslo, Norway, the results of CONSENSUS I were announced. This trial documented a survival benefit of an ACE inhibitor that was so striking (Figure 3B)22 that a member of the audience stood up and said that these results could not be true because, to paraphrase, "No other
vasodilator has this marked effect on survival. This led me to suggest that the improved prognosis might not be due to the vasodilator effect of the inhibiting angiotensin II production, but instead to a different response not known at that time. Clearly, no one at the Oslo meeting was aware that research had already begun that was to show that angiotensin II also stimulates proliferative responses.24

The context for both these experimental and clinical findings came into focus at a second meeting, held in Boston in 1987, which made it clear that deterioration of the hypertrophied heart is not due simply to continued overload, highlighted the importance of maladaptive hypertrophy as a cause for the poor prognosis in patients with chronic heart failure.26 It remained simply to figure out how hypertrophy can be both adaptive and maladaptive, and at the same time, in the same patient!

Figure 4. Effect of captopril on diastolic pressure-volume relationships in rats following myocardial infarction (MI). Left ventricular diastolic volumes (abscissa) and pressures (ordinate) after 3 months are shown for noninfarcted control rats (shaded area, mean ±2 SD), infarcted hearts of untreated rats (○), and infarcted hearts of rats treated with captopril (■). The difference between the latter is significant (P<0.05).


HEART FAILURE

AS A CONSEQUENCE OF ARCHITECTURAL ABNORMALITIES IN THE HEART (AGAIN)

Although advances in hemodynamics during the 20th century had relegated studies of the architecture of the failing heart to the background, the earlier work had not been entirely forgotten. Felix Meerson, who in the 1950s was the first to use modern methods to study overload-induced myocardial deterioration in animal models, described three phases that are similar to those proposed by Osler in 1892 (Table I).10,11

In the 1960s and 1970s, after cardiology rediscovered the Law of Laplace (which although known to 19th-century physiologists, had been forgotten since the 1920s), at least 3 groups found that the initial adaptive hypertrophic response in patients with aortic stenosis and insufficiency normalizes wall stress.14 This finding, which made it clear that deterioration of the hypertrophied heart is not due simply to continued overload, highlighted the importance of maladaptive hypertrophy as a cause for the poor prognosis in patients with chronic heart failure.26 It remained simply to figure out how hypertrophy can be both adaptive and maladaptive, and at the same time, in the same patient!

PROLIFERATIVE SIGNALING AND SURVIVAL IN HEART FAILURE

The first clue that overload changes the molecular composition of the heart had come in 1962, when Norman Alpert and Michael Gordon reported a reduction in the ATPase activity of myofibrils isolated from failing human hearts. This study heralded a still growing body of knowledge that has characterized molecular changes in the failing heart, such as reversion to the fetal phenotype, and is now describing the proliferative signaling pathways that initiate adaptive and maladaptive hypertrophy.27-33

At the same time that the molecular mechanisms responsible for deterioration of the failing heart were coming into focus, progress continued in efforts to prolong survival in patients with heart failure. Virtually all large clinical trials in heart failure enrolled patients with a low ejection fraction, often called systolic heart failure, where progressive dilatation is a major consequence of maladaptive hypertrophy. The most remarkable finding was the beneficial effect of β-blockers, which because of their negative inotropic effect had been almost universally viewed a decade earlier as contraindicated in these patients. As had happened before, the extent of the benefit was unexpected and, for
those who did not believe that the failing heart is energy-starved, counterintuitive. Another remarkable finding was that spironolactone, a potassium-sparing diuretic that had been used for decades, also improves prognosis.

It is probably significant that the drugs that prolong survival in systolic heart failure also inhibit remodeling, these include nitrates, ACE inhibitors, angiotensin II receptor blockers, β-blockers, and aldosterone antagonists. Furthermore, cardiac resynchronizing therapy (CRT) and left ventricular assist devices (LVADs), which also improve prognosis, reverse many features of maladaptive hypertrophy, including reversion to the fetal phenotype and remodeling. Although a rigorous assessment of the impact of these new therapeutic approaches on survival has not been carried out, comparisons of heart failure trials in the 1980s and early 1990s with those reported in the past few years suggest that life expectancy has been doubled.

CONCLUSION

The emergence of the new stem of molecular biology clearly represents a major addition to the heart failure bush. Although these new stems will be rooted in the clinical syndrome, history tells us that they are likely to emerge from unexpected places on the growing bush of basic knowledge.

REFERENCES

My bibliography, rather than listing original sources, cites reviews, many of which I have written, that reference the texts and papers discussed in this article. The focus on the Western tradition reflects my personal interests, and should not be construed as undervaluing work done in other cultures.


18. Katz AM.
A growth of ideas: role of calcium as activator of cardiac contraction.

19. Katz AM.
*Physiology of the Heart.* 4th ed.

20. Harris P.
Contractility revealed.

Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration cooperative study (V-HeFT).

22. CONSENSUS Trial Study Group.
Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study.

23. Pfeffer JM, Pfeffer MA, Braunwald E.
Influence of chronic captopril therapy on the infarcted left ventricle of the rat.

24. Katz AM.
Angiotensin II: Hemodynamic regulator or growth factor?

25. Katz AM.
Molecular biology in cardiology, a paradigmatic shift.

26. Katz AM.
Cardiomyopathy of overload. A major determinant of prognosis in congestive heart failure.

27. Bueno OF, Molkentin JD.
Involvement of extracellular signal-regulated kinases 1/2 in cardiac hypertrophy and cell death.

28. Hoshijima M, Chien KR.
Mixed signals in heart failure: cancer rules.

29. Akazawa H, Komuro I.
Roles of cardiac transcription factors in cardiac hypertrophy.

30. Lips DJ, deWindt IJ, van Kraaij DJW, Doevendans PA.
Molecular determinants of myocardial hypertrophy and failure: alternative pathways for beneficial and maladaptive hypertrophy.

31. Frey N, Katus HA, Olson EN, Hill JA.
Hypertrophy of the heart. A new therapeutic target.

32. Izumo S.
Molecular basis of heart failure. In: Mann DL, ed.

Adaptive and maladaptive hypertrophic pathways: points of convergence and divergence.

See also:

*Heart Failure.*
SOIL AND SEEDS: THE CIRCULATION

The extensive and variegated canopy that represents our modern understanding of hypertension has its origins centuries ago in early theories related to the circulation. As long ago as the 5th century BCE in Greece, Hippocrates propounded on the presence of arteries and veins, although he believed the veins carried air. Six hundred years later, Galen proposed the existence of blood in both arteries and veins. He believed the blood and arteries filled the body with life-giving energy and that the liver and veins provided further nourishment and growth. The heart was considered to be a warming machine and blood flowed both backward and forward with no recognized connection between arteries and veins. These teachings essentially went unchallenged for more than a thousand years, although notably, early Egyptian interpretations of the blood flow through the body were in some respects more coherent.

William Harvey was born in 1578 in Kent, the eldest of a week of sons. After attending university at Cambridge, he studied medicine at Padua and was subsequently admitted to the Royal College of Physicians in London. He was later to be Physician to both James I and Charles I. In 1616, he gave his first lecture on the circulation. In 1628, he published his classic Exercitatio Anatomica de Motu Cordis et Sanguinis. His elegant writings were based on careful observation, experimental procedures, and quantitative reasoning. Harvey refuted Galenic views and clearly demonstrated the one-way circulation of blood. He did not identify the capillary circulation, but deduced its presence: “blood passes from arteries to veins directly by anastomosis or indirectly through pores in the flesh.” This deduction was confirmed through the direct microscopic observations of Marcello Malpighi, an Italian physiologist and pioneer of microscopical anatomy. Malpighi’s first Royal Society publication in 1661 correctly described capillary connections and flow between arteries and veins. In his writings, Harvey had recognized the “hardness due to tension” of the contracting heart as it “ejects into the arteries” and that “blood is forced by the pulse in the arteries continually and steadily to every part of the body.” His principal conclusions were related to the circular and continuous nature of blood flow in the animal body accomplished by the pumping action of the heart. Thus, the soil was prepared and the seeds sown for what was to ensue over the next 300 years as blood pressure measurement techniques, and disease mechanisms were slowly unraveled.
ROOTS AND TRUNK: BLOOD PRESSURE MEASUREMENT

The truncal position for hypertension historically may best be accorded to the British theologian, inventor, and scientist Stephen Hales (*Figure 1*), who was reportedly the first person to measure blood pressure experimentally in 1733. His renowned efforts, however, required considerable subsequent technical refinement. Such people as Ludwig, von Basch, Riva-Rocci, and Korotkoff made key contributions during the following century, as practical and reliable methods of measurement were developed leading into 20th century practice. Stephen Hales was one of the most renowned British scientists of his time. Born in 1677 and educated privately, then proceeding to Corpus Christi College, Cambridge, he was ordained and inducted to the “Perpetual Curacy” of Teddington in 1709. His interest in scientific experiments dated from his Cambridge years and his subsequent research ranged widely across animal and plant physiology and the nature of air. He undertook experiments on food preservation and ventilation, succeeding in getting artificial ventilators fitted in prisons, greatly improving sanitary conditions. In 1733, he reported to the Royal Society *An Account of some Hydraulic and Hydrostatical Experiments Made on the Blood and Blood-Vessels of Animals*. This account was subsequently published with other experiments including some on kidney and bladder stones. This is how he describes his most famous blood pressure experiment:

Experiment I. In December I caused a mare to be tied down alive on her back; she was 14 hands high, and about 14 years of age, had a fistula on her withers, was neither very lean nor yet lusty; having laid open the left crural artery about 3 inches from her belly, I inserted into it a brass pipe whose bore was 1/6 of an inch in diameter; and to that, by means of another brass pipe which was fitly adapted to it, I fixed a glass tube, of nearly the same diameter, which was 9 feet in length: then untying the ligature on the artery, the blood rose in the tube 8 feet 3 inches perpendicular above the level of the left ventricle of the heart: but it did not attain to its full height at once; it rushed up about half way in an instant, and afterwards gradually at each pulse 12, 8, 6, 4, 2, and sometimes 1 inch; when it was at its full height, it would rise and fall at and after each pulse 2, 3, or 4 inches; and sometimes it would fall 12 or 14 inches, and have there for a time the same vibrations up and down, and at and after each pulse, as it had, when it was at its full height, to which it would rise again, after forty or fifty pulses.

Hales went on to measure the jugular venous pressure, which he found to be 12 inches when the horse was quiet and 52 when the horse struggled (*Figure 2*). From these experiments, he estimated man’s blood pressure to be about 7.5 feet—quite close considering how crude his apparatus was.

Thus the science of blood pressure measurement was born. Hale’s experiment on this and several other horses, however, entailed much more than blood pressure measurement alone, including observations on blood volume (derived from exsanguination of the animals), the systemic and pulmonary circulations, and cardiac function.

It was more than 100 years before Hales’ observations were put to medical use. The introduction of the mercury hydrodynometer in the early 1800s by Poiseuille allowed reduction of the pressure column...
to a practical height. Human blood pressure was first measured in 1847 using Carl Ludwig’s kymograph with catheters inserted directly into the artery. Ludwig’s kymograph consisted of a U-shaped manometer tube connected to a brass pipe cannula into the artery. The manometer tube had an ivory float onto which a rod with quill was attached, which sketched onto a rotating drum. In 1881, Ritter von Basch invented the sphygmomanometer, which allowed indirect noninvasive measurement of human blood pressure. His device consisted of a water-filled bag connected to a manometer, which recorded the pressure required to obliterate the arterial pulse. This design apparently never gained a following from physicians of the time generally skeptical of new technology, and several different versions and improvements followed. These culminated in the development of the mercury sphygmomanometer by Scipione Riva-Rocci in Italy in 1896. This was the prototype of the modern instrument. It employed a narrow inflatable cuff encircling the upper arm to constrict the brachial artery, the cuff being inflated by a rubber bulb and connected to a glass manometer filled with mercury. The systolic blood pressure was determined by distal palpation of the radial artery. Soon after Riva-Rocci’s technique was described, L. Hill and H. Barnard in England in 18974 reported on their apparatus, which used an inflatable cuff and a needle pressure gauge to provide an oscillatory method of measurement of both systolic and diastolic pressure. Finally, this sequence of development of instrumentation was completed in 1905 by a Russian physician, Nikolai Sergoevich Korotkoff (Figure 3).

Korotkoff was born in Kursk in 1874, where he received high school education, and graduated with distinction from the Moscow University Medical School in 1898. He worked as a physician for the Red Cross in the Far East during The Boxer Rebellion in China in 1900, for which service he was honored. He later completed his residency in Moscow and then worked at the Military Medical Academy in Saint Petersburg. He worked for a short period in China during the Russian-Japanese war in 1904-1905 and also in Siberia. He finished his career as senior physician at the Mechnikov Hospital in Saint Petersburg, dying at a young age in 1920.

In 1905, in a presentation to the Imperial Military Academy, Korotkoff outlined a new auscultatory method to measure blood pressure in humans. This method was later described in detail for the first time in his dissertation for the advanced scientific degree of Doctor of Medical Sciences, which was presented in 1910 to the Scientific Council of the Imperial Military Medical Academy. Korotkoff’s method of blood pressure measurement was derived from observations he made treating wounded soldiers during the Russian-Japanese war. In attempting to predict the outcome of ligation of arteries of traumatized limbs, he systematically listened to the arteries to estimate the potential strength of arterial collaterals after major vessel ligation. He established that certain specific sounds were audible during decompression of the arteries and this formed the basis of his proposed new method of blood pressure measurement. The initial presentation made by Korotkoff in 19056 is recorded remarkably concisely in less than a page in the Imperial Military Academy literature:

The cuff of [a] Riva-Rocci [manometer] is placed on the middle third of the upper arm. The pressure within the cuff is quickly raised up to complete cessation of circulation below the cuff. Then, letting the mercury of the manometer fall, one listens to the artery just below the cuff with a child’s stethoscope. At first, no sounds are heard. With the falling of the mercury in the manometer, down to a certain height, the first short tones appear; their appearance indicates the passage of part of the pulse wave under the cuff. It follows that the manometric figure at which the first tone appears corresponds to the maximal pressure. With the further fall of the mercury in the manometer one hears the systolic compression murmurs, which pass again into tones (second). Finally, all sounds disappear. The time of the cessation of sounds indicates the free passage of the pulse wave; in other words, at the moment of the disappearance of the sounds the minimal blood pressure within the artery preponderates over the pressure in the cuff. It follows that the manometric figures at this time correspond to the minimal blood pressure.

Korotkoff considered the tones and murmurs to be caused by pulse wave compression and vibration of vessel walls influenced by the elastic properties of the arteries. A series of later studies by Korotkoff and various colleagues validated these
initial observations and showed close correlation with invasive methods of measurement. The method quickly received wide recognition and was soon incorporated into standard medical practice.

**BRANCHES: BLOOD PRESSURE AND DISEASE**

During the period in which blood pressure assessment techniques were being developed, the first significant clinical observations, which tentatively related blood pressure and disease, were also being made. Richard Bright in his classic paper in 1836 reported on one hundred cases with albuminous urine, and noted that pathological changes in the kidney are often accompanied by cardiac left ventricular hypertrophy and apoplectic brain disorders. While he did not appreciate the importance of these observations in relation to blood pressure, he did speculate that small-vessel disease might require increased cardiac force to overcome higher flow resistance. Bright’s seminal paper can be seen historically to have initiated an increasingly intensive train of pathophysiological enquiry continuing through to the present day.

Sir George Johnson described arterial hypertrophy in his *Diseases of the Kidney* published in 1852. He related capillary obstruction to increased pressure and this in turn to the occurrence of cerebral hemorrhage in Bright’s disease. However, in his interpretation of the cardiac and vascular abnormalities that both he and Bright observed, he wrongly attributed them to intoxicating changes in the quality of the blood. Sir William Gull, Royal Physician, and Henry Sutton subsequently challenged Johnson’s interpretation of the arterial changes in Bright’s disease. Their joint publication in 1872 described hyaline fibroid changes in the arterioles and capillaries and they noted that these could occur in the absence of renal disease. They concluded that the vascular disease could be primary, but were unable to clearly distinguish between primary renal disease and that secondary to hypertensive vascular damage.

The first appreciation of the likely importance of hypertension in causing secondary renal disease, cerebral hemorrhage, or heart failure is found in a paper published by Frederick Mahomed, Resident Medical Officer of the London Fever Hospital, in 1874. In a series of clinical observations, which were assisted by sphygmographic recordings of systolic blood pressure, Mahomed emphasized that previous to the commencement of any kidney change, or to the appearance of albumen in the urine, the first condition observable is high tension in the arterial system.

Although the term Bright’s disease was retained, this was the first recognition of “essential hypertension,” a term later attributed to Frank, from 1911. Further confirmation of the existence of hypertension in the absence of renal disease was provided in the first Hunterian Society lecture delivered by Sir Clifford Allbutt in 1875 and published in the *Transactions* of the Society. in which he described six cases of hypertension and associated clinical features in some detail and recorded his opinion:

that the rise of pressure in these cases is unaccompanied by any clinical evidence of disease of the kidneys or of any other organ, unless dilatation of the left ventricle of the heart be regarded as a disease.

Thus, by the beginning of the 20th century, the measurement trunk was firmly established and had given origin to the first major branches representing an understanding of the importance of high blood pressure in disease and the existence of primary and renal hypertension. However, the canopy, which now depicts our modern understanding of pathophysiology was to develop rather slowly and unevenly over the next several decades. Indeed, some branches bloomed well ahead of others, providing a patchy appearance for most of the century. The increasingly intensive epidemiological, clinical and basic research of the past three decades or so, coupled with advances in therapy, have provided seemingly mature and balanced foliage which now appears well nourished in most parts.

**BRANCHES BLOOMING: TOWARD A MODERN UNDERSTANDING OF THE PATHOPHYSIOLOGY OF BLOOD PRESSURE**

The notion of circulating pressor substances had its origins in the observations of Bright and Johnson who favored an intoxication theory of vascular disease. Robert Tigerstedt, Professor of Physiology in Stockholm, had hypothesized that the manifestations of uremia were related to some systemic secretion from the kidney. In pursuing this hypothesis, he discovered a rabbit renal cortical extract with prolonged pressor action, as described in a joint publication with P. E. Bergman in 1897 (*Figure 4, next page*). They chose “to call this substance, for the sake of brevity, by the name Renin.” They concluded that:

The experiments carried out by us in this paper have established that a pressure-raising substance is formed in the kidney, which provides its effect essentially on the peripheral vascular nerve centers.
The connection of this sequence of renin production causing increased vascular resistance was also provisionally linked to cardiac hypertrophy. However, the biochemical findings of Tigerstedt and Bergman were not replicated and it was to be more than thirty years before the renin-angiotensin-aldosterone system riddle was progressed further toward a solution. In the interim, the chloride retention theory of Ambard and Beaujard13 gained some support. They proposed that hypertension arose from nonadaptation to saline saturation. They rejected the alternative theses of viscosity or increase in blood mass as factors in hypertension and reasoned that the close relationship of chloride excess and arterial tension was most important. Subsequent controversy over the relative importance of salt in hypertension has continued to the present. Landmark mid-century contributions, which have exemplified this include those related to the Walter Kempner rice-fruit salt-restriction diet (1948)14 and the salt excess hypothesis of Dahl and Lowe (1954).15

In 1934, Harry Goldblatt, a Cleveland physician, reported on his experiments, which successfully resulted in the first animal model of chronic hypertension.16 His hypothesis was that a reduction in the lumen of the renal arteries was the prime cause of essential hypertension. He placed clamps to partially occlude the renal arteries of dogs, observing subsequent rises in blood pressure (Figure 5).16 Goldblatt was unaware of the earlier discovery of renin, but proposed that the decrease in blood supply caused the kidney to release a vasopressor substance. In 1939, Goormaghtigh from Ghent, Belgium, was the first to identify changes in the juxtaglomerular apparatus and relate them to Goldblatt’s hypertension, suggesting an endocrine mechanism.17 Clear connection between the Goldblatt model and renin awaited further delineation of the renin-angiotensin-aldosterone system. The realization that renin acted upon a plasma factor to produce a short-acting pressor substance was pursued by various groups, and two in particular who published their work simultaneously in 1940, Braun-Menendez and colleagues from Buenos Aires,18 stating:

The pressor and vasoconstrictor properties of the venous blood from kidneys in acute ischemia, extracts of which contain a pressor substance (hypertensin) which is also formed in vitro when blood proteins are incubated with renin. Experiments indicate that renin is an enzyme, blood pseudoglobulins the substrate, and hypertensin the reaction product.

Similar findings were reported by Page and Helmer from Indianapolis.19 It was some time later before hypertensin and angiotonin were uniformly designated angiotensin. Intensive work during the 1950s and 60s from numerous groups led to accurate delineation of the renin-angiotensin-aldosterone system.
Notable contributions were those from Leonard Skeggs and colleagues from Western Reserve University, Cleveland who described hypertensin I and hypertensin II and a converting enzyme in horse blood, and the work of Elliott and Peart from London who similarly reported the amino acid sequences of bovine hypertensin. Braun-Menendez and Page also made history by writing a joint paper in *Science* in 1958, in which they conflated the former’s term “angiotonin” with the latter’s “hypertensin,” to coin “angiotensin,” which became a household word in no time.

Definition of the renin-angiotensin-aldosterone system set the stage for a new exploratory phase in therapy with various possible antagonists. In 1971, Ferreira and colleagues from Sao Paulo, Brazil and also New York published a landmark paper in *The Lancet.* It had been recognized that the venom of the South American pit viper *Bothrops jararaca* lowered blood pressure through bradykinin potentiation achieved by inhibiting the kininase enzyme responsible for bradykinin clearance. Further, it was also recognized that this kininase was identical to angiotensin-converting enzyme. Ferreira and colleagues synthesized a bradykinin-potentiating pentapeptide, which blocked in vivo conversion of angiotensin I to the active hypertensive peptide angiotensin II in rats. They suggested this might form a basis to determine the contribution of the renin-angiotensin system to various hypertensive states, commenting that the short duration of effects of this bradykinin-potentiating factor constituted an obvious limit for its therapeutic use. More active peptides were synthesized, but required parenteral administration. In 1977, Miguel Ondetti, Bernard Rubin, and David Cushman from the Squibb Institute for Medical Research in Princeton, New Jersey, described their design of an orally active specific inhibitor of angiotensin-converting enzyme (ACE) in rats. The design had been derived from hypothetical modeling of the active site of angiotensin-converting enzyme based on the known structure of closely related enzymes and specifically that of the zinc-containing metalloprotein pancreatic carboxypeptidase A (Figure 6). Thus, the ACE inhibitors were born. The next two decades saw a veritable explosion of clinical research with these agents, which saw their use extended from hypertension to heart failure treatment, then to myocardial infarction and cardiac remodeling, and finally to vascular protection in high-risk people, including diabetics. There is no better recent example in cardiovascular therapeutics of the effective linkage between basic and clinical research endeavors to improve the understanding of disease mechanisms and clinical outcomes.

Concurrent with elucidation of the renin-angiotensin-aldosterone system, other important and related clinical aspects of hypertension were debated and studied. The importance of sodium retention in renovascular hypertension was described by John Merrill and colleagues from Boston in 1961. Kolff’s group from Cleveland who in 1964 proposed both renal and renovascular components for renal hypertension. In a series of clinical studies of the effect of nephrectomy and transplantation, they concluded that when the renal component was dominant, the management of the hypertension by means of salt and water regulation was difficult. When the renal com-

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Figure 6. Schematic representation of the binding sites of pancreatic carboxypeptidase A and at the hypothetical active site of angiotensin-converting enzyme.

ponent was removed by bilateral nephrectomy, the resultant renopri-
val hypertension responded easily to salt and water restriction. A suc-
cessful kidney homotransplant then converted the renopri-
val hypertension to normotension.

Another debate that continued during this same time period centered
on the role of heredity in essential hypertension. In 1947, Robert Platt
hypothesized that essential hypertension was a hereditary disease
conveyed as a Mendelian dominant with a rate of expression of more
than 90%. Sir George Pickering, Director of the Medical Clinic of
St Mary's Hospital and later regius professor at Oxford, contested
this view, fostering a debate in the journals that ran over many years.
Pickering, whose view eventually prevailed, argued that blood pres-
sure was a continuous variable and not a familial dominant character-
istic as believed by Platt. Pickering concurred with Page's mosaic the-
ory that essential hypertension was multifactorial, resulting "from a
constellation of facets, one or even none being more or less dom-
nant."

Fifty years later it is notable that clinical practice often still reflects
the erroneous view that essential hypertension is a discrete disease
entity. The integration of blood pressure with other risk factors into an
assessment of absolute cardiovascular risk as a starting point for
discussion of management is still not commonplace, although uni-
formly recommended in modern evidence-based guidelines.

Pickering wrote discursively and provocatively about the nature of
hypertension. A quotation from his chapter on the nature of essential
hypertension is a particularly apt conclusion to this historical account:

A concept is an instrument for thought and thought begets action.
Concepts and practice are not separate and distinct, they are merely
different phases of a man's behavior. It is in the hope that the new con-
cept may prove a better instrument of thought than the old that I end.

CONCLUSION

This historical account brings us to the threshold of the modern era of
molecular and cellular biology in the latter part of the 20th century. The
 canopy of the tree of knowledge for hypertension continues to thicken
in many parts as research in cardiovascular molecular medicine flour-
ishes. New and broader insights into hypertension causation in mod-
ern societies alter the hue of some parts, pharmacogenomics and im-
proved drug treatments suggest that the mature specimen will be
truly worthy of admiration.

We have certainly benefited greatly from the efforts of those mentioned
in this review and a host of others unmentioned. History highlights the
importance of continuing to foster a spirit of open enquiry and cele-
brating discovery.

REFERENCES

1. Hales S. Statistical Essays Containing Haemo-
2. Lyons AS, Petrucelli RJ. Medicine, an Illustrated History. New
4. Hill L, Barnard H. A simple and accurate form of sphygrometer
or arterial pressure gauge contrived for clinical use. BMJ. 1897:904.
5. Korotkoff NS. Experiments for determining the strength of
arterial collaterals. Saint-Petersburg, Russia: Imperial Military
6. Korotkoff NS. On methods of studying blood pressure
7. Bright R. Tabular view of the morbid appearances in
one hundred cases connected with albu-
8. Johnson G. On Diseases of the Kidney, Their
Pathology, Diagnosis and Treatment. London, UK: Parker & Son; 1852.
9. Gull WW, Sutton HG. On the pathology of the morbid state com-
monly called chronic Bright's disease with
10. Mahomed FA. The etiology of Bright's disease and the
11. Allbutt C. Seneile plethora or high arterial pressure in elderly persons.
Skand Arch Physiol. 1890:7:8:223-271.
Arch Gen Med. 1904(8H 1):520-533.
14. Kempner W.
Treatment of hypertensive vascular disease with rice diet.

15. Dahl LK, Love RA.
Evidence for a relationship between sodium chloride and human essential hypertension.
*Arch Int Med.* 1954;94:525-531.

The production of persistent elevation of systolic blood pressure by means of renal ischemia.

17. Goormaghtigh N.
Existence of an endocrine gland in the media of the renal arterioles.

18. Braun-Menendez E, Fasciolo JC, Leloir LF, Munoz JM.
The substance causing renal hypertension.

19. Page IH, Helmer OM.
A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator.

20. Skeggs LT, Marsh WH, Kahn JR, Shumway NP.
The existence of two forms of hypertensin.

21. Elliott DF, Peart WS.
Amino-acid sequence in a hypertensin.
*Nature.* 1956;177:527-528.

22. Braun-Menendez E, Page IH.
Suggested revision of nomenclature: angiotensin.

23. Kreiger EM, Salgado HC, Assan CJ, Greene LLJ, Ferreira SH.
Potential screening test for detection of overactivity of renin-angiotensin system.

24. Ondetti MA, Rubin B, Cushman DW.
Design of specific inhibitors of angiotensin-converting-enzyme: new class of orally active anti-hypertensive agents.

25. Merrill JP, Giordano C, Heetderks DR.
The role of the kidney in human hypertension.
1. Failure of hypertension to develop in the renoprival subject.

Effect of bilateral nephrectomy and kidney transplantation on hypertension in man.

27. Platt R.
Heredity in hypertension.

28. Pickering G.
The nature of essential hypertension.
Ischemic Heart Disease: from a sudden death in Chicago to fibrinolysis and angioplasty

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Angina pectoris was named and accurately described by Heberden in 1772, but coronary thrombosis was only formally recognized as the cause of acute myocardial infarction by Herrick at the beginning of the 20th century. Diagnosis of acute myocardial infarction was facilitated by the ECG findings noted by Pardee, Parkinson, and Bedford. No effective treatment (other than bed rest) was available until the development of defibrillation and closed chest cardiac resuscitation by Zoll and Kouwenhoven in the 1950s. Since then, mortality has been greatly reduced by the use of antiplatelet and antithrombotic drug therapies as well as fibrinolysis and angioplasty. Prevention through reduction in risk factors and secondary prevention with drugs has proven to be extremely effective and will doubtless further contribute to reducing mortality in coming decades.

Keywords: coronary thrombosis; ischemic heart disease; myocardial infarction; sudden death; electrocardiography; coronary care unit

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Myocardial infarction is one of the most familiar ailments known to today’s increasingly medically mature “lay” population the world over. Knowledge of this syndrome has undergone one of the tree symbolizing James Herrick’s recognition of the underlying disease in the coronary arteries, from which grow three trunks of pathophysiology, diagnosis, and the thickest of them all—and quite fortunately might one add—management.

THE SEEDS:
WILLIAM HEBERDEN

The seeds of the tree were sown by a master clinician, William Heberden (Figure 1), in 1772. In a presentation to the Royal College of Physicians in London, Heberden (1710-1801) described “a disorder of the breast,” which he named angina (from the Greek, meaning strangling or suffocation), with an accuracy never bettered:

Those who are afflicted with it are seized while they are walking, more especially if it be up hill, 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 this uneasiness vanishes...

The termination of the angina pectoris is remarkable. For, if no accidents intervene, but the disease go on to its height, the patients all suddenly fall down, and perish almost immediately.1

John Hunter (1728-1793), the greatest surgeon of his day, performing, at Heberden’s request, autopsies...
of patients having so perished, “could discover no fault in the heart, in the valves, in the systemic arteries…” Heberden, having offered an unmatchable delineation of a symptom, and without a clue as to the pathological substrate of the disorder, classified it as “a spasmodic, not inflammatory complaint,” presumably similar to a condition such as epilepsy. He offered even less guidance as to its treatment, freely confessing “I have little or nothing to advance.”

However, postmortems soon revealed telltale abnormalities. The eminent Quaker physician John Fothergill (1712-1780, Figure 2) called upon surgeons to conduct a postmortem in one of his patients, a 58-year-old man with “a spasm in the breast… chiefly when he walked up hill,” who had died suddenly. They found “near the apex a small white spot, as big as a sixpence, resembling a cicatrix.”2 A second patient, with a similar history, was autopsied, this time again by John Hunter, who reported:

Many parts of the left ventricle… were become almost white and hard, having just the appearance of a beginning ossification… The two coronary arteries, from their origins to many of their ramifications upon the heart, were become one piece of bone.

Fothergill commented, anticipating what today is described in terms of mismatch of oxygen delivery and demand:

Under such circumstances, it is impossible [for the heart] to bear with impunity the effects of sudden and violent agitation, whether they arise from gusts of passion, or suddenly accelerated muscular motion.5

Within his own lifetime, Heberden’s new entity had acquired an accurate pathological explanation, ascribing angina to a disease of the coronary arteries. Yet, although prescient, Fothergill’s findings failed to convince all, and progress stalled. Some 75 years after his death, William Stokes (1804-1878), the Dublin physician, whose name is commemorated in Stokes Adams attacks and Cheynes-Stokes respiration, commented:

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.4

**THE ROOTS**

New impetus to the knowledge of myocardial infarction required transplantation of our tree to Germanic soil. In Vienna, Karl Rokitansky (1804-1878), a physician turned pathologist, described “fatty degeneration” of cardiac muscle as “very frequently associated with ossification of the coronary arteries.”5 In Leipzig, Carl Weigert (1845-1904) published a landmark study of coronary thrombosis and embolism generally regarded as the first manual of myocardial infarction histology, and Julius Cohnheim (1839-1884, Figure 3), in 1882, incorporated its conclusions into his own pathology textbook, assigning the majority of “so-called cardiac infarcts” or fatty degeneration to advanced coronary artery sclerosis and superimposed thrombosis.7 However, Cohnheim remained skeptical as to whether the connection between coronary thrombosis and angina was causal or coincidental. What was missing was incontrovertible evidence, from the cadaver and/or living patient, of a kind inconceivable in his day, and that was only ultimately obtained a century later by coronary angiography. Once again, the growth of the ischemic heart disease tree of knowledge slowed down, until it found fertile ground in the USA.

**THE BASE OF THE TREE: JAMES HERRICK, THE PIONEER**

James Herrick of Chicago (1861-1954) is widely acknowledged as the first to describe the causes of myocardial infarction as we know it today (Figure 4, next page). It was he, more than anyone else, who made clinicians aware that patients suffering a “coronary thrombosis” had a characteristic clinical presentation and, sometimes, survived. Curiously, when he presented his initial 1912 paper on the subject, entitled Clini-
Electrocardiography was for Herrick’s coronary thrombosis what Heberden’s angina had never had: coronary thrombosis could now be diagnosed during life.

While it is Herrick who deserves the credit for drawing the attention of the Western world to this common condition, there were many others, as he acknowledged, who had previously reported survival from coronary occlusion. Perhaps foremost among these were Obrastzow and Straschesko of Kiev who described the diagnosis of patients with coronary artery thrombosis at the first Russian Congress of Internal Medicine in 1909. Even after the publication of Herrick’s seminal paper, it took a considerable time before clinicians accepted the diagnosis. Herrick describes how an unnamed American physician said that to make a clinical diagnosis of coronary thrombosis “was ridiculous because it was impossible.”

In the United Kingdom, it was a paper by McNee of Glasgow in 1925, describing his experience in the United States, that really put coronary thrombosis on the British agenda. Even then, few cases were recognized until Parkinson and Bedford of London described the clinical picture of the condition together with the sequential changes in the electrocardiogram in 1928. The diagnosis of “coronary thrombosis” was made with increasing frequency in the 1930s. At that time, there was speculation as to whether the rise in incidence was real, due to increasing recognition, or to the aging of the population. By the 1970s, when the “epidemic” of this syndrome seems to have peaked, it became clear that there had been a real increase in the frequency of the disorder, but the reason for this remains a matter of conjecture. An important observation was that of Morris. Based on the meticulous postmortem data from the London Hospital, he found that the numbers of cases of coronary heart disease increased sevenfold between 1907-1914 and 1944-1949, yet there was an apparent reduction in the extent of coronary atheroma. It was thought that this discrepancy might be accounted for by an increase in thrombosis as an etiological factor.

**THE THREE TRUNKS**

After this brief overview, it is now time to look at how, from the study base of the ischemic heart disease tree, multiple trunks grew, each of which developed a profusion of branches and dense foliage. These are the trunks of pathophysiology, diagnosis, and—undoubtedly the most vigorous trunk of the three—management.

**The trunk of pathophysiology**

It was not long after Heberden had described and named angina pectoris in 1772 that the pathology of coronary artery disease was first elucidated by Parry, Jenner, and others. As mentioned above, a century was to pass before the clinical syndrome of myocardial infarction was recognized. In the intervening period, there were many reports of abnormalities in the coronary arteries and in the myocardium, but they were not linked to infarction. Furthermore, it was believed that the coronary arteries were end arteries and, therefore, that their obstruction would be fatal. The evolving concepts of atherosclerosis are described by Anton Becker elsewhere in this issue of *Dialogues.* The role of thrombosis in patients dying acutely of coronary disease was widely recognized, both Obrastzow and Herrick using this term in their description of the clinical syndrome. Physicians in the middle of the twentieth century, such as Levine, used to refer to their patients as suffering a coronary thrombosis rather than a myocardial infarction. Yet Levine questioned the role of thrombosis in causing infarction as, in the succeeding decades, did a number of eminent pathologists including Willam Roberts, who wrote in 1972:

The infrequency of thrombosis in patients dying suddenly of cardiac disease and in those with transmural necrosis who never had shock or congestive heart failure suggests that the thrombi may be consequences rather than causes of acute myocardial infarction.
This observation, which we now recognize as having resulted from post-mortem lysis of intracoronary clots, cast doubt on the potential role of thrombolysis. Some elegant studies eventually put an end to this heresy. Fulton of Glasgow\(^\text{12}\) gave radiolabeled fibrinogen to patients coming into hospital with chest pain. In those who died, he used autoradiography to provide evidence as to whether thrombosis had occurred prior to or after the fibrinogen injection. Thrombosis was found in all cases, and most cases demonstrated thrombosis that was radionegative, i.e. it had preceded the injection. Further evidence of its essential role was provided by the in vivo angiographic studies of DeWood of Spokane,\(^\text{13}\) which demonstrated thrombus when the patient was first examined, but occluded arteries often opened spontaneously in the next few hours.

Constantinides of Vancouver\(^\text{14}\) is credited with being the first to report, in 1966, that it is usual to find fissuring of an atheromatous plaque underlying the thrombus, although “rupture of an atheromatous abscess” had been described in the 19th century. A number of pathologists, notably Davies\(^\text{15}\) of London, Falk of Copenhagen, and Libby of Boston, have demonstrated that, prior to rupture, the offending plaque is the victim of a “self-destruct” inflammatory process, involving high concentrations of macrophages and metalloproteinases (Figure 5).

In the 1970s, Reimer, Jennings and coworkers\(^\text{16}\) reported the spread of a “wave” of necrosis from the subendoocardial to the subepicardial tissue over a period of some 4 to 6 hours, which occurs after a coronary vessel is occluded in animal models (Figure 6). Patchy areas might survive, depending upon collateral supply. There was evidence that reperfusion might save some tissue if instituted early enough. Initially, this was thought to imply that fibrinolysis was unlikely to be successful unless initiated very early, but human observations have shown that, although the earlier reperfusion is started the better, some benefit is achieved even as late as 6 to 12 hours.

### The trunk of diagnosis

Two main types of test have evolved to validate the diagnosis of myocardial infarction—the electrocardiogram and measurements of cardiac proteins released in the blood.

Herrick, in his publication of 1918, commented on alterations in the contour of the T wave, his colleague Smith having observed similar changes in dogs that had undergone coronary ligation. A more detailed description of the changes was provided by Pardee of New York in 1920. He referred to the fact that the T wave does not start from the zero level... and... quickly turns away.

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**Figure 5.** Occluding coronary thrombosis due to plaque disruption. There is a lobulated mass of thrombus, one part in the plaque, another occluding the lumen. The two lobes join through the disrupted plaque cap.


**Figure 6.** Progression of cell death versus time after left circumflex coronary artery occlusion. Necrosis occurs first in the subendothelial myocardium. With longer occlusions, a wavefront of cell death moves from the subendocardial zone across the wall to involve progressively more of the transmural thickness of the ischemic zone. Thus, there is typically a large zone of subepicardial myocardium in the ischemic bed that is salvageable by early reperfusion, but that dies in the absence of such an intervention. In contrast, the lateral margins of the infarct are established as early as 40 minutes after occlusion and are sharply defined by the anatomical boundaries of the ischemic bed.

*Reproduced from reference 16: Reimer KA, Jennings RB. The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest. 1979;40:533-544. Copyright © 1979, Nature Publishing Group.*
in a sharp curve.” In 1928, Parkinson and Bedford of London integrated clinical observations and laboratory findings and described the characteristic evolution of the ECG changes. Although Woberth and Wood had introduced precordial leads in 1932, these were not widely used by physicians until after World War II. Unipolar chest leads, pioneered by Wilson, became standard only in the 1950s.

The accurate diagnosis of myocardial infarction was greatly aided by the development of blood tests for cardiac markers. In 1954, LaDue, Wroblewski, and Karmen, in New York, introduced cardiac enzyme estimations. Cardiac muscle is rich in glutamic oxaloacetic transaminase, and they found that the serum level of this enzyme appeared in the blood of dogs after experimental coronary artery ligation and in humans after infarction. Other enzymes, such as creatine kinase and specific isomers, have subsequently been used in the diagnosis of myocardial infarction. The development of troponin as a marker of cardiac necrosis by Hamm of Bad Nauheim and Katus of Heidelberg has substantially enhanced the sensitivity and specificity of cardiac markers.

The trunk of management

General

From the time that myocardial infarction became accepted as a clinical condition, the keystone of management was rest. Because pathological studies had shown that it can take up to 6 to 8 weeks for firm scarring of the lesion to occur, it was considered that to minimize the risk of ventricular rupture, this was the appropriate duration for strict bed rest. Some authorities recommended absolute rest for most of this period, forbidding these patients even to brush their own teeth.


Rest in bed should continue for from 6 to 8 weeks to ensure firm cicatrization of the ventricular wall; during the whole of this period the patient is to be guided by day and night nursing and helped in every way to avoid voluntary movement or effort. Patients have lost their lives and especially those who have early recovered from their symptoms by neglect of these precautions.

Even as late as 1959, Wood recommended total bed rest for 3 to 6 weeks. Levine and Lown had, in fact, put forward the concept of the armchair treatment in 1952, but this more liberal approach took a long time to gain acceptance. Over the succeeding decades, however, patients were confined to bed for shorter and shorter periods, so that by the 1990s, patients were allowed up within 24 to 48 hours if their progress was uncomplicated.

Until the end of the 1950s, aside from the use of β-adrenergic agonists to treat cardiogenic shock, there was little effective treatment for patients with a myocardial infarction. Trials in both the United States and the United Kingdom suggested that anticoagulant treatment reduced mortality substantially and patients were admitted to hospital for this to be initiated. With the benefit of hindsight, it can be appreciated that the trials were defective and that the benefit, if any, was mainly achieved by preventing the pulmonary embolism that was a common complication in patients treated by complete immobilization.

Management of cardiac arrest and Coronary Care Units (CCUs)

It was known that heart attacks often caused sudden death due to ventricular fibrillation, but this was regarded as irreversible. However, in 1955, when Claude Beck, a surgeon in Cleveland, corrected this arrhythmia in a 65-year-old physician, using an open thoracotomy, the possibility of successful resuscitation became a reality. With remarkable foresight, he wrote,

This one experience indicated that resuscitation from a fatal heart attack is not impossible and might be applied to those who die in the hospital and perhaps those who die outside the hospital.

He coined the phrase “hearts too good to die,” thus challenging the prevailing pessimism about the potential of resuscitation. In 1956, Zoll in Boston introduced external electrical defibrillation and, shortly afterwards, Kouwenhoven, Jude, and Knickerbocker, of Baltimore, showed the effectiveness of combining mouth-to-mouth breathing, sternal compression, and closed-chest electrical defibrillation in restoring normal cardiac function in the victims of ventricular fibrillation. (It is, perhaps, worth mentioning that sternal compression, artificial ventilation, and the passing of electrical shocks through the chest were all described in 1775 in the Proceedings of the Royal Humane Society of London, but this information may not have reached America at this time because other issues might have seemed more pressing!)

Experiences in the Royal Infirmary, Edinburgh, in 1960, showed that while the potential for cardiac resuscitation in myocardial infarction was great, this could not be achieved with the current organization of hospitals. Patients with myocardial infarction were scattered throughout the medical wards and were being cared for by staff without the necessary expertise or equipment. This led Julian22 to write, in 1961:
Many cases of cardiac arrest associated with acute myocardial ischaemia could be treated successfully if all medical, nursing and auxiliary staff were trained in closed-chest cardiac massage and if the cardiac rhythm were monitored by an electrocardiogram linked to an alarm system. The provision of the appropriate apparatus would not be prohibitively expensive if these patients were admitted to special intensive-care units. Such units should be staffed by suitably experienced people throughout the 24 hours.

The first coronary care units (CCUs), as they came to be known, were created in Sydney, Kansas City, Philadelphia, and Toronto in 1962, and new units sprang up rapidly in the succeeding years, particularly in the United States. Although it was soon shown that cardiac resuscitation was saving many lives, it was obvious that this arrhythmia should be prevented, if possible. A strong correlation was reported between what were termed “warning arrhythmias” and the subsequent development of ventricular fibrillation. This led Lown to claim that if warning ventricular arrhythmias were treated promptly with lidocaine, primary ventricular fibrillation did not occur. As a consequence, nurses were taught that they must be able to identify and treat the relevant arrhythmias. Immense resources were devoted to this end, but it eventually became apparent that the “warning arrhythmias” were not as predictive as had been believed and that routine use of lidocaine might cause more deaths from asystole than they saved from ventricular fibrillation.

The introduction of CCUs was not without controversy; the eminent epidemiologists Archie Cochrane (commemorated by the Cochrane Reviews) and Geoffrey Rose being particularly skeptical. They were impressed by two randomized clinical trials, based in Bristol and Nottingham, which claimed to show that CCUs achieved no reduction in mortality. However, in retrospect, it is apparent that these trials were too small and deeply flawed. Indeed, the large trials that have established the effectiveness of many treatments in the management of myocardial infarction would not have been practicable without the environment provided by the CCUs.

Although the CCUs were effective in reducing the mortality of those patients who reached hospital, epidemiological studies showed that a high proportion of patients died of myocardial infarction in the community. Pantridge of Belfast, recognizing this problem, instituted a doctor-manned Mobile CCU and reported encouraging findings in 1966. This was taken up only slowly as few centers considered that this was an economic use of highly qualified medical personnel. When it was found that paramedics could be as effective as doctors in this context, prehospital coronary care became widespread.

Cardiogenic shock, acute heart failure, and infarct size limitation

By the end of the 1960s, it became clear that, with the successful prevention and treatment of ventricular fibrillation, malfunction of the heart as a pump, leading to cardiogenic shock and cardiac failure, was now the main mechanism of death in myocardial infarction. Hypotension is a common feature of myocardial infarction; it was traditionally treated with vasoconstrictors or inotropic drugs in the belief that restoration of blood pressure was the priority, in spite of the fact that this might result in a reduction in cardiac output. In 1959, Paul Wood, in his classic textbook, described the reports of the benefits of norepinephrine, in one case reducing the fatality of shock from 80% to 48%. More carefully conducted experiments showed that this and similar drugs were actually harmful. Indeed, although it is still common practice to use drugs such as dopamine, their benefit remains unproven. While most cases of severe and persistent hypotension are a result of extensive myocardial damage, a substantial proportion in the early hours are associated with bradycardia (sometimes with heart block) and are a consequence of the induction of the Bezold-Jarisch reflex in some patients with inferior or posterior infarction. At one time, it was fashionable to treat such cases with artificial pacing; in one New York hospital in the 1960s, some 30% of patients had pacing electrodes inserted. However, as Pantridge showed in his experience with a mobile CCU, most cases will respond well to the intravenous injection of atropine if given early enough.

The introduction of invasive hemodynamic monitoring with the Swan-Ganz catheter greatly enhanced the understanding and facilitated the treatment of pump failure. In spite of this, the results of treating shock and heart failure remained poor. It was observed that these conditions were closely related to the extent of muscle necrosis and it was concluded that their prevention could be achieved only if myocardial damage could be limited. The National Institute of Health–led Myocardial Infarction Research Units in the United States provided evidence from animal experiments that a variety of drug therapies could reduce the extent of damage. Among these, there was particular interest in β-blockers, calcium channel blockers, and hyaluronidase. Experiments in humans failed to replicate the promising laboratory experience. β-Blockers were, indeed, found to reduce mortality in the first Inter-

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national Study of Infarct Survival (ISIS-1), but the beneficial effect was probably due mainly to the prevention of cardiac rupture rather than to infarct-size limitation.

The idea of infarct size limitation was critically important, but it had to await successful reperfusion of the occluded artery before the concept was realized in clinical practice.

**Fibrinolysis**

Sherry and his colleagues in St Louis had pioneered the use of intravenous streptokinase in 1958, but this excited little interest. In 1960, Boucek and Murphy in Miami reported favorable experiences when they undertook what they described as “segmental perfusion of the coronary arteries with fibrinolysin following a myocardial infarction,” in which they triggered release of fibrinolysin into the coronary sinus relevant to the infarct-related artery. There was little interest in fibrinolytic therapy in the English-speaking world, but it became widely used in the Soviet Union and Germany. Indeed, there was considerable opposition to this treatment for a variety of reasons, particularly in the United States. For one thing, the role of thrombosis was seriously questioned by the highly regarded pathologists Roberts and Spain. For another, there were doubts about the safety of thrombolysis both because of the risks of bleeding and also because reperfusion had been shown to cause myocardial damage and arrhythmias in animal experiments. At least 22 clinical trials of fibrinolytic therapy were undertaken in the 1970s and 1980s, but the results were not convincing. The scenario changed with the publication of the Gruppo Italiano per lo Studio della Soppravvivenza nell’Infarto miocardico (GISSI) and ISIS-2 trials in 1988-1989. Furthermore, the latter trial showed that aspirin also reduced mortality whether it was combined with streptokinase or not (Figure 7). However, it was evident that this form of therapy was not beneficial for all infarction patients. The trials found no evidence of benefit in patients who did not exhibit Q waves (what had previously been termed transmural infarction). Subsequently, myocardial infarction patients were categorized as having ST-segment elevation or non-ST-segment elevation infarction, the former being recommended for fibrinolytic treatment and the latter not.

Following these trials, fibrinolytic therapy, together with aspirin, became widespread and was incorporated into the guidelines for the management of myocardial infarction produced by the American College of Cardiology and the European Society of Cardiology.

**Percutaneous coronary intervention**

Although Grünzig of Zürich had pioneered angioplasty in 1977, he and others were, for many years, hesitant about utilizing this technique in patients with acute myocardial infarction. More recently, a number of well-conducted clinical trials have demonstrated that percutaneous clinical interventions are at least as effective, if not more so, than fibrinolytic treatment in preventing death and morbidity after myocardial infarction, and have fewer major side effects, notably stroke.

**Other advances**

A number of drug therapies have been tried out in the acute phase of myocardial infarction. Although some benefit has been claimed for the calcium channel blockers verapamil and diltiazem, other drugs in this class have proved disappoint-

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**Figure 7.** Second International Study of Infarct Survival (ISIS-2) trial of streptokinase and aspirin. Cumulative vascular mortality on days 0-35 of patients allocated to active streptokinase only; active aspirin only; both active treatments; and neither.

may be partly spurious as modern methods of diagnosis detect more small, low-risk, infarcts. In view of the relatively low mortality, at least in younger patients, it is doubtful if much further improvement in the management of patients who are admitted to hospital with acute myocardial infarction can be anticipated.

The large number of deaths from myocardial infarction outside hospital remains challenging, but perhaps not adequately appreciated. Data from three British cities in the 1988 UK Heart Attack Study showed that of 3523 heart attacks, 1172 (33%) of patients died outside hospital and an additional 12% in hospital.26 Although patients with infarction are being treated earlier than previously, one can only expect a major impact on this problem by prevention, which might be achieved by improved diet, less smoking, and the better treatment of hypertension, diabetes and the other precursors of coronary heart disease.

REFERENCES


16. Reimer KA, Jennings RB. The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest. 1979;40:633-644.


Atherosclerosis has plagued human-kind since ancient times, and its understanding has much evolved over the centuries. For Rokitansky, a proponent of the ancient humoral theory, the thickening of the arterial wall was due to deposits derived from the blood. For Virchow, the father of cellular pathology, thickening resulted from a cellular reaction. For both, fat deposition was the result of secondary degeneration. Anitschkow showed that atherosclerotic lesions resulted from the combined effect of hypercholesterolemia (toxic injury) and hypertension (mechanical injury). Other landmarks include the discovery of the scavenger receptors and of the cellular cholesterol cycle, and the identification of platelet-derived growth factor, which gave rise to the response-to-injury hypothesis. With some modifications, this concept still prevails today.

**Atherosclerosis: from Egyptian mummies to immune-mediated intraplaque inflammation**

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Atherosclerosis has its roots many thousand years ago: the earliest documented evidence comes from Egyptian mummies. The term atherosclerosis, however, was first coined by Lobstein in the 1820s, a professor of pathological anatomy at the University of Strasbourg and—to the best of my knowledge—the first-ever appointed professor of pathological anatomy. In his *Treatise of Anatomical Pathology* (Paris, 1829), he not only introduced the name, but also justified it by describing the disease as *“composé d’artère et de sclérose, d’épaississement avec induration”* (freely translated as: composed of rigid arteries with wall thickening and hardening). If Lobstein failed to attribute an inflammatory cause to the disease, this was because he lacked the technology to detect inflammation in the postmortem studies that he performed. In his opinion, the disease started as a nutritional disorder of the wall of the artery, followed by abnormal tissue proliferation of the inner layers. The cause of all these processes, however, remained obscure. Nevertheless, Lobstein’s point of view is of major interest because it departed from the classic humoral theory that had held sway over medical thinking for centuries as an explanation for disease processes. His views clashed with those of the celebrated Austrian pathologist...
and one of the founders of modern pathological anatomy, Baron Karl von Rokitansky (1804-1878), who invoked the old humoral theory to explain the development of atherosclerosis, (Figure 1). An exponent of the Viennese School of Medicine and the author of the great Manual of Pathological Anatomy (1842-1846), Rokitansky stated, in his classic work on arterial diseases, published in 1853, that arteriosclerosis consisted in a thickening of the vascular wall that he attributed to the action of the circulating blood mass:

...einer exzedierenden Anbildung und Auflagerung von innerer Gefäßhaut aus der Blutmasse und stellt gleichsam eine Hypertrophie der inneren Gefäßhaut dar [an excess buildup and deposition of inner vessel wall originating in the blood, representing a hypertrophy of the inner vessel wall].

THE EMERGING TRUNK: SEMINAL DISCOVERIES IN ATHEROSCLEROSIS

This concept was seriously challenged by Rudolf Virchow, the father of cellular pathology, (Figure 2), who in 1858 published his landmark work, entitled Cellular Pathology and its Foundation on Physiological and Pathological Histology. In his opinion, cell damage was the key factor involved in basically all forms of diseases. As for atherosclerosis, he considered the thickened inner wall of the arteries as resulting from chronic inflammation, analogous to the thickened endocardium in chronic endocarditis. He thus termed the process leading to atherosclerosis or endarteritis chronica deformans. It is important to realize that in his view inflammation was basically a nutritional disorder. Endarteritis started as a thickening of the inner arterial wall, in which connective tissue cells also participated. These cells accumulated more nutrients than other components, resulting in proliferation, on the one hand, and fatty transformation, on the other. In addition, according to Virchow, a second mode of fatty change existed, not associated with inflammation, which he considered “a pure passive process of degeneration.” As a consequence, Virchow made a distinction between superficially located fatty deposits, including the “fatty wear and tear”—in other words, the lipid-rich ruptured plaque in our current terminology—and the more deeply situated atheroma related to the endarteritis. The former condition, in his opinion, should not be classified as atherosclerosis. Virchow’s concepts on atherosclerosis remained popular for a considerable length of time. In subsequent years the concept that “inflammation” was the key factor in the genesis of atherosclerosis became widely accepted, even though the original insights gradually shifted, in particular because of the work of Cohnheim (1877). For Cohnheim, the development of connective tissue in the intima was interpreted as the expression of proliferative inflammation with little exudation. Questions were raised as to whether or not white blood cells could be involved in the proliferative process and whether the inflammation could originate in the adventitia and from there spread along the vasa vasorum into the intima (an opinion upheld by Koester, around 1875-1876). Moreover, Cohnheim stated that there could be no inflammation without vessels, and this created a problem in explaining the origin of atherosclerosis in small arteries without vasa vasorum.

These were fascinating speculations for the time, and certainly so when put in perspective with our present understanding. The most important development at the time, however, was that, with the shift in the concept of inflammation, the opinion about the accumulation of fat also changed. The latter came to be considered as secondary fatty regression of the poorly vascularized connective tissue layers in the intima.

The main focus of interest in the genesis of atherosclerosis, therefore, concentrated on proliferative inflammation with connective tissue thickening of the intima as a result.

Another development of interest during that period was the observation by Langhans in 1866 that dilated and tortuous arteries showed diffuse thickening of the intima, like that seen in atherosclerotic arteries with localized intimal thickening, which he called “atherosclerosis diffusa et nodosa.”

Thoma, in the late 19th century—early 20th century, while agreeing that the main abnormality in atherosclerosis was intimal thickening, had noted in neonates that the disease occurred preferentially between the site of attachment of the ligament of Botal and the origin of the umbilical arteries—an observation shown by subsequent investigators to be only partially true. However,
it led Thoma to formulate a new pathogenetic concept. In his view, the intimal thickening compensated for a mismatch between postnatal vessel size and the amount of blood transported. For him, the trigger for intimal thickening was the low velocity of the blood. By introducing this concept, Thoma was among the first to ascribe functional significance to mechanical factors in the genesis of arteriosclerosis. It is fascinating also to realize that already at that time he convincingly showed that luminal diameter remained unchanged in spite of the presence of local intimal thickening, unless the disease was far advanced: a concept attributed to Glasgow and colleagues, following their publication in 1987, and now widely known as positive remodeling.

Amidst these constantly evolving changes in concepts and insights, Marchand, in 1904, by coining the term atherosclerosis, introduced a change in semantics that signaled a major conceptual shift. This was because he considered the soft atheroma rather than the hardened artery as the most characteristic pathologic feature of the disease. Although it was widely recognized that Marchand was right, the fact that the origin of the fatty debris remained controversial urged most authorities to continue using the term arteriosclerosis until better understanding had been achieved. As a consequence, it took a long time before the term atherosclerosis eventually became accepted and even today there remains some debate as to the precise definition of either term. Personally, I have used the term arteriosclerosis as a generic term referring to any diseased artery characterized by sclerosis, ie, hardening of its wall, such as Mönckeberg sclerosis. The term atherosclerosis I have used only for those disease processes in which intimal lesions resulted from a chronic proliferative inflammatory process associated with intracellular and extracellular lipid accumulation. In my experience, this approach works well in daily practice, although I accept that every now and then it may be impossible to be certain. But then, the precise naming of things often tends to become a bit arcane!

Jores, professor of pathological anatomy in Kiel in the early 1900s, should be credited for his contribution to the understanding of the disease. Although Jores still believed that the lipids that had accumulated in atherosclerotic lesions resulted from a degenerative process, his attribution of a pathogenetic role to a physiologic adaptive process was an important breakthrough. Unaware of Jores’ statements at the time, I wrote in 1985 that the musculoelastic layer, because of its smooth muscle cell content, provided a fertile soil for the development of an atherosclerotic lesion, and I still consider this an important prerequisite in the genesis of the disease.

Like Marchand and Thoma, Jores also concluded that intimal thickening did not fulfill the criteria for an inflammatory reaction. They considered the genesis of the disease as a nutritional disorder of the artery wall, in the sense that the densely packed architecture of the elastic-hyperplastic layer interfered with the adequate supply of nutrients, subsequently resulting in intimal proliferation. Adopting this view, Jores also challenged the distinction be-

![Figure 3. Drawing of a localized intimal thickening with “atheromatous,” which we now would call an atherosclerotic plaque, in a coronary artery. (a) Media. (b) Hyperplastic-elastic layer (musculoelastic layer). (c) Collagen-rich part of the plaque. The light areas are sites of lipid degeneration. Reproduced from: Jores L. Arterien. In: Henke und Lubarsch. Handbuch der speziellen Pathologischen Anatomie und Histologie. Zweiter Band, Herz und Gefässe. Berlin, Germany: Verlag von Julius Springer; 1924. Copyright © 1924, Springer-Verlag.](image-url)
tween superficial (primary degeneration) and deep lipid deposition (related to endarteritis chronica), as introduced by Virchow. It is from this time that Virchow’s concept of arteriosclerosis as an inflammatory disease was gradually challenged, and eventually abandoned.

Aschoff, a contemporary of Jores, and his pupils, largely endorsed the opinions of Jores. They looked upon arteriosclerosis as intimal proliferation starting at birth and progressing with age. They described three periods in this process: a first period immediately after birth, characterized by the development of elastic fibers in the intima; a second period during which the histological picture did not change much and very little actually happened; and a third period characterized by the development of a connective tissue layer in the intima. This stage could be complicated by fatty degeneration, leading to a condition that Aschoff called senile sclerosis. According to Aschoff, the cause of this disease, including the presenile and juvenile forms, was “wear and tear” of the elastic inner layers of the artery. Again, this represented a mechanical approach to the pathogenesis of arteriosclerosis. A negative consequence of Aschoff’s work was that for a very long time the pathogenesis of arteriosclerosis was considered by many to be an inevitable result of aging.

**EARLY ANIMAL EXPERIMENTS: THE ATHEROSCLEROSIS TREE’S BRANCHES**

In the early 20th century, several experiments were performed in an attempt to shed light on the development of arteriosclerosis. Of these experiments, those performed by Russian investigators (Ignatowski, Chalarow, and Anitschkow) were the most promising. In a series of publications (1913, 1914, 1922), Anitschkow showed that feeding cholesterol to rabbits (later also guinea pigs) resulted in an accumulation of fat in the intima of the aorta, very much alike that seen in humans.

However, the problem with the initial experiments was that the amount of cholesterol necessary to induce these changes was exceedingly high and could in no way be compared with the situation in humans. In subsequent experiments, Anitschkow was able to show that by raising the blood pressure through ligation of the aorta, the same result could be obtained with much lower doses. He observed a swelling of the subendothelial layer and the appearance of lipid-laden (xanthoma) cells. He concluded that cholesterol from the blood plasma had infiltrated into the vessel wall and proposed that arteriosclerosis resulted from the combined effect of a toxic insult (hypercholesterolemia causing vessel wall damage) and a mechanical insult (hypertension).

Although Anitschkow’s hypotheses met with much skepticism—which remains to this very day—his experimental observations nevertheless had a major impact upon our appraisal of the significance of the lipid deposits, which are widely considered as the histological hallmark of arteriosclerosis, and at the same time as an epiphenomenon (secondary degeneration) of the disease process. I believe it is fair to state that the confrontation between the experimental animal studies carried out by Anitschkow and the findings from detailed morphologic studies in humans was instrumental in promoting further studies into the genesis of arteriosclerosis, in particular the role of cholesterol, and that this was much aided by the explosive development of novel laboratory techniques arising hand in hand with the birth of new disciplines (immunology, molecular biology, genetics, etc).

**HOW DID IT ALL CONTINUE? THE TREE BEARS ITS FRUITS**

Following World War II, the emphasis of atherosclerosis research initially shifted from Western Europe to North America. In this era also some misconceptions originated as to the early pathogenetic concepts promoted by Rokitansky and Virchow (vide supra). Certainly, Rokitansky, as the protagonist of the humoral theory, had proclaimed that the intimal thickening was derived from the blood, but he tried to reconcile the ancient concepts with modern anatomical knowledge. It goes a bit far, therefore, to consider Rokitansky the father of the thrombotic or encrustation theory as envisioned today. The same applies to the contributions regarding the pathogenesis of arteriosclerosis promoted by Virchow. Certainly, Virchow, as the father of cellular pathology, considered arteriosclerosis as a cellular reaction, which at the time was named “inflammation,” but which in its initial context had very little to do with the use of this term nowadays. Moreover, Virchow did not really promote the concept that influx of plasma constituents, with subsequent metamorphosis, caused the appearance of lipid material. And so, it is a misconception to attribute the so-called filtration theory to Virchow. These comments are not intended to devalue the significant contributions by either man, but merely to put the development of our insight into the genesis of atherosclerosis in a correct historic perspective. It is beyond the scope of this review to provide a comprehensive overview of the developments of the
past few decades regarding the pathogenesis of atherosclerosis. I have therefore selected a few aspects, which, in my opinion, have had a major impact on our current understanding.

The cellular composition of the atherosclerotic plaque

In the early 1960s, several investigators (eg, Haust, Geer, Wissler) pointed out that smooth muscle cells constituted a major component of the atherosclerotic lesion. The presence of a high proportion of smooth muscle cells in the elastic-hyperplastic intimal layer was also confirmed, justifying the introduction of the term musculoelastic layer. The recognition of smooth muscle cells, rather than fibroblasts, as the principal cell type opened new avenues for the study of the proliferative response underlying plaque formation. The smooth muscle cells were initially thought to originate in the media, which in essence is correct, but, in the setting of atherosclerosis, the musculoelastic layer could well be the main contributor; hence my above comment on the fertile soil. It also appeared that smooth muscle cells could exhibit different phenotypes, ranging from the mature contractile type to the synthetic type. The latter variety refers to a cell poor in contractile elements, but rich in endoplasmic reticulum and capable of producing extracellular matrix components—this is the type of smooth muscle cell involved in proliferative processes. This provided the basis for the understanding of the occurrence of cellular lesions with little collagen as well as of those almost solely composed of collagen.

It was also discovered that the vast majority of lipid-containing cells within the atherosclerotic lesions are macrophages rather than smooth muscle cells. The introduction of immunohistochemical techniques provided a firm footing for this observation while at the same time contributing in a major way to the identification of other cell types. From all this emerged new pathogenetic concepts based on the potential of cell-to-cell interactions. Thus, the identification of lymphocytes led to a breakthrough in our current understanding of the disease, as discussed in the section on intraplaque inflammation. The prominent role of macrophages in the atherosclerotic process became clear following the identification of the scavenger receptors and of the intracellular cholesterol cycle by Brown and Goldstein in 1983. The discovery of oxidatively modified lipoproteins in atherosclerotic lesions led to the hypothesis that uptake via the scavenger receptors resulted in intracellular lipid accumulation and foam cell formation, ultimately contributing to cell death and atheroma formation. It was found that macrophages function not only as scavengers, but also produce enzymes, cytokines, and growth-regulating molecules. Macrophages were shown to derive from blood monocytes, recruited via the expression of endothelial leukocyte adhesion molecules (eg, vascular cell adhesion molecule–1, intercellular adhesion molecule–1, E-selectin), a phenomenon shown in animal studies to be enhanced by hypercholesterolemia. The functional importance of endothelial cells had only recently been shown by Furchgott and Zawadski (1980), revealing the obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. This was the beginning of the understanding that endothelial cell dysfunction could interfere with the delicate balance between the mitogenic and vasomotor effects of endothelial cells and thus upset vascular homeostasis. The notion that endothelial cells do not just line the inner vessel wall, but play a pivotal role in maintaining the proper balance between the blood and tissue compartments, has had a major impact on our current understanding of the pathogenesis of atherosclerosis.

The evolution of the response-to-injury concept

In 1974, Russell Ross (Figure 4) and coworkers identified, in vitro, a platelet-derived serum factor that stimulated the proliferation of arterial smooth muscle cells. This observation prompted Ross and Glomset in 1976 to propose their response-to-injury theory for the pathogenesis of atherosclerosis. One of the important aspects of this hypothesis is that it linked, for the first time, a specific molecule (platelet-derived growth factor) to atherosclerosis. At the same time, Ross and Glomset considered endothelial denudation a prerequisite, causing platelet adhesion and the release of growth factor (Figure 5).

Proliferation of smooth muscle cells then leads to the formation of an intimal lesion. With restoration of the endothelial lining, the lesion could regress, but in case of persist-
ent or repeated injury—e.g., due to hypercholesterolemia—the lesion progresses to the classic plaque composed of smooth muscle cells and lipid. In 1986, Ross updated his original response-to-injury concept, recognizing the fact that endothelial cell adhesion and invasion of mono-

- the vast majority of atherosclerotic plaques that had led to clinical complications (myocardial infarction, stroke, etc) exhibited a particular morphology. These lesions contained a large lipid core—the atheroma—covered on the luminal side by a thin fibrous cap, which of-

- rather than smooth muscle cells. We and others, like Hansson et al in Sweden and Libby et al in the USA, had previously shown the presence of intraplaque inflammation within the atherosclerotic plaque, which most likely resulted from an adaptive immune response. As a result of these and subsequent findings, much research today is devoted to the study of potential antigens responsible for triggering the inflammatory response. These include oxidized low-density lipoprotein (oxLDL), as well as other proinflammatory and immunogenic agents such as stress proteins and infectious agents. The significance of the inflammatory concept is further emphasized by the fact that we and others were able to show, using coronary atherectomy specimens, that patients with unstable clinical conditions (unstable angina, acute myocardial infarction) had significantly more intraplaque inflammation than those with stable conditions. Similarly, patients with acute coronary syndromes exhibit signs of systemic immune activation, revealed by raised plasma levels of inflammatory cytokines and acute-phase reactants, such as C-reactive protein (CRP).

The question can be raised, of course, as to whether atherosclerosis is an adaptive immune response from the very start or whether the immune reaction modifies an already existing disease process. Be that as it may, our current insight—at least from my viewpoint—is best summarized by a quote from Ross’ last review, published in January 1999 in the New England Journal of Medicine, a few months before his death:

The lesions of atherosclerosis represent a series of highly specific cellular and molecular responses that can best be described, in aggregate, as an inflammatory disease.

Atherosclerosis: an inflammatory disease

Clinical-pathological studies, in particular the meticulous autopsy-based studies performed by Michael Davies in London, had shown that

"INJURY" (mechanical, chemical, immunology, etc)

Repeated or chronic "INJURY" e.g. chronic hypercholesterolemia

Figure 5. The original diagram illustrating the "response-to-injury" concept explaining the genesis of atherosclerosis.

**FURTHER READING**

Becker AE, de Boer OJ, van der Wal AC.
The role of inflammation and infection in coronary artery disease.

Brown MS, Goldstein JL.
A receptor-mediated pathway for cholesterol homeostasis.

Brown MS, Goldstein JL.
Lipoprotein metabolism in the macrophage: implications for cholesterol deposition in atherosclerosis.

Davies MJ.
The birth, growth, and consequences of the atherosclerotic plaque.

Hansson GK, Holm J, Jonasson L.
Localisation of T lymphocytes and macrophages in fibrous and complicated human atherosclerotic plaques.

Hansson GK.
Cell-mediated immunity in atherosclerosis.
*Curr Opin Lipidol.* 1997;8:301-311.

Jores L. Arterien.
In: Henke and Lubarsch, eds.

Libby P.
Inflammation: a common pathway in cardiovascular diseases.

Libby P, Hansson GK.
Involvement of the immune system in human atherogenesis: current knowledge and unanswered questions.

**Ross R. Glomset JA.**
The pathogenesis of atherosclerosis.

**Ross R.**
Atherosclerosis—an inflammatory disease.

**Ross R.**
The pathogenesis of atherosclerosis: a perspective for the 1990’s.

**Ross R.**
The pathogenesis of atherosclerosis—an update.

**van der Wal AC, Becker AE, van der Loos CM, et al.**
Fibrous and lipid-rich plaques plaques are part of interchangeable morphologies related to inflammation: a concept.

**van der Wal AC, Becker AE, van der Loos CM, et al.**
Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterised by an inflammatory process irrespective of the dominant plaque morphology.
*Circulation.* 1994;89:36-44.

**van der Wal AC, Das PK, Bentz van de Berg D, et al.**
Atherosclerotic lesions in man. In situ immunophenotypic analysis suggesting an immune mediated response.
The tree trunk for electrocardiography and arrhythmias is Willem Einthoven (Figure 1), who invented the ECG. Following his discovery, the work of early experimentalists like Wenckebach, Lewis, and Scherf, and basic scientists like Mayer, Mines, and Garrey facilitated the growth of a field that has known extraordinary success in diagnosing and treating cardiac disease. Yet, there can be no tree without a seed, and it is with seeds that we will start...

**THE SEEDS**

The recognition of electrical phenomena is as old as ancient China and Greece: Thales of Miletus (c 624 – c 545 BC) noted that amber rubbed with wool attracts light objects; amber is important to electricity as its ancient Greek name is ἐλεκτρον (electron). Although Thales could not find any immediate use for his discovery, he clearly wanted it to go down in history: “I will be sufficiently rewarded if when telling it to others you will not claim the discovery as your own, but will say it was mine.” In 1994, the Greek government commemorated Thales’ discovery on a postage stamp (Figure 2, next page).

The first English-language use of “electricity” as a medical term is generally attributed to Sir Thomas Browne, who discussed the medical properties of the lodestone in 1646. “Electricity” debuted as a scientific term in 1690: while Shakespeare labored over Hamlet, his countryman, William Gilbert, published De Magnete, in which he postulated a relationship between electricity and magnetism. Had Thales, Browne, and Gilbert not co-conspired over the centuries, we assume the electrocardiogram would have been differently named. In 1752, Benjamin Franklin reported his kite experiment, a landmark in research on electricity that led to the invention...
of the lightning rod. Although others replicating Franklin’s experiment had the ill fortune to be electrocuted, Franklin survived, much to the benefit of the American Revolution, French parlors, and numerous biographers. Importantly, Franklin also proposed the concept of positive and negative charges, laying a cornerstone in our library of electrical phenomena.

In 1791, a year after Franklin’s death, Luigi Galvani published De Viribus Electricitatis in Motu Musculari Commentarius. Among his discoveries was that frogs’ legs twitched during metallic contact between muscle and crural nerve. Whether his initial insight derived from a laboratory assistant’s chance juxtaposition of scalpel and muscle or an accident in Galvani’s kitchen as his wife prepared frogs’ legs for supper is uncertain. Not at all certain were subsequent experiments leading to Galvani’s conclusion that animal electricity is generated via an animal electric fluid. He considered the greatest sources to be brain and nerve. Given his understanding that an electrical stimulus precedes muscle contraction, Galvani might be considered the first electrophysiologist.

Galvani’s contemporary, Alessandro Volta, viewed electricity differently. He juxtaposed discs of copper and zinc, each pair separated from the next by saline-moistened cardboard, to build a “Voltaic pile,” and demonstrated the generation of charge in various ways: touching one finger to each end of the pile caused a tingle; applying tongue and finger elicited taste, finger and ear, a buzz. He concluded that electricity was derived from metal, and interpreted Galvani’s experiment (which Volta replicated) as demonstrating that the frogs’ legs were an electroscope rather than a source of electricity.

Subsequently, many contributors improved on the production of sources of electricity and/or means for recording the contractions of and signals generated by muscles. Noteworthy is Matteucci’s demonstration of an electrical current associated with each heartbeat (1842), Dubois-Raymond’s description of action potentials related to the heartbeat (1843), and Burden Sanderson and Page’s recording of two phases of the heartbeat (1878, 1884).

Burden Sanderson and Page made their recordings thanks to Gabriel Lippmann’s development of the capillary electrometer in 1872. The principle on which it was based was the change occurring in surface tension at a mercury/sulfuric acid interface in a capillary tube (Figure 3A) as potential difference varied between the liquids. In Lippmann’s electrometer, a droplet of mercury resided in the capillary, sensitive to and moving with very small changes in the electrical field. An important modification was provided by Étienne Jules Marey, who used the movement of mercury to deflect a beam of light, enabling photographic recording.

In the late 1880s, Augustus Waller used Lippmann’s capillary electrometer to record electrical potentials from animals (notably, his bulldog, Jimmy, immortalized in an early photographic plate, standing in four pans of water) and humans. Why Einthoven rather than Waller is commemorated as the father of electrocardiography in part relates to the technical advances Einthoven developed and in part to Einthoven’s recognition of the clinical applicability of electrocardiography. Indeed, in 1893, Einthoven was already presenting to Dutch audiences examples of the future clinical applicability of both electrocardiography and phonocardiography. In contrast, Waller had stated “I do not imagine that electrocardiography is likely to find any very extensive use in the hospital. It can at most be of rare and occasional use to afford a record of some rare anomaly of cardiac action.”

**THE TRUNK**

According to contemporaries, including Sir Thomas Lewis and the Nobel Prize committee, Einthoven invented the ECG. Understanding who coined the term “electrocardiogram” is more challenging. Waller credited Einthoven, and the printed record supports Waller’s contention. In 1912, Einthoven used the word “electrocardiogram” in print for the first time, but attributed the term to Waller. However, Waller never used the term in a publication until 1917. According to still another source, Einthoven coined the term, but then attributed it to Waller as a sign of respect. Have there been any such signs of generosity of late?

Regardless of who was being generous to whom, history has come to consider Einthoven the “trunk” of modern electrocardiography. The reasoning was summarized by Carl Wiggers as follows.

In 1889, A. Waller had reported that electrical currents generated during the heart beat could be taped from the body surface and recorded by capillary electrometer. Human elec-
trocardiography may thus be said to have been born in Oxford, England. However, since Waller went to great pains to rule out any possible clinical application of the procedure, this proved to be a stillbirth. Waller’s conclusion need not surprise us if we view again the wholly unsatisfactory character of his records—it is at this point that we gain a good insight into Einthoven’s genius—a human trait that Carlyle has defined as ‘the ability to take infinite pains.’

Who was Einthoven, where did he come from, what exactly did he do? A good source of information was his student, H. A. Snellen, whose biography of Einthoven1 we summarize here. Einthoven’s ancestry is traceable to the mid 1700s when a Jewish merchant, David Joseph, left the Rhineland to settle in Eindhoven, Holland. At times he used the name Enthoven, then a common practice to denote place of origin. When the Napoleonic Code required all persons to take a last name, David Joseph’s grandsons chose different routes: one selected as family name, Hoven, the other, Einthoven. Salomon Jurdan Einthoven (Willem’s grandfather-to-be), a surgeon, moved to Groningen, joined the Dutch Reformed Church and married the daughter of the professor of physics and astronomy at the university. Their son, Jacob Einthoven, died when Willem was six, and his mother took the family back to Holland. They settled in Utrecht where Einthoven studied classical languages and then medicine. While preparing for a career in ophthalmology and a return to the Dutch East Indies, he studied with Herman Snellen (the grandfather of Einthoven’s biographer) and Franz Donders, and in 1885 obtained his doctoral degree with a thesis on Stereoscopy through differences in color. The quality of his thesis brought him the professorship and chair in physiology at Leiden in 1886, at age 25.

Einthoven’s initial research focused on vision and on respiration. However, when his brother-in-law, Willem de Vogel, commenced doctoral research at the laboratory in 1891, Einthoven gave him a choice of subjects and de Vogel selected cardiac electrical activity. Waller and Bayliss and Starling had already published their own (personal) cardiograms using Lippmann’s capillary electrometer. Their recordings were marred by the slow voltage/time course of the device, reflecting the friction and the inertia of the mercury in the column, and the pres-

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Figure 3. Evolution of the ECG. Panels A, B, C, relate to Lippmann’s capillary electrometer. Panel A: (a) Mercury reservoir ending in glass capillary; upper half filled with mercury. (b) Lower half of capillary and reservoir, both filled with sulfuric acid. Panel B: Waller’s cardiogram: t = time; h = external pulsation from heart-beat; e = electrical activity of heart. Panel C: Einthoven’s recording using capillary electrometer. Upper: A, B, C, D waves; Lower: mathematically corrected waves, now designated PQRS. Panel D: String galvanometer: (upper), poles $P$ and $P_1$ of electromagnet and aperture for string $A-A_1$. Note holes for viewing via microscopes: (lower) electromagnet with string in place and two microscopes. Panel E: Einthoven’s ECG recordings. See text for discussion.

ence of only two deflections (Figure 3B). By 1902, Einthoven had improved the sensitivity of the Lippmann device such that four deflections were visible (labeled A, B, C, D) in a recording from both upper extremities (Figure 3C, upper). Einthoven also modified a method originally described by Burch for skeletal muscle studies to correct his recordings mathematically (Figure 3C, lower). He now designated the wave forms PQRST. The reasons for the change in nomenclature were first, to avoid confusion between uncorrected and corrected records and second, to permit addition of further letters should earlier or later waveforms be discovered.

As good as the capillary electrometer had become, it was still slow and the requirement for mathematical correction of each waveform too labor-intensive for widespread clinical application. Hence, Einthoven adapted a galvanometer invented by Deprez and d’Arsonval. Whereas earlier galvanometers incorporated a magnetized needle that moved when current flowed through a wire coil, Deprez and d’Arsonval designed a fixed magnet and a coil that could move within the field. A pointer attached to the coil moved over a calibrated scale, providing the recording. The result was a rapid enough trace, but one not sufficiently sensitive to record the ECG. This required Einthoven to make a variety of changes in the weight and operation of the coil, his ultimate design used a thin quartz wire coated with silver or gold placed between the poles of an electromagnet. The quartz was made thin enough (initially about 3 microns) by melting it, fixing one end to an arrow and then shooting this with a bow.

Each pole of the electromagnet was perforated such that the string could be illuminated and visualized using two microscopes (Figure 3D). Einthoven noted that this was not the first use of a string in an electric field: in 1897, Ader had reported such a device. This was used as a receiver for transatlantic communication of code, was never intended for use as a galvanometer, and had only 1/100 000 the sensitivity of Einthoven’s device. Indeed, the signals recorded by Einthoven in 1902-1906 (eg, Figure 3E) are readily recognizable and interpretable via today’s ECG standards.

Einthoven reported the development of the string galvanometer in 1901 and ECGs were published in 1903. The technical advances of “telecardiograms” and diagnosis of arrhythmias. Regrettably, the cooperation between research laboratory and clinical unit was short-lived: this has been variously attributed to the clinicians’ jealousy of the scientists’ ability to diagnose extrasystoles even before the clinicians were aware of them, and their additional dismay that in an enterprise whose cost was to be equally divided, the credit accrued largely to Einthoven.

With this linkage lost, a major boost to the investigative and clinical application of string galvanometry came via a contact made by Thomas Lewis. In 1908, Lewis asked Einthoven for a reprint of the “telecardiogram” paper that had impressed him for a variety of reasons, likely including Einthoven’s recordings of ventricular hypertrophy, U waves, ventricular premature depolarizations, bigeminy, atrial flutter, and heart block. As for Einthoven, he assessed the value of his device as...
follows in a 1922 letter to Lewis (as quoted by Snellen12) “An instrument takes its true value not so much from the work it possibly might do, but from the work that it really does.”

There is not the space to write more about Einthoven’s research. Following his invention and perfection of the string galvanometer, he continued to investigate the relationship between cardiac electrical and mechanical activity. He was awarded the Nobel Prize in 1924, and in 1927 died of cancer. We conclude this section with a Carl Wiggers quote from Einthoven, a few words that cut to the core of our profession: “The truth is all that matters: what you or I may think is inconsequential.”

**INTRODUCTION TO THE BRANCHES**

Before discussing the major branches of electrocardiography/arrhythmias, there are several milestones to be noted. In 1920, Hubert Mann described an electrocardiographic analysis, the “monocardiogram,” that evolved into the vectorcardiogram. Also in 1919, James Herrick published the first ECG of a myocardial infarction in a patient. In 1930 and 1932, respectively, Frank Wilson, Charles Wolferth, and Francis Wood described the use of chest leads, and in 1934, Wilson described his central terminal, which, used as a reference, permitted the unipolar limb leads to be recorded. Finally, in 1942, Emanuel Goldberger added the augmented unipolar limb leads to Einthoven’s original three leads and to the six chest leads of Wilson and of Wolferth and Wood, providing the 12-lead ECG that is used to this day.

The advances in electrocardiography were accompanied by a renaissance in all areas of electrophysiology, which has grown by moving across disciplines, resulting in further discoveries throughout the twentieth century. Major advances include Tawara’s description of the atrioventricular (AV) node (1906), Keith and Flack’s description of the mammalian sinoatrial (SA) node (1907), Mines’ descriptions of reentry (1913, 1914), Graham, Ling, and Gerard’s invention and use of the glass microelectrode (1946, 1949), Hodgkin and Huxley’s voltage clamp of the squid axon (1940s), Alanis et al.’s registration of electrical activity of the His bundle (1958), Scherlag et al.’s His bundle catheter recordings in humans (1968), Neher and Sakmann’s development of the patch clamp (1978), Numa’s use of gene cloning to describe the molecular structure of voltage-gated ion channels and provide new insights into structure-activity relationships (1980s-90s), and MacKinnon’s description of structure of a Saccharomyces (yeast) potassium channel (1998). While each development has been of signal importance, one could reasonably argue that with the exception of Mines, Alanis, and Scherlag, the direct contributions of the individuals mentioned were primarily focused on a different area of interest and only secondarily impacted on the field of arrhythmias and electrocardiography.

**THE FIRST BRANCHES—THE FIRST HALF OF THE TWENTIETH CENTURY**

Here, we include persons whose work and in some cases personalities dominated the development of basic and clinical electrophysiology: Karel Wenckebach, George Ralph Mines, Thomas Lewis, Frank Wilson, and David Scherf.

**Karel Wenckebach**

Karel Wenckebach (Figure 5) was born in The Hague and raised and educated in Utrecht, earning his medical degree in 1888. His initial research interest was embryology, but color blindness limited his interpretations of histologic stains and this disability led him to physiology. In 1891, he entered clinical practice, becoming interested in irregularities of the heartbeat. He resumed the study of physiology in Utrecht in 1896.

Figure 5. Karel Wenckebach. © Natuurinformatie.

In 1898, Wenckebach described extrasystoles, and, in 1899, a unique periodicity in a patient’s pulse. Aid ed by his mentor, Theodor Engelmann, Wenckebach studied this periodicity in frog heart in which both the atrial and ventricular pulses could be recorded simultaneously and the time between pulses measured using a tuning fork. We emphasize that these painstaking and accurate studies were performed before the ECG had been invented (Wenckebach described his periodicity using smoked drum kymograph tracings of jugular venous and carotid pulsations) and before the SA and AV nodes had been structurally identified.

However, once Einthoven developed his string galvanometer, Wenckebach used it in 1906 to demonstrate the progressive prolongation of
the PR interval that precedes the dropped beat in what is now called Wenckebach periodicity.

In 1901, Wenckebach was named chair of medicine at the University of Groningen. His 1903 book, *Die Arrhythmie als Ausdruck Bestimmter Funktionsstörungen des Herzens [Arrhythmia as the Expression of Specific Function Disorders of the Heart]*, became a classic. From 1911-1914, he chaired the department of medicine at the University of Strasbourg and from 1914-1929 held the chair in medicine at the University of Vienna. He died in Vienna in 1940.

**George Ralph Mines**

Born in 1886, Mines (Figure 6) trained in physiology at Cambridge, was appointed to the chair in physiology at McGill at age 29, and was found dead in his laboratory shortly thereafter, apparently the victim of self-experimentation. Mines and his contemporary, Walter Garrey, pioneered the study of reentry, and both were inspired by Andre Mayer's studies (1906, 1908) of ring-like structures cut from the muscular tissue of the subumbrella of the jellyfish *Scypho-medusa cassiopeia*. Mayer used mechanical stimulation and photographic plates, respectively, to induce and record a contraction wave that continued to circulate: “...upon momentarily stimulating the disk in any manner, it suddenly springs into rapid, rhythmical pulsation so regular and sustained as to recall the movement of clockwork.”

Mines and Garrey noted independently in 1914 that for the initiation of reentry, an area of unidirectional block must be present. Mines’ experiment was performed on a ring-shaped preparation cut from dog-fish auricle. Normally, a stimulus induced two contraction waves that traveled in opposite directions, meeting on the far side of the ring, where they were extinguished. However, he repeated

...the stimulus at diminishing intervals and after several attempts started a wave in one direction and not in the other. The wave ran all the way around the ring and continued to circulate going around about twice a second. After this had continued for two minutes extra stimuli were thrown in. After several attempts the wave was stopped.14

Not only did Mines describe unidirectional block here, but provided an observation that came to underlie antitachycardia pacing.

Mines also described the relationship between conduction velocity and refractory period, pointing out that reentrant arrhythmias are more likely to occur “when conduction velocity is low and refractory period duration is short.” He also recognized the need to differentiate reentry from other mechanisms:

The chief error to be guarded against is that of mistaking a series of automatic beats originating in one point of the ring and traveling round it in one direction only owing to complete block close to the point of origin of the rhythm on one side of this point... Severance of the ring will obviously prevent the possibility of circulating excitations, but will not upset the course of a series of rhythmic spontaneous excitations unless by a rare chance the section should pass through the point actually initiating the spontaneous rhythm.14

Mines’ prescience was perhaps best illustrated when he linked his experiments on reentry in the ring-like structures to his understanding of Kent’s work, stating “in light of the new histological demonstrations of Stanley Kent that the muscular connection between auricles and ventricles in the human heart is multiple... supposing that for some reason an impulse from the auricle reached the main AV bundle, but failed to reach its “right lateral” connexion. It is possible then that the ventricle would excite the ventricular end of this right lateral connexion, not finding it refractory as it normally would at such a time. The wave spreading then to the auricle might be expected to circulate around the path indicated.”

Mines added that the rhythm might become self-sustaining and in so doing would provide “...a type of rhythm known to occur both under experimental conditions and in disease.”

In fact, Mines described the Wolff-Parkinson-White (WPW) syndrome 16 years before the authors whose name it bears reported that self-same arrhythmia. And many investigators who followed failed to link Mines’ seminal observations to the mechanism of the arrhythmia. Not until the 1960s was the record set straight, based on the work of the Durrer group in Amsterdam and the Sealy group in Durham.

A fitting comment on the failure of so many authors to recognize Mines’ discovery and the pivotal role it
played in our knowledge of arrhythmias was that attributed to Carl Wiggers. “To enjoy the thrill of discovery, don’t go to the library.”

**Thomas Lewis**

Thomas Lewis (Figure 7) was born in 1881, studied medicine at University College, Cardiff, and University College Hospital, London, and joined the staff of the London Chest Hospital in 1907. In 1909, James MacKenzie persuaded Lewis to become the founding editor of the *British Heart Journal* (now *Heart*), the journal that published most of his subsequent research.

Yet, after 1920, Lewis’ interest in electrocardiography waned, and he began to study the peripheral circulation. His professed to being “weary of being tied to an instrument... the ‘cream was off’... there were no new things to be discovered in the field of electrocardiography.”

Lewis was knighted in 1921, suffered his first myocardial infarct in 1927, remained active despite advancing coronary artery disease, and died of a myocardial infarction in 1945.

**Frank N. Wilson and David Scherf**

Although they never worked together and in fact had different viewpoints and different approaches to electrocardiographic and arrhythmia research, we consider Wilson and Scherf together as they were not only unique scientists, but important transitional figures. Both were born in the same decade (Wilson in 1890 in Michigan, Scherf in 1899 in the Austro-Hungarian Empire) Wilson died in 1952, Scherf in 1977. Wilson received his MD degree from the University of Michigan in 1913. He obtained a string galvanometer in 1914, and commenced a lifetime of electrocardiographic and vectorcardiographic research. Thomas Lewis was a major influence on Wilson, not only because of Lewis’ eminent position in electrocardiography at the beginning of Wilson’s career, but also because he was the commander of the English rehabilitation hospital at which Wilson was stationed during World War I. In the 1920s to early 1930s, Wilson’s research into bundle branch block, ventricular hypertrophy, body surface distribution of electrical potentials, the ventricular gradient, and electrocardiographic theory culminated in his introduction of precordial leads into electrocardiography. Not only was he the leading electrocardiographic researcher of his time, but he was also a bridge between the early scientists in the field (Einthoven and Lewis) and the practitioners of modern electrocardiography.

Scherf graduated from the University of Vienna Faculty of Medicine, where he studied under Wenckebach. On the ascendancy of fascism, he moved to New York, where he chaired the Cardiology Division at New York Medical College until his retirement. He then remained active in teaching, especially in New York, where he was a source of inspiration to, among others, Brian Hoffman, Paul Cranefield, and their students. Scherf was both an outstanding animal experimentalist and an early “translational scientist” carrying his experimental work to the bedside. In 1932, he and Holzmann suggested the short PR interval and delta wave of WPW syndrome were likely the result of conduction through an accessory pathway. Earlier, he had described Wenckebach periodicity in the bundle branches, and made a number of observations regarding...
NEW GROWTH: BEGINNING OF THE MODERN ERA OF ARRHYTHMOLOGY

The individuals we discuss were not only outstanding investigators in their own right, but were recognized in an informal survey (see acknowledgements) as founders of the modern schools of arrhythmology. In selecting them we have deliberately not listed those whose contributions might have been thought of as largely clinical (eg, Louis Katz, Alfred Pick, Richard Langendorf, Mauricio Rosenbaum) or largely in the basic sciences (eg, Denis Noble). Rather, these are all individuals who have “bridged the gap,” between that which is basic and that which is clinical. The only possible exception to the statement regarding bridging the gap is Silvio Weidmann, who, in a field of godfathers, is generally considered the “capo di tutti capi.”

In addition to Weidmann, we include Gordon Moe, Brian Hoffman (partnered with Paul Cranefield) and Dirk Durrer.

Silvio Weidmann

Swiss-born Weidmann (1921-2005, Figure 8) worked in the department of physiology of the University of Berne from 1951 to 1986, and chaired it from 1968-1986. Although his interest was basic physiology rather than electrocardiography/arrhythmias, his studies were central to the development of approaches that translate basic to clinical research. Weidmann’s direction in science was crystallized during a visit to the laboratory of Alan Hodgkin in Cambridge in 1948. (Hodgkin shared the 1963 Nobel Prize with Andrew Huxley and John Eccles for their work on the ionic mechanisms underlyning neuronal action potentials).

Hodgkin had learned how to pull glass microelectrodes from Gilbert Ling in Chicago, and refined the recording technique. He told Weidmann: “Here is a powerful tool. Prod around in nature, but keep skeletal muscle reserved for me.”16 Weidmann later wrote: “A remark by Hodgkin, in 1949, is still in my ears: You can now rediscover the whole of cardiac electrophysiology.”16 In retrospect, some of Weidmann’s contributions might be called rediscoveries, such as the confirmation that the cardiac action potential has an overshoot, which had been proposed by Engelmann et al in 1873.17 But his originality and the elegance of his techniques make him one of the founding fathers of cardiac cellular electrophysiology. He and Edouard Coraboeuf from the Sorbonne were the first, in 1949, to record transmembrane potentials of cardiac fibers with microelectrodes. Among Weidmann’s subsequent contributions, the most important are probably the demonstration that the availability of the rapid inward sodium current is dependent on the level of the membrane potential, the cable analysis of ventricular muscle, and, above all, the proof that the heart functionally behaves as a syncytium. In the latter study, Weidmann showed, by measuring the diffusion of radiopotassium, that the intercalated disk has a low resistance, allowing the longitudinal flow of ions, and other small molecules, from cell to cell.

Dirk Durrer

Dirk Durrer (Figure 9) was born in 1918 in the Netherlands, and died in 1984 in Amsterdam. In 1957, he became the first professor of cardiology at the University of Amsterdam. One of Durrer’s enduring characteristics was his insistence on bridging basic and clinical science. A key element in his career was his collaboration with the physicist L. H. van der Tweel. In the early 1950s, van der Tweel designed and built a 4-channel oscilloscope, allowing photographic recordings of extracellular electrograms. In articles published in the American Heart Journal in 1953 and 1954, Durrer and van der Tweel described the spread of activation in the canine left ventricular wall, and settled the question of which deflection in both unipolar and bipolar electrograms reflects local activation.18 Further contributions included the 1961 demonstration of delayed, fractionated activity, proving the persistence of electrical activity in a healed infarct, and intraoperative mapping in 1967, identifying the earliest excited epicardial area in a patient with WPW syndrome.19 Perhaps the most influential paper is the 1967 study on the role of electrically induced premature beats on the initiation and termination of tachycard-
Gordon Moe was awarded his PhD degree from the University of Minnesota in 1940, trained with Carl Wiggers at Case Western Reserve University, and subsequently received the MD degree at Harvard. From 1943 to 1950, he was on the faculty of the University of Michigan, where his career overlapped that of Frank Wilson. The remainder of Moe’s academic career was first at the State University of New York at Syracuse and then, from 1960 until his death in 1989 as Director of Research at the Masonic Medical Research Laboratory in Utica, New York. Moe’s major contributions to research on arrhythmias were in our understanding of reentry. He conceived of the multiple wavelet hypothesis, which explored the interaction of reentrant circuits in fibrillating chambers. He brought to this work not only a keen understanding of physiology, but of modeling as well. This carried over to his research on other conduction abnormalities such as reflection as well as to abnormalities of impulse initiation. The work of the Moe laboratory on delayed afterdepolarizations in the early 1970s was concurrent with that of the Hoffman laboratory on the same phenomenon. The net result of both laboratories’ efforts was the understanding that arrhythmias not only are caused by abnormal automaticity or abnormal conduction, as had been the gospel until then, but that afterdepolarizations and resultant triggered activity were important as well. Both laboratories were to acknowledge the root of this work in earlier studies by Segers and by Bozler in the late 1930s and early 1940s as well as the major contributions of David Scherf and associates to our clinical understanding of triggered activity.

Brian F. Hoffman

Brian Hoffman received his MD degree from the Long Island College of Medicine in 1947 and joined the faculty of the department of physiology of the SUNY Downstate Medical Center in 1949. In 1963, he was appointed Professor and Chairman of Pharmacology at Columbia University, a position he held until his retirement in 1995. Hoffman’s cellular electrophysiologic studies of sinus node characteristics and AV conduction are among the significant early experiments that demonstrated the function of these sites in the conduction system. In his laboratory, techniques for His bundle recording and pacing and the means for extracellular recording of electrical activity were developed to a point where his former student, Benjamin Scherlag, working with Anthony Damato, could consistently record His bundle activity in human subjects22 (independent work on the subject was earlier reported by Paul Cranefield, Hoffman described cellular mechanisms by which slow conduction, summation, and reentry could occur in small bundles of cardiac fibers. Prior to these studies, reentry had a sound basis experimentally (ie, it had been studied extensively in nonmammalian and to a lesser extent in mammalian tissue), but the cellular mechanisms that permitted it to occur in the intact heart had not been recognized. Hoffman also worked extensively in the field of antiarrhythmic pharmacology, contributing importantly to our information in that arena. His 1960 book, Electrophysiology of the Heart, coauthored with Paul Cranefield, remains one of the classic publications in electrophysiology.

AND NOW THE FOREST....

A little-known byproduct of the Vietnam War was the impetus it gave to clinical electrophysiology in the United States, when many who became leaders in clinical electrophysiology spent their military service time in the US Public Health Service, in the clinical laboratory of Anthony Damato in Staten Island. The worldwide growth of the field has been to a degree that Einthoven predicted, but that would have amazed Waller and even Lewis. The application of electrophysiologic techniques to the development of pacemakers and cardioverter-defibrillators—based in large part on the work of Zoll, Mirowski, Lown, and others—and the impressive benefits these inventions have brought to society are now readily appreciated. It is estimated that nearly 1 000 000 devices per year are implanted worldwide annually, each with the poten-
tial to save and prolong a life. This observation permits us to come full circle and to conclude with a quote from Einthoven’s Nobel Prize lecture. His words not only say much about Einthoven, the man, but say so much about our scientific discipline, its core, and the people in it.

A new chapter has been opened in the study of heart diseases, not by the work of a single investigator, but by that of many talented men, who have not been influenced in their work by political boundaries and, distributed over the whole surface of the earth, have devoted their powers to an ideal purpose, the advance of knowledge by which, finally, suffering mankind is helped.

We thank the following individuals for providing us with suggestions regarding the branches identified: Charlie Antzelevitch, Penelope Boyden, Masayasu Hiraoka, Jose Jalife, Andre Kleber, Robert Myerburg, Leonid Rosenshtraukh, Yoram Rudy, Peter Schwartz, Marc Vos, Albert Waldo, Hein Wellens, and Douglas Zipes. In addition, we thank Laureen Pagan for her careful attention to the preparation of this manuscript. Finally, our gratitude to Phyllis Katz and Marina Ximeris for their assistance in matters relating to Greece, ancient and modern.

REFERENCES


Autonomic biology grew slowly from puzzling observations made using crude techniques in the late 1800s. Its development was refined in the great universities of Cambridge and Oxford, but it was the financial strength of giant corporations and foundations, along with the development of new therapies, that moved the field forward. Talented biochemists, pharmacologists, and vascular and molecular biologists have made seminal contributions to our understanding of autonomic biology. The field is rich with Nobel laureates. Interdisciplinary teams were the rule and not the exception. Laboratory mishaps and small conferences also played an important role. The development of autonomic biology is a clear example of how basic and clinical science, academia and industry, and ultimately talent, have combined to enrich the field of medicine.

Among the ten seminal concepts of cardiology that this issue of Dialogues is looking at from a historical perspective, and which can be likened to trees in a vast forest, autonomic biology probably is one of the youngest trees, with the fastest growth. Before the technical term of “autonomic” had been explicitly defined, there was a long period of subterranean growth of the root system, reflecting the slow and methodical process that led to the discovery and understanding of the autonomic nervous system. The actual moment the seedling broke through the earth and the term “autonomic” was coined can be pinpointed to 1898. The “trunk” is most definitely represented by E. P. Sharpey-Schafer, who as Professor of Medicine at the University of London and a member of the Department of Medicine at St Thomas’ Hospital Medical School, moved the field forward most forcibly in the 1940s and 1950s. As a practicing physician, he was able to carry out detailed studies in patients, which defined how the circulation was regulated under a variety of stressful conditions. We probably owe Sharpey-Schafer the greatest debt of gratitude for paving the way for several Nobel Prize-winning discoveries that changed the way we treat patients. This essay focuses on the process of discovery rather than the specific discoveries in an attempt to identify the seedling, roots, trunk, and branches provided by those who have made the most meaningful contributions to autonomic biology.

The Seedling

As always, terminology is important. The expression “autonomic nervous system” was probably introduced in 1898, when John Newport Langley (1852-1925) (Figure 1, next page), a Cambridge physiologist, used it to imply that its actions were independent, but still “...under control of a higher power.” Langley believed that the innervation of glands and involuntary smooth muscles was governed by a system that was independent of the voluntary nervous system.1 Langley’s report, which was not widely accepted, used the terms “sympathy” and “sympathetic.” Prior to the 19th century, knowledge of the autonomic nervous system was based almost exclusively on animal and human dissections. Albert Rognard and Paul Laye (1861-1890) studied the stimulation of the vagus nerve and the secretion of gastric juice in beheaded animals. Camillo Golgi (1844-1926) deserves credit for pointing out that the whole nervous system is like a net or net-
work (a reticulum), while Santiago Ramon y Cajal (1852-1934) first proposed that each nerve cell was a single or independent unit. Both shared the Nobel Prize for Physiology or Medicine, in spite of having never reconciled their divergent views. Charles Sherrington (1857-1952), using much improved histological techniques, proposed the word “synapse” in 1897 to describe the terminal neuron and its effector organ. Sherrington and Edgar Douglas Adrian shared the Nobel Prize in Physiology or Medicine in 1932 for their discoveries regarding the function of neurons.

Walter Gaskell (1847-1914), another Cambridge physiologist, deserves much of the credit for elucidating the anatomic complexities of the autonomic nervous system. Gaskell also delineated the morphology and the function of the two separate arms of the autonomic nervous system—what we now refer to as sympathetic and parasympathetic, and coined the terms “visceral” and “involuntary.” There was disagreement about a possible third network, the “enteric” nervous system. Langley, a contemporary working in the same department who used drugs to investigate and differentiate the two arms of the autonomic nervous system, confirmed Gaskell’s work, and postulated the existence of a mechanism whereby these nerves communicated with the effector organ—but he doubted the existence of chemical messengers.

### THE ROOTS

Henry Dale (1875-1968) (Figure 2), a student of Gaskell and Langley, moved from Cambridge at the suggestion of Henry Wellcome to the Wellcome Physiologic Research Laboratories to study ergot alkaloids. His early contemporary at Cambridge, Thomas Elliott (1877-1961), had observed that stimulation of the hypogastric nerve could be mimicked by the action of a substance he called “adrenaline.” When he presented his results to the Physiological Society in 1904, he suggested that adrenaline was liberated from autonomic nerves. His work, which at the time was considered “ambiguous,” was probably the first formal suggestion of chemical neurotransmission. Dale observed that ergot “paralyzed” the structures that adrenaline stimulated but unlike Elliot, never proposed a formal explanation. Dale, however, went on to study with George Barger (1878-1939), a chemist with whom he described the structure of adrenaline and related amines. Together, they coined the term “sympathomimetic.” Dale remained mystified about why large doses of adrenaline caused “vasoconstriction,” whereas small doses caused “vasodilation,” and privately referred to this as “the central mystery.” To Dale, however, belongs the notion of chemical neurotransmission, later to be proven, and again the subject of a Nobel Prize in 1970 for Sir Bernard Katz (1911-2003). It was also Dale who first proposed the terms “cholinergic” and “adrenergic,” a usage he believed would assist clear thinking. These discoveries relating to “chemical transmission of nerve impulses” won Dale the Nobel Prize in 1936.

The American physiologist Walter B. Cannon (1871-1945) provided further support for the observations of Dale and colleagues, but Cannon and Arturo Rosenblueth (1900-1970) obfuscated these issues by coining new terminology, including the terms sympathin E (excitatory) and sympathin I (inhibitory),5 which was promoted by their popular book, *Autonomic Neuro-effector Systems*. Some thought the book unnecessarily complicated. Ray Ahlquist, using a range of adrenergic agonists, first postulated the terms α-receptors and β-receptors in 1948, which allowed reinterpretation of previous confusing work. In the 1950s and 1960s, it became clear that not all autonomic nerves were adrener-
Burnstock (born 1929), who suggested that other neurotransmitter chemicals could also be released,7 for which he was criticized, was ultimately proven correct, as the number of known neurotransmitters continues to grow.

THE TRUNK

Professor Edward Peter Sharpey-Schafer (1908-1963) (Figure 3) was one of the grandsons of the English physiologist Sir Edward Albert Sharpey-Schafer (1850-1935), who invented the first prone-pressure method (Schafer method) of artificial respiration, and made important contributions relating to adrenaline, insulin, and the pituitary and other endocrine glands. The younger Sharpey-Schafer was a highly respected cardiologist and clinical physiologist at University College Hospital in London, who was described as having “the highest IQ and the lowest pH in England.” He and colleagues produced a stream of 27 papers mainly in the 1950s and 1960s related to the autonomic nervous system and the peripheral circulation in heart failure, shock, and syncope. The work was done on patients in his laboratory at St Thomas’ Hospital. The papers, many of which were written by him as sole author, are short (1-2 pages) and to the point. Sharpey-Schafer was able to measure venous and arterial tone, and like many great physiologists, he took advantage of emerging technology to advance his understanding of physiology.8 In 1958, he published a paper describing patients who developed spontaneous nausea during N2O anesthesia for tooth extraction, or following the administration of apomorphine for chronic alcoholism (Figure 4).9 He found nausea led to peripheral vasodilation, a fall in diastolic pressures of the heart, hypotension, and syncope. He postulated that virtual emptying of the ventricular chamber during systole activates an afferent mechanism that produces fainting,9 which also occurs when sublingual nitroglycerin causes hypotension, bradycardia, and syncope. His observations remain an integral part of the fundamental mechanism of neurocardiogenic syncope as it is understood today.

Sharpey-Schafer devised a method for measuring changes in the tone of forearm veins, a technique later taught to me (G. S. F.) by Jay N. Cohn in Minnesota and used by us to study reflex control mechanisms and various drug therapies in patients with heart failure in the 1970s and 80s. Sharpey-Schafer observed that venous tone was increased in patients with heart failure, but fell toward normal when treatment was given.10 He also showed that adrenalin and other amines constricted veins, whereas nitrates dilated the venous system, which led him to suggest that the sympathetic nerv-
THE BRANCHES

The fact that Sharpey-Schafer could develop and maintain a hospital-based laboratory to study human subjects and patients with circulatory dysfunction was the key to translating observations that previously could only be made in the physiological animal laboratories. His work led to the development of numerous “human physiology” laboratories, headed by such luminaries as Shillingford, Braunwald, Gorlin, Cohn, Chatterjee, and other investigators, some of whom participated in the Myocardial Infarction Research Units (MIRUs) funded in the United States by the National Institutes of Health (NIH) in the 1970s. It became clear that critically ill patients could be safely studied at the bedside. The branches grew out, however, in many directions. The central theme was circulatory physiology and its interaction with the autonomic nervous system. Neurohormones, nitric oxide, and the pharmacology of the adrenergic receptor came somewhat later.

Ray Ahlquist

As mentioned, Ahlquist (1914-1983) should be credited with organizing and finally resolving some of the ambiguities regarding the autonomic nervous system, particularly the terminology. Working at the Medical College of Georgia in Augusta, he defined the two major classes of “adrenoceptors,” with a range of different potencies for catecholamines. He predicted that α-receptors would be more sensitive to norepinephrine, whereas β-receptors would be preferentially more sensitive to isoproterenol, and least responsive to norepinephrine. Of course, today we know there are numerous subtypes of “adrenoceptors”, but Ahlquist’s explanation of sympathetic nervous system receptors has withstood the test of time and is still used today. Ahlquist also went on to define cholinergic receptors, including muscarinic, ganglionic, and somatic subtypes, and brought clarity to the field of autonomic biology.

Sir James W. Black

Sir James Black (Figure 6) was responsible for a major “branch” in the development of our understanding of autonomic biology. He was the fourth of five boys born in 1924 into a staunch Baptist home in Uddingston, Scotland, and chose to study medicine under the influence of an older brother, William, at St Andrews University. It was there that he began his disciplined studies under the tutelage of D’Arcy Wentworth Thompson, the great Victorian polymath. Black married shortly after graduation and joined the Physiology Department under Professor R. C. Garry.

In 1947, Black moved to Singapore to the King Edward VII College of Medicine. He returned in 1950 to the University of Glasgow, where, in 1956, stimulated by Ahlquist’s work, he set out to find a specific adrenergic receptor antagonist. He worked in the Pharmaceuticals Department of ICI (Imperial Chemical Industries), the giant British chemical company, from 1958 to 1964; there he changed from being a physiologist to a pharmacologist. Black and Brian Prit-
By 1963, Black was interested in starting a new program at ICI. Propranolol had become a reality, and he wanted to use this as a model to develop a histamine receptor blocker to reduce gastric acid. He moved to Smith, Kline and French Laboratories (SKF) to run their Biologic Research Lab in 1964, where, with William Duncan heading the Biochemistry Department, they maintained a productive partnership at SKF for 15 years. Black assembled a highly successful team, and modeling the histamine program after the β-receptor program, launched the H2-receptor blocker program in 1972, that was to lead to the discovery of cimetidine.

From 1973 to 1977, Black served as the University College of London (UCL) Chair of Pharmacology. By academic standards, his teaching and research ideas were considered too wispy and expensive, and in 1977 he left to join John Vane's group at the Wellcome Foundation. From 1977 to 1984, he worked at the Foundation, but was disappointed with his managerial role, and began to pursue analytical pharmacology in a small, independent, academic research unit within the Foundation. King's College of London and their medical school smoothed difficulties in Black's small academic unit through their support. In intellectual terms, surrounded by talented young researchers and PhD students, Sir James Black found his niche. In 1988, he was awarded the Nobel Prize in Physiology or Medicine, shared with Gertrude Elion and George Hitchings, for their discoveries of important principles for drug treatment.

Black used many tools during the process of his discoveries, starting with physiology, moving to pharmacology, and working closely with biochemists. He demonstrated the power of a multidisciplinary approach and the usefulness of moving between industry and academy. His work could not have been done without the resources available from both enterprises.

**Sir John R. Vane**

Sir John Vane (1927-2004) (Figure 7) was born in Tardebigg, Worcestershire, one of three children. He attended the University in Birmingham, but believed that his chemistry classes lacked for suitable training in experimentation, and moved to Oxford to study pharmacology. There he joined Professor Harold Burn in 1946 who provided Vane with lasting inspiration. Vane went on to share the Nobel Prize in Physiology or Medicine in 1982 for the discovery of prostaglandins and related substances. He is widely recognized for his work on the antiplatelet effects of aspirin.

Most of Vane's time was spent at Oxford, though he did a 2-year stint in Yale. He then returned to the UK, and joined W. D. M. Paton's Department of Pharmacology, at the Institute of Basic Medical Sciences, eventually located at the Royal College of Surgeons in London. It was here that Vane and his group developed the cascade superfusion bioassay technique that made it possible to measure the instantaneous release of vasoactive hormones into the circulation or in the fluid perfusing isolated organs. Like so many great scientists, a methodological breakthrough allowed Vane and his colleagues to create new ideas and move his field forward.

In 1973, like Henry Dale, Vane was recruited to work at the Wellcome Foundation as Group Research and Development Director, and like Dale, he accepted the appointment and had no regrets, despite warnings from friends and colleagues. It was here that prostacyclin was discovered and its pharmacology developed. Working with Salvador Moncada, he went on to make major discoveries related to endothelial relaxing factor, later discovered to be nitric oxide (NO). Vane forged the link between aspirin and prostaglandins, but had phenomenal success in the broad area of vascular biology, especially the vasoactive properties of smooth muscle unrelated to the autonomic nervous system. Like Black, he moved between academy and industry with ease, worked in small groups, and had no formal training in biology.

**Robert F. Furchgott**

Robert Furchgott (Figure 8, next page) was born in 1916 in Charleston, SC. He studied at the University of...
North Carolina, took his PhD at Northwestern University, and had various positions at NIH, Geigy, Cornell, Washington University and a long tenure at SUNY Downstate, where he performed his most important work. Furchgott shared the Nobel Prize in Physiology or Medicine with Louis Ignarro and Ferid Murad in 1998 for discoveries concerning NO as a signaling molecule in the cardiovascular system.

Within the first few years of high school, Furchgott knew he would like to be a scientist. His studies were primarily in biochemistry and physiology. His early work concerned the structure and function of proteins and red blood cell membranes. He did graduate work at Cold Spring Harbor where he learned a more quantitative approach to biology, and worked at Cornell University after being awarded his PhD at Northwestern. He stayed at Cornell from 1940 to 1949. The practical needs of the war years turned his interests toward circulatory shock and the cardiovascular system. He then began his groundbreaking work with isolated smooth muscle preparations. He moved to Washington University in 1949 where he worked with Oliver Lowry from 1949 until 1956. For Furchgott, this was a time of great interdisciplinary activity between biochemistry, physiology, and pharmacology. In 1956, he moved to Brooklyn (SUNY) where he has remained ever since. In May 1978, an accidental finding as a result of a technician’s error changed the course of research in his laboratory and led to the seminal discovery relating to endothelium-derived relaxing factor (EDRF).15 Prior to his Nobel award-winning work, he had become a smooth muscle pharmacologist, and studied sympathetic postganglionic denervation, and how specific drugs potentiate the response of effector organs. He studied a large number of receptor theories and mechanisms, and published a classification of adrenoceptors, differentiating them by pharmacological procedures.

Louis J. Ignarro

Louis Ignarro (Figure 9) was born in 1921 in Brooklyn. He received his bachelor’s degree in Pharmacy from Columbia in 1962, and was granted in Physiology or Medicine in 1998 with Furchgott and Murad. Following his training at Minnesota, which he considered the best pharmacology department in the country, Ignarro left for NIH where he studied the chemistry of β-adrenergic receptors. Here he worked with such luminaries as Brodie and Axelrod. He went from NIH to Geigy, where he took an interest in cyclic GMP, moving to Tulane in 1973 as an Assistant Professor of Pharmacology. The study of cGMP led to work on blood vessels, nitroglycerin, and eventually nitric oxide, that allowed Ignarro to elucidate the mechanism of nitroglycerin as a vasodilator, and how NO activates guanylate cyclase.16 In 1985, Ignarro moved to UCLA. In the summer of 1986, he and Furchgott presented the results of experiments demonstrating that EDRF was NO at a small conference on vascular biology held at the Mayo Clinic organized by Paul Vanhoutte. Ignarro recognized that the naturally occurring physiological neurotransmitter involved in the penile erectile response in mammals was NO released from nerves. He also distinguished himself as an outstanding classroom teacher, being awarded 10 Golden Apple awards at UCLA.

Paul Vanhoutte

Paul Vanhoutte, (Figure 10), was born (1940) and educated in Belgium. He held a variety of tenured positions at the University of Antwerp (1973-1981), the Mayo Clinic (1981-1989), and Baylor College of Medicine (1989-1995), and interacted with American and European specialists in biomedical science. Vanhoutte studied smooth muscle pharmacology extensively during his career. During his tenure as Director of Discovery Research at
Servier (1995-2004), he supervised the discovery and preclinical development of drugs designed for the treatment of cardiovascular diseases, diabetes, obesity, central nervous system disorders, cancer, and osteoarthritis. His research interests are in cardiovascular pharmacology and therapeutics, in particular, endothelium-dependent relaxation, hyperpolarization, and contraction. His major scientific contribution has been to appreciate and analyze the importance of endothelial cells in the control of the underlying vascular smooth muscle in health and disease, and to highlight the complexity of that regulatory balance.

**Robert Lefkowitz**

Robert Lefkowitz, (Figure 11), born in 1943, is a graduate of the prestigious Bronx School of Math and Science in New York and is currently Duke Professor of Biochemistry at Duke University. His contributions to our understanding of the biochemistry and molecular biology of the β-adrenoceptor are monumental. In a series of important papers, Lefkowitz and colleagues described the structure, function, and mechanism of activation and desensitization of the adenylate cyclase–coupled β-adrenergic receptors. Since β-adrenergic receptors are the primary myocardial targets of the sympathetic nervous system, this work carries special significance for cardiologists. Lefkowitz demonstrated posttranslational molecular modifications of the human β2-adrenergic receptor, pointing out the uniqueness of the molecule, which has no introns to be spliced out during its biochemical construction. Such observations have implications for evolitional theory, and their importance extends well beyond the information used for drug development.

**CONCLUSION**

The road to success in the study of autonomic biology is crowded with Nobel laureates who made seminal contributions to this difficult, but exciting field. It is also a textbook example of how the roots engendered the trunk and the branches of the tree; eg, how thoughtful observations using whole animal preparations led first to the discovery of effector molecules, and ultimately to an understanding of the cellular signaling systems that mediate critical biologic responses. As with many scientific disciplines, it took time to establish the nomenclature, which to some extent held up early progress. Clarity was brought to the field by the development of new techniques and methodologies. Today, all this important work has come to fruition in the form of a much more precise understanding of the interface between molecules such as NO and smooth muscle biology. Much of this work has also led to an appreciation of the endothelium as the body’s largest organ. It is likely that new drugs and therapies will be targeted to specifically enhance the production of NO and diminish nitrosative stress.

**REFERENCES**

1. Langley JN.
On the union of cranial autonomic (visceral) fibers with the nerve cells of the superior cervical ganglion.
*J Physiol.* 1898;23:240-270.

2. Gaskell WH.

3. Elliot TR.
On the action of adrenaline.
*J Physiol* (Lond.). 1904;31:20–21.

4. Dale HH.

5. Cannon WB, Rosenblueth A.

6. Ahlquist RP.

7. Burstock G.
Do some nerve cells release more than one neurotransmitter? *Neuroscience.* 1976;1239-1248.

8. Sharpey-Schafer EP.
Mechanism of acute hypotension from fear or nausea. 
BMJ. 1958;1:878-880.

10. Sharpey-Schafer EP, Ginsberg J. 
Humoral agents and venous tone: effects of catecholamines, 5-hydroxytryptamine, histamine, and nitrates. 

11. Sharpey-Schafer EP. 
Venous tone: effects of reflex changes, humoral agents and exercise. 

Postural changes in the peripheral blood flow of normal subjects with observations on carotidal fainting reactions as a result of tilting, the lordotic pressure, pregnancy and spinal anesthesia. 

13. Ahlquist RP. 
Adrenergic receptors and others. 

14. Vane JR, Anggard EE, Botting RM. 
Regulatory functions of the vascular endothelium. 

15. Furchgott RF, Zawadzki JV. 
The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. 

16. Ignarro LJ. 
Nitric oxide: a novel signal transduction mechanism for transcellular communication. 

17. Lefkowitz RJ. 
β-Adrenergic receptors: recognition and regulation. 

See also: 
Endothelium. 
Dialogues Cardiovasc Med. 1998;3(No. 4): 185-244 (entire issue). 
Kinin Receptors and Endothelium-Dependent Responses. 
Endothelium-Dependent Contractions. 
Cardiac Surgery: from a Stabbing in the Chest to the Artificial Heart

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The tree of cardiac surgery emerged from seeds that were sown a mere century ago when effective means to manage cardiac trauma and the advent of reliable methods of pulmonary ventilation permitted open-chest operations. Initial successes led to early surgical attempts to correct or palliate “approachable” lesions such as mitral stenosis and patent ductus arteriosus with the heart still beating. The need to stop the heart in order to do more elaborate repairs stimulated seminal work on hypothermia and the landmark development of cardiopulmonary bypass, the two golden keys that opened the door to the remarkable accomplishments of contemporary cardiac surgery, epitomized by cardiac transplantation—severely restricted due to the continued shortage of donor hearts—and intensive efforts to develop a reliable permanent total artificial heart.

Applying the “tree metaphor” to the topic of cardiac surgery perhaps first conjures up a vision of the tools needed for “invasive” tree husbandry: axe, saw, pruning knife, secateur, and others. One way this topic might have been approached is therefore from the technological side, describing the increasing sophistication of techniques and procedures and implements. Instead, I have chosen a somewhat (though not entirely) different approach that is more attuned to the clinical point of view that characterizes Dialogues: I have attempted to show how the various pathological situations themselves influenced surgical technique, and how surgery was above all a matter of urgency. There is indeed a logical progression from the immediate seminal threats posed by trauma and valvular disorders (the latter having triggered the transition from closed-chest surgery to open-heart surgery), before surgical technique branched out—and continues branching out—toward the entire range of pathological situations in which it has a vital role to play.

The Roots

Trauma

It is ironic that trauma should have contributed so much to the development of cardiac surgery. The latter had its halting beginning in 1896 when Ludwig Rehn of Frankfort successfully repaired a right ventricular stab wound. Although Rehn’s operation was not the first attempt, it was his landmark report of success that moved cardiac surgery into the realm of the possible.1

Ventilatory control

The primary problem that delayed progress in thoracic cardiac surgery was the lack of an effective means of avoiding the adverse consequences of pneumothorax. The development of intratracheal insufflation by Meltzer and Auer in 19092 therefore permitted future cardiothoracic operations by maintaining ventilatory exchange and expansion of the lungs.

Internists and surgeons

Following Rehn’s report, several internists suggested that mitral stenosis might be relieved by surgery. One of them, Sir Thomas Lauder Brunton (Figure 1, next page), sparked a storm of controversy with his 1902 Preliminary note on the possibility of treating mitral stenosis by surgical methods, published in The Lancet.3 Though the time was wrong, Sir Thomas’ suggestion was right and ultimately would come to fruition. Two decades would pass until the surgical relief of mitral stenosis again would be considered. At Boston’s Peter Bent Brigham Hospital, the

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distinguished physician Samuel A. Levine, defying Sir James Mackenzie’s view that it was the myocardium and not the narrowed valve that was the dominant problem, collaborated with Elliot C. Cutler, the Peter Bent Brigham Hospital surgical chief, who, in May 1923, successfully operated on a 12-year-old child with mitral stenosis. Utilizing a knife inserted via the left ventricle, Cutler incised the mitral valve with the intent of creating an acceptable degree of mitral regurgitation. Despite its apparent success, Sir James caustically wrote Dr Levine:

What a foolish thing you have done. It doesn’t matter that the patient lived. You, of all physicians, should know that patients with mitral stenosis are in trouble primarily because of their sick myocardium and not because of the narrowed valve orifice.

Cutler subsequently performed six additional operations; all six patients succumbed. In retrospect, a dominant factor in the deaths was the misguided hypothesis that mitral regurgitation was a more readily tolerated lesion than mitral stenosis. Only two years after Cutler and Levine’s report, the principles upon which contemporary mitral stenosis surgery are based were established by Henry S. Souttar, in London, in a landmark operation he performed in May of 1925 on a 19-year-old girl. Of importance, endotracheal intubation was employed, which permitted transpleural exposure and facile left atrial entrance so that digital dilatation of the mitral stenosis could be performed. Although the patient recovered, Souttar never was referred another patient. He later wrote, “…the physicians declared that it was all nonsense and …the operation was unjustifiable.” However, in the light of history, Souttar’s operation was instrumental in orienting the future direction of valvular surgery.

**THE TRUNK AND BRANCHES**

**Early congenital cardiovascular disease surgery**

In the 1930s, as a consequence of increased use of endotracheal intubation, convenient access to the mediastinum and pleural spaces made surgery of congenital cardiovascular disease possible. Patent ductus arteriosus ligation was first suggested by the Boston surgeon John C. Munro in 1907, but he was unable “to inspire the pediatric specialist with my views.” Three decades later, in 1938, at Boston’s Children’s Hospital, Robert E. Gross successfully ligated the patent ductus arteriosus in a 7-year-old girl. He also developed a method of coarctation excision with aortic reanastomosis, which was reported in 1945, as was an identical operation independently developed in Sweden by Clarence Crafoord. Experiments that “failed” were seminal in the development of the shunt operation to palliate tetralogy of Fallot. In 1938, Alfred Blalock, in Nashville, Tennessee, conducted experiments in which he was unable to produce an experimental model of pulmonary hypertension in dogs by increasing pulmonary blood flow through a subclavian artery–to–pulmonary artery shunt. After Blalock had been appointed chairman of surgery at Johns Hopkins, his colleague, the renowned pediatric cardiologist Helen B. Taussig, suggested that the “failed” shunt would be “all that was necessary for the cyanotic child.” History was made! In November 1944, Blalock successfully performed his first “blue baby” operation on a severely cyanotic infant.5

**World War II: impact on cardiac surgery**

In 1944, Lieutenant Colonel Dwight E. Harken, and colleagues, began a series of 134 operations in which foreign bodies were removed from the heart and great vessels. Remarkably, there were no deaths. Carried out before the era of cardiopulmonary bypass, Harken’s experience was a landmark. Precise operative management, endotracheal anesthesia, use of whole blood, the recently available penicillin, and skilled postoperative management constituted the elements of success. Moreover, Harken anticipated that these methods could be utilized in a postwar surgical attack on heart disease.

**Closed cardiac surgery after World War II**

The end of World War II coincided with resurgent attempts to attack mitral stenosis surgically. In 1948, within the space of 13 weeks, Charles Bailey, Philadelphia; Dwight Harken, Boston; and Russell Brock, London—each operating without knowledge of the others’ activities—had independently replicated Souttar’s operation and made modern intracardiac surgery a reality.6,7 By establishing an operation for mitral stenosis, in which a finger inserted through the left atrial appendage of...
the beating heart was used to dilate the valve, these pioneers opened the door to progress in the management of other stenotic and regurgitant valvular lesions. Performed largely with digital guidance, these early operations often were more ingenious than effective. In September 1952, Charles Hufnagel successfully implanted a self-contained ball valve (Figure 2) in a patient with severe aortic regurgitation. Since cardiopulmonary bypass was not yet available, Hufnagel inserted the valve in the descending thoracic aorta. While the hemodynamic result was suboptimal, the operation was the first instance of complete prosthetic valve implantation in man.8 The ball-valve prototype became the design for valves employed in the open-heart era.

The open-heart surgery era

Hypothermia

Despite the ingenuity of closed cardiac operations, management of more complicated lesions clearly required direct vision of the interior of the heart. Because only brief intracardiac exposure (2 to 3 minutes) would be possible with normothermic vena caval occlusion, the use of hypothermia to prolong this period was explored in the late 1940s by Wilfred Bigelow and his colleagues in Toronto (Figure 3). They documented in animals that hypothermia reduced total body oxygen consumption pari passu with temperature drop,9 seminal data that made possible the first direct vision repair of pulmonary valve stenosis and atrial septal defects, in 1952.

Cardiopulmonary bypass

On May 6, 1953, a groundbreaking event in cardiac surgery occurred when John H. Gibbon, utilizing cardiopulmonary bypass successfully closed an atrial septal defect in an 18-year-old girl (Figure 4). The idea for this technique had its origin in 1931 when, as a research fellow at the Massachusetts General Hospital, Gibbon saw the futility of an unsuccessful pulmonary embolectomy. Nineteen years of research preceded Gibbon’s success, much of the effort having been conducted with his wife, Mary. Her memories of the development of the heart-lung machine have been recorded by Schumacker10 and Eloesser.11 As noted by Eloesser:

Gibbon’s idea and its elaboration took their place among the boldest and most successful feats of man’s mind. Not a Deus ex machina, but a machina a Deo...

Heparin, which was the sine qua non in Gibbon’s research, had been discovered in 1915 by Jay McLean, a student awaiting entrance to Johns Hopkins Medical School. In 1933, Charles Best and his colleagues, in Toronto, succeeded in purifying heparin. It was Best who generously shared their heparin with Gibbon so that he could proceed with his research.12 After visiting Gibbon, John W. Kirklin and his colleagues constructed an improved version of the Gibbon pump-oxygenator and on March 23rd, 1955, successfully performed their first intracardiac operation, the beginning of what would become one of the two pre-

Figure 2. The Hufnagel ball-valve prosthesis, which was implanted in the descending thoracic aorta. Nylon rings secured the valve to the aorta.

Figure 3. Wilfred G. Bigelow (born 1913), whose work on hypothermia was fundamental in advancing the entire spectrum of cardiac surgery. From the Canadian Medical Hall of Fame. All rights reserved.

Figure 4. John H. Gibbon (1903-1973), who was the first to successfully perform an open-heart operation, on May 6, 1953, with his heart-lung machine that made the procedure possible after two decades of research. © The National Library of Medicine.
eminent programs in open heart surgery—both in Minnesota. Beginning in August of 1954, C. Walton Lillehei and colleagues performed their first open-heart operation with parabiotic use of a parent as an oxygenator, thereby making possible intracardiac operations in children. The method was highly successful, but the possibility of donor complication and limitation of the method to pediatric cases impelled Lillehei to assign a research fellow, Richard DeWall, to the development of a pump-oxygenator. DeWall’s success was aided by the earlier work of Leland Clark and colleagues who had developed a bubble oxygenator in 1950 with effective debubbling capability. Beginning on May 13, 1955, it was DeWall’s bubble oxygenator that made possible Lillehei’s extraordinary cardiac surgical program. In 1944, Willem Kolff and T. J. Berk reported on their experience with a hemodialysis unit, which they had constructed from a washing machine. They noted that venous blood entering the dialyzing tubes emerged arterialized, an observation that was to have long-ranging implications for it presaged the future development of the membrane lung by Kolff and others. The findings of William Lee and colleagues, in 1961, were an impetus for membrane lung development. They documented the adverse effect of denaturation of plasma proteins and release of fat emboli by bubble oxygenators. Today’s low-prime, efficient, and disposable membrane lung plays a dominant role in clinical cardiopulmonary bypass.

**Perfusion hypothermia**

The combined use of hypothermia and cardiopulmonary bypass—perfusion hypothermia—is routinely employed in the performance of complex intracardiac and aortic operations. Perfusion hypothermia was made possible by the contributions of Bigelow and two others. Unaware of the Bigelow studies in the late 40s, which were then unpublished, Ite Boerema and colleagues, in Amsterdam, carried out cooling and rewarming studies in dogs through an arteriovenous shunt utilizing an extracorporeal heat exchanger. In the 1950s, Frank Gollan and colleagues, utilizing a blood oxygenator that incorporated a heat exchanger, documented that profound perfusion cooling and rewarming could be accomplished with survival of the animal (Figure 5). Gollan utilized Ringer’s solution to prime the cardiopulmonary bypass unit, a hemo-dilution concept that had made survival possible in dogs cooled as low as 1.5˚C and provided the basis for the protocol employed today in which perfusion hypothermia permits a safe period of circulatory arrest and a bloodless surgical field.

![Figure 5. Frank Gollan's data on experimental cooling and rewarming, utilizing a pump-oxygenator with a heat exchanger as a component of the extracorporeal circulatory system. Reprinted from reference 14: Gollan F et al. Studies on hypothermia by means of a pump-oxygenator. Am J Physiol. 1952;171:331-340. Copyright © 1954, American Physiological Society.](image)

**THE LEAVES AND FRUITS: CONTEMPORARY CARDIAC SURGERY**

Myocardial protection

Two requirements during intracardiac surgery are maintenance of myocardial integrity and a bloodless operative field. Efforts to accomplish these goals have been comprehensively reviewed by Hearse, Brain-bridge, and Jynge. In 1955, Dennis Melrose and colleagues made a vital contribution in approaching the goal of direct vision cardiac surgery when they arrested the heart with potassium citrate. Elective cardiac arrest was soon abandoned because of myocardial damage, and it would be years until it would again be explored. In the interim, the earlier work of Bigelow et al (1950) provided the basis for cooling the heart by perfusion of the aortic root (Gott, Cross, 1957) and topical cardiac cooling (Shumway, 1959). In the 1960s, chemical cardioplegia was reexamined by a number of German investigators: Hölscher, Bretschneider, and Kirsch and colleagues, each group having developed different formulations that were utilized clinically as early as 1964. In London, at the Rayne Institute at St Thomas’ Hospital, studies involving David Hearse, a laboratory scientist and one of the two coeditors of this journal, initiated a series of studies, in association with a cardiac surgeon, Mark Brainbridge, which resulted in a chemical cardioplegia formulation that retained an essentially extracellular ionic character. Introduced clinically in 1975, the cold (4˚C) chemical cardioplegia formulation has been widely adopted. A number of significant contributions were also made by Gerald...
Buckberg and colleagues in Los Angeles, including the use of blood as the vehicle for infusing the chemical cardioplegia, thereby improving buffering and oxygenating capacities.

Open cardiac correction in infants

In the early years of cardiopulmonary bypass, mortality was high in infants undergoing open intracardiac surgery. An essential contribution was made in 1963 by Horiiuchi et al when they reported excellent survival in infants less than 1 year of age utilizing only 25°C surface cooling with the procedure performed under total circulatory arrest. With improved heat exchangers, cardiopulmonary bypass played an increasingly prominent role (Hikasa, 1967; Barratt-Boyce, 1970). Current methods employ only cardiopulmonary bypass for both cooling and rewarming and permit both neonates and infants to undergo intracardiac operations with remarkably high survival rates.

Direct vision valve replacement

In 1960, using a valve design based on Hufnagel’s ball valve concept, Dwight Harken was the first to succeed in performing aortic valve replacement with subcoronary implantation of a caged ball valve prosthesis designed by an engineer, W. Clifford Birtwell. In the same year, utilizing Hufnagel’s concept, Albert Starr successfully performed mitral valve replacement with a caged ball valve prosthesis designed by another engineer, Lowell Edwards. Within several years, the latter valve was widely utilized. By the end of the 60s, other prostheses (leaflet, tilting disc, etc) had been utilized clinically, but serious design flaws frequently required urgent prosthesis removal and replacement. Whatever the design, the “bête noire” of all mechanical prostheses has been thromboembolism, even despite the use of warfarin. In 1955, D. W. Gordon Murray, Canada, inserted an aortic homograft in the descending thoracic aorta of a patient with aortic regurgitation, a procedure that presaged later homograft use in subcoronary aortic valve replacement.

While remarkably effective, the availability of homograft aortic valves was a problem that quickly led to the exploration of xenografts. In 1964, Carlos Duran and Alfred Gunning, in Oxford, performed the first clinical aortic valve replacement with a stent-mounted freeze-dried xenograft porcine valve bioprosthesis. A year later, Jean Claude Binet, Duran, and Alain Carpentier, in Paris, reported their early experience with formalin-preserved frame-mounted porcine xenograft valve bioprostheses. However, within a few years, the formalin-preserved xenograft valve bioprostheses failed and had to be replaced. It was only when Carpentier found that gluteraldehyde fixation and preservation would provide long-term durability, that the use of stent-mounted xenograft valve bioprostheses rapidly spread.

Direct vision repair

Whenever possible, valve repair is always preferable to replacement. Although others had described repair methods, it was not until Carpentier’s operative descriptions involving leaflet and chordal restructuring and annular stabilization with prosthetic annuloplasty rings that predictable valve repair became a reality.

Myocardial revascularization

In 1910, Alexis Carrel suggested the possibility of coronary artery bypass in patients with angina. Fifty years would pass before Carrel’s suggestion would become a reality. It was only when coronary arteriography was discovered by accident at the Cleveland Clinic by F. Mason Sones in 1958 that a rational basis for coronary artery bypass was established and initiated by Donald Effler and Rene Favoloro at that institution.

Sequelae of myocardial infarction

Surgery has played a selective role in managing acute sequelae of myocardial infarction (ventricular septal and papillary muscle rupture). Excision of a left ventricular aneurysm—a more chronic complication of myocardial infarction—was first performed before cardiopulmonary bypass by Bailey in 1955 and 3 years later by Denton Cooley, in Houston, employing cardiopulmonary bypass. An important contribution was reported in 1985 by Adib Jatene, in Brazil, when he combined left ventricular aneurysm excision with reconstruction of the ventricular cavity to reduce volume overload.

Pacemakers

During their hypothermia studies, Bigelow, Callaghan, and Hopps devised a pacemaker with electrodes positioned either transvenously or by direct suture to the heart. Their effort was shared with Paul Zoll and colleagues, in Boston, who developed and clinically utilized a unit with externally applied electrodes (1952). Development of transistors (1950s) permitted totally implantable pacemakers (Senning, Sweden, and Chardack, USA). A major advance was the successful transvenous positioning of pacing electrodes by Furman and Robinson (1958). Continued progress has resulted in a spectrum of physiologically based atrioventricular pacing devices.
**Arrhythmia surgery**

In 1967, Dirk Durrer and colleagues, Amsterdam, made a major contribution to the understanding and management of arrhythmias when they documented by intraoperative mapping in patients with Wolff-Parkinson-White syndrome that atrioventricular conduction occurred over an accessory pathway. Employment of Durrer’s mapping approach permitted operative management of Wolff-Parkinson-White (Dwight McGoon, Will Sealy, USA). In 1982, James Cox, USA, performed the first cryoablation for reentrant arrhythmias, which evolved into the maze operation to control atrial fibrillation or flutter.

**Thoracic aortic aneurysms, dissections, and vascular grafts**

The idea of a surgical approach to aortic aneurysms was first implemented in 1902 by Rudolph Matas, in New Orleans, when he sutured an aneurysmal sac from within. Eight years later, Alexis Carrel hypothesized that aortic aneurysms could be excised and replaced “by a vascular [graft] transplantation...” It was not until 1948 that Carrel’s concept would become a reality, when Robert Gross and colleagues replaced resected aortic segments with homografts. Contemporary management of aortic aneurysms and dissections (resection and replacement) began in 1953 when Michael DeBakey and Denton Cooley, in Houston, reported successful resection and homograft replacement of a descending thoracic aortic aneurysm. Homograft supply problems made the search for a synthetic vascular graft essential. An important advance was made in 1952 by Arthur Voorhees and colleagues, in New York, when—by accident—they found that cloth could be utilized to fabricate vascular grafts. The availability of both synthetic vascular grafts and profound perfusion hypothermia has made possible excision and replacement of ascending, transverse arch, and thoracoabdominal aortic aneurysms and dissections (Borst et al, 1964; Griep et al, 1975).

**Heart, heart-lung transplantation**

Cardiac transplantation has been established as an effective method in managing patients with end-stage cardiac failure. Research began with the seminal experiments of Alexis Carrel and Charles Guthrie in 1905 when they attempted heterotransplantation of the heart and heart and lung in animals. In 1933, Frank Mann and colleagues, at the Mayo Clinic, performed heterotopic cardiac transplantation and concluded that rejection was “due to some biological factor...” It would be a decade (1944) until Peter Medawar proved that rejection was due to an immunological reaction. Shumacker et al has emphasized the many contributions made by the remarkable Soviet investigator, Vladimir Demikhov, who first carried out heterotopic transplantation of the heart in 1940, and heart and lung in 1946, but his prodigious efforts became widely known only when his 1960 monograph, *Experimental Transplantation of Vital Organs*, was translated into English (1962). The cardiac transplantation method employed today was developed at Stanford by Richard Lower and Norman Shumway in 1960. According to Shumway, the idea evolved from their myocardial protection (topical cooling) experiments. After one hour of aortic cross-clamping on cardiopulmonary bypass, they decided to remove the heart and then resuture it into position. Subsequently, they utilized the hearts of donor dogs and performed allotransplants, a remarkable feat that was carried out before chemical immune suppression was available. Clinical cardiac transplantation began almost four decades ago (Barnard, Shumway). Although early mortality was high because of rejection, efforts—primarily by Shumway’s group and Keith Reemtsma, at Tulane—improved the ability to diagnose (endomyocardial biopsy) and immunologically manage this devastating complication. The first successful clinical heart-lung transplant was performed by Bruce Reitz and the Stanford team in 1981, thirty-five years after the first experimental heterotopic heart-lung transplant by Demikhov.

**Left ventricular assist devices, artificial heart**

In 1954, Clarence Dennis’ group, in Brooklyn, first employed a pump-oxygenator to support a nonsurgical patient in severe cardiac failure. In 1961, the concept of afterload reduction utilizing “arterial counterpulsation” was described by Harken et al and further developed into the intra-aortic balloon pump by Moulopoulos et al in Cleveland. In the early 60s, Spencer and DeBakey and colleagues reported on the use of a left ventricular assist device in post-cardiac surgical patients. In recent years, left ventricular assist devices have been utilized as bridges to cardiac transplantation. Because of continued shortage of donor hearts, left ventricular assist devices are now being utilized for long-term mechanical support. The development of the artificial heart was first explored by the remarkable Vladimir Demikhov (1937). Two decades later (1958) Willem Kolff and his colleague, Tetsuzo Akutsu, reported on their first total artificial heart implantation in an animal. The first clinical implantation of a total arti-
ficial heart was carried out in 1982 by Kolff’s group in Utah. Total artificial hearts also have been employed as bridges to cardiac transplantation (Cooley, Pierce, Copeland), but a reliable permanent total artificial heart is a goal that has yet to be accomplished.

RETROSPECT AND PROSPECT

The cardiac surgical tree has grown remarkably! It has been eight decades since the first mitral valve operations were performed by Elliott Cutler and Henry Souttar, and five decades since the first successful open-heart operation by John Gibbon employing a heart-lung machine. Advances since those days have been breathtaking, but the past surely is prologue to another era, which, in time, will bring unimaginable approaches to the management of cardiovascular disease.

So many worlds, so much to do, so little done, such things to be.

Alfred Lord Tennyson

REFERENCES

1. Rehn L.
Über penetrierend Herzwunden und Herznaht [Penetrating heart wounds and suture of the heart].

2. Meltzer SJ, Auer J.
Continuous respiration without respiratory movement.

3. Brunton L.
Preliminary note on the possibility of treating mitral stenosis by surgical methods.

4. Gross RE, Hubbard JP.
JAMA. 1939;112:729-731.

5. Blalock A, Taussig HB.
The surgical treatment of malformations of the heart in which there is pulmonary stenosis or atresia.

6. Johnson SL.

7. Westaby S, Bosher C.

8. Hufnagel CA, Harvey WP.
Bull Georgetown Univ Med Ctr. 1952;6:60-61.

9. Bigelow WG, Lindsay WK, Harrison RC, Gordon RA, Greenwood WF.
Oxygen transport and utilization in dogs at low temperatures.

10. Shumacker HB Jr.

11. Eloesser L.
Milestones in chest surgery.


Denaturation of plasma proteins as a cause of morbidity and death after intracardiac operations.

14. Gollan F et al.
Studies on hypothermia by means of a pump-oxygenator.

15. Gollan F, Tysinger DS Jr, Grace JT, Kory RC, Meneely GR.
Hypothermia of 1.5˚C in dogs followed by survival.

16. Hearse DJ, Brainbridge MV, Lyne P.

17. Carpentier A.
Cardiac valve surgery: the French correction.

18. Voorhees AB Jr, Jeretzkli A, Blakemore AH.
The use of tubes constructed from Vinyon “N” cloth in bridging arterial defects. A preliminary report.


20. Spencer FC.
Intellectual creativity in thoracic surgeons.


22. Akutsu T, Kolff WJ.
Permanent substitutes for valves and hearts.

See also:
Preconditioning.
**GENETICS AND MOLECULAR BIOLOGY:**
from a monastery garden to rebuilding the heart

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The advent of molecular cardiology stems from advances in knowledge of genetics spanning over 400 years. The seeds of what was to grow into a forest of knowledge were planted by Harvey, Leeuwenhoek, and Virchow. Mighty trunks arose from the works of Darwin, Galton, and Gregor Mendel (pea breeding experiments). Branches started shooting out with experiments on the fruit fly (Drosophila) and the works of Morgan, Garrod, Fisher, Haldane, and Penrose. After that, discoveries simply bloomed, culminating in human molecular genetics, the human genome projects, and the beginnings of the postgenomic era in which we are just starting to find out how the whole thing works. In this forest, molecular cardiology is but one tree, yet one that holds enormous promise for the future.

If I have seen further it is by standing on the shoulders of giants

*Sir Isaac Newton (1642-1727)*

**A**lthough Isaac Newton’s modest statement in a letter to Robert Hooke has been reinterpreted by modern historians as a veiled insult to his colleague, it is certainly pertinent to the difficult task of trying to trace the origins of the applications of genetics and developmental biology to modern cardiology. Indeed, the arboreal metaphor requested by the Editor is almost impossible to sustain, given the enormous forest of multidisciplinary knowledge that has formed the basis for our current understanding, limited as it is, of the function of our genomes in health and disease. But after all, Ramon Llull, the “enlightened doctor” whose *Arbor Scientiae*, across the centuries, is providing the framework for this issue of *Dialogues*, devised not one, but sixteen “trees of knowledge,” as I discovered when perusing his biography. Well did he realize that knowledge was a forest, and so, after all, I feel quite comfortable writing this review under the Magister’s benevolent gaze.

**THE EARLY SEEDS**

In his investigation of the origins of classical genetics, Carlson describes some of the seeds that led to this field becoming an interdisciplinary science at the beginning of the 20th century. Starting in 1651 with William Harvey’s identification of the egg as the basis of life, “ex ova omnia,” he describes Robert Hooke’s account (in his book *Micrographia*) of how cork is composed of trillions of cells, and Antoni van Leeuwenhoek’s descriptions of spermatozoa in his semen. Later, these discoveries were to lead Mathias Schleiden and Theodor Schwann to develop cell theory and Rudolf Virchow to propose that all cells arise from preexisting cells. However, during the 17th and 18th centuries, views on the mechanisms of embryological development were incompatible with any logical theory of heredity.

**THE TRUNKS:**
THE BIRTH OF GENETICS IN THE 19TH CENTURY

Three unrelated events in the middle of the 19th century, two of them in the same year, together with an increasing understanding of the properties of cells, were to revolutionize biology in general and the understanding of genetics in particular: on November 4th, 1859, the first edition of Charles Darwin’s *The Origin of Species* was published; on February 8th and March 8th, 1865, the Moravian monk Gregor Mendel (Figure 1) presented his studies entitled *Experiments in Plant Hybridization* to the Natural Science Soci-
ety in Brunn, now Brno, Moravia, and subsequently published them in the Society's proceedings; and in the same year an Englishman, Francis Galton, published two short papers entitled *Hereditary, Talent, and Character*. These events laid the ground for the understanding of how species have developed, the genetic mechanisms involved, and the practical applications of the science of hereditary for the study of human characteristics, and, later, inherited diseases. However, if we have to identify a “founder” tree, it must surely be Gregor Mendel.

Mendel spent most of his working life in the Augustinian Monastery in Brunn, combining religious duties with a passionate interest in science (*Figure 2*). Although sometimes depicted as a lonely monk whose hobby happened to be breeding flowers, he was in fact part of a lively scientific community in which animal and plant breeding, because of their commercial importance, were of major interest. He was stimulated to carry out his famous breeding experiments by observations on ornamental plants, for which he tried to breed new color variants by artificial insemination. In the end he selected peas for his experiments. As the result of studies carried out on some 28,000 plants between 1854 and 1863 he was able to formulate the way in which units of heredity, later called genes, are passed from generation to generation according to two simple mathematical laws. First, genes segregate; members of the same pair of genes, alleles, are never present in the same gamete, but always separate and are transmitted in different gametes. Second, genes assort independently; members of different pairs of genes move to gametes independently of each other. Or, to put it in a nutshell, alleles segregate; non-alleles assort.

Mendel's work was largely forgotten until it was rediscovered independently by several workers at the beginning of the 20th century. At first, it was the subject of great controversy, but thanks to strong protagonists, notably the English biologist William Bateson, it gradually came to be accepted. The word gene seems to have been first coined by a Danish botanist, Wilhelm Johannsen, in 1911. Apparently, he did not like the term unit character, which was becoming popular, and suggested instead the word gene, a shortening of pangenes which had been derived from Darwin's theory of pan-genesis. During the latter part of the 19th century, chromosomes were identified and it was suggested that they might be vehicles for genetic transmission.

Hence the scene was set for the development of the classical era of genetics, the exploration of Darwinian evolution and the understanding of the genetic basis for how it had come about, and the early beginnings of human genetics and its applications.

THE BRANCHES: CLASSICAL GENETICS AND THE BEGINNINGS OF HUMAN BIOCHEMICAL GENETICS

The period from the turn of the century up to the end of World War II was an extremely productive time for the development of genetics in general, and human genetics in particular. Although there are many branches, those that seem most relevant to the development of molecular cardiology are the breeding experiments with the fruit fly, *Drosa-*
phila, by Thomas Hunt Morgan, the first application of statistical methods to study the behavior of genes in populations, begun by Francis Galton in the late 19th century, and continued by Karl Pearson, Ronald Fisher, and “JBS” Haldane (always known as “JBS” to distinguish him from his famous father, “IB”) in England, and Sewall Wright in the United States, and the first description of inborn errors of metabolism by Archibald Garrod in England. The story of the development of genetics during this period is covered by Carlson1 and the early development of human and clinical genetics is described by Weatherall.3

The early studies of the Drosophila group worked out the true significance of sexual reproduction and meiosis. Although Mendel’s laws had dealt with the inheritance of a particular gene, Morgan’s group and Bateson in England pointed out that if two genes are on the same chromosome, and especially if they are close together, they will tend to be inherited together, the genes are then said to be linked. When the parental chromosomes become closely opposed at meiosis, crossing over of genes may occur so that the two characters determined by them will part in some of the offspring. These observations were the basis of the first maps of genes on chromosomes. Furthermore, Hermann Muller established that genes can change their structure—that is, undergo mutation—a process that can be speeded up under certain conditions, exposure of cells to radiation for example.

The first serious efforts to measure inheritability in human populations were made by Francis Galton, an English polymath who was born in the same year as Mendel. Having been left a large inheritance on the death of his father, which freed him from any need to earn a living, he spent his life traveling and making numerous important contributions to exploration and to the biological sciences. He became fascinated by how talent appears to run in families, particularly those of Lord Chancellors, and he was interested from the beginning in attempting to improve the human species by selective breeding. In this sense he was undoubtedly the father of the eugenics movement, which did so much damage to the name of genetics, particularly in World War II. His early studies were summarized in 1869 in his book, Hereditary Genius, a second edition of which was published in 1892. Although much of his thinking about genetics was confused because, unlike Mendel, he was most interested in traits that did not follow simple patterns of inheritance, he was, nonetheless, the initiator of quantitative human genetics at the turn of the century, those who followed him, Karl Pearson, Ronald Fisher and “JBS” Hal-dane, were later to lay the foundations of human population genetics. However, the main branch that was to establish genetics as an important part of clinical medicine stemmed from the work of the English physician Archibald Garrod (Figure 3), and led to the beginnings of an understanding of the biochemical basis of human genetic disease and, in the longer term, of how genes function.4 In June 1908, he delivered a series of lectures at the Royal College of Physicians, London, to be published in The Lancet later the same year. This work was extended and formed the basis for his famous book Inborn Errors of Metabolism, which described several rare diseases that, Garrod realized, with some prompting from William Bateson, were due to inherited defects in the body’s chemical pathways.

Garrod’s work, like that of Mendel, was ignored for many years. Its true value became apparent only after advances in biochemistry led to recognition of the importance of the genetic regulation of metabolic pathways. Indeed, it was not until the early 1940s that the elegant studies by the American scientists George Beadle and Edward Tatum on the bread mold Neurospora demonstrated that the primary action of a gene is to direct the production of a specific protein. In a lecture delivered in Stockholm in 1958 on the occasion of the award of the Nobel Prize to Beadle and Tatum, and in a generous tribute to the work of Garrod, the prize winners said, “In this long and round-about way, first in Drosophila and now in Neurospora, we have rediscovered what Garrod had seen so clearly many years before.”4

Genetics flourished in England during the first half of the 20th century. The work of Fisher, Haldane, and later Lionel Penrose established the
is needed to convert a piece of coded information into a string of amino acids, and, more importantly, to put them in the right order every time.

The first hint that DNA, discovered by Friedric Miescher in the mid-19th century, is the informational molecule came from the work of an English bacteriologist, Fred Griffith, who discovered that whatever causes virulence could be transferred between different strains of bacteria. The transforming factor was identified as DNA in a series of beautifully executed experiments by Oswald Avery, Colin MacLeod, and Maclyn McCarty, in the USA. The story of the extraordinary years that followed, during which the work of Avery and his colleagues was finally accepted and the structure of DNA was established by James Watson and Francis Crick (1953), has been told on many occasions. Over the next few years, the genetic code was deciphered, the cellular machinery whereby its information can be transferred from the nucleus to the cytoplasm by messenger RNA was determined, and the way in which the latter can act as a template for protein synthesis, was fully worked out.

Undoubtedly, the years that followed Watson and Crick’s seminal discovery were among the most exciting in the history of human biology. It was a period of the coming together of the remarkable discoveries in phage and microbial genetics with new technology for cloning and sequencing genes, and for starting to understand how they are regulated.

At the same time there was a much quieter and generally unsung revolution starting in the medical sciences. As mentioned earlier, up to the end of the World War II, genetics had virtually no impact on clinical medicine. Things changed quite dramatically during the 1950s and, whereas the early development of human genetics took place largely in the UK, the major developments in clinical genetics occurred in the USA. During the late 1950s, several departments of medical genetics were established, sometimes by those who had come to genetics almost by chance. For example, Victor McKusick at Johns Hopkins Hospital trained in cardiology and for some years led a schizophrenic existence between the arcane world of spectral phonocardiography and the study of the inherited disorders of connective tissue. It was undoubtedly his work on the latter conditions that led to the realization that medical genetics was here to stay. In 1957, he was invited by the Chairman of Medicine at Hopkins to develop a Division of Medical Genetics. At about the same time, Arno Motulsky established a similar department in Seattle, others rapidly followed.

By the late 1950s, remarkable progress had been made in clinical genetics. Many single-gene disorders had been defined at the protein level, a large number of syndromes associated with abnormalities in the number or structure of chromosomes had been delineated, and by twin studies and other indirect approaches some indication of the complex heritability of common diseases that did not follow a Mendelian pattern of inheritance had been characterized. But what was going on in the cell nucleus at the level of the genes themselves still remained a mystery, a situation that was soon to change dramatically.

The story of how clinical genetics moved into the molecular era provides yet another string of branches. A seminal event, and one which occurred in the distinctly nonarboREAL environment of a train journey,
was a conversation between Linus Pauling and William Castle on an overnight journey between Denver and Chicago in 1945. Castle told Pauling that he and his colleagues had noticed that the red blood cells of patients with sickle cell anemia have an unusual appearance when viewed under polarized light. As a protein chemist, Pauling was intrigued by this observation and realized that the changes that Castle had noted might mean that the defect in sickle cell disease is within the hemoglobin molecule. This turned out to be the case; in 1949, Pauling and his colleagues coined the term “molecular disease” to describe sickle cell anemia.\(^8\)

These findings were confirmed in 1956, when Vernon Ingram, a young protein chemist working in Cambridge observed that sickle cell hemoglobin differs from normal hemoglobin by a single amino acid substitution, valine for glutamic acid in one of the pair of peptide chains of globin, thus moving the story of gene action from Beadle and Tatum’s “one gene–one enzyme” to “one gene–one peptide chain.” The story of how scientists of diverse disciplines and backgrounds descended on the hemoglobin field in the late 1950s has been recounted recently.\(^9\) As a result, the genetics of hemoglobin and its disorders became extremely well characterized and was ready-made for the application of the technology of molecular biology which became available in the period after 1970. First, by molecular hybridization or Southern blotting (Figure 4),\(^10\) and later by cloning and sequencing of globin genes both in health and disease, a remarkable picture emerged of the molecular pathology of a group of common genetic diseases.

These early successes in human molecular genetics resulted from research in which the abnormal gene product was known and therefore in which it was possible to devise gene probes to study the gene in question. At first, it was difficult to imagine how it would be possible to define the molecular pathology for diseases about which nothing was known of the abnormal gene product. The discovery of restriction enzymes, enzymes that cut DNA at predictable base sequences, and the finding that there is remarkable individual diversity with regard to the base-structure of the genome, led to the concept of using restriction enzyme polymorphisms as potential linkage sites throughout the human genome. In studies of this kind, families were examined both for the presence of a particular restriction enzyme marker and for the disease or other trait that was being studied. If the disease and marker were on different chromosomes they would be found together as often as they were apart in different generations. On the other hand, if they were close together, independent assortment of this kind would not occur. After
establishing a linkage of this type, and by some ingenious genetic engineering, given the rather picturesque name of chromosome walking, it became possible to move from the marker towards the gene of interest. This unlikely activity, originally called reverse genetics, but later rechristened positional cloning, became one of the most important developments in molecular medicine. Its early successes included the discovery of the genes for muscular dystrophy and cystic fibrosis. Many other genes for the monogenic diseases were found in this way subsequently (Figure 5). Furthermore, it became clear that each of us is unique with respect to the structure of our DNA, a finding that led to the development of “DNA fingerprinting” (Figure 6).

With increasing knowledge about the location of genes on different chromosomes, it is not surprising that, with the development of increasingly rapid automated gene sequencing techniques, thoughts turned to the long-held dream of clinical geneticists that it might be possible to determine the complete sequence and, ultimately, a detailed map of the human genome. The first part of this remarkable achievement was completed in both private and public sectors in 2001.12,13

CARDIOLOGY IN THE MOLECULAR ERA

How has cardiology fared during this period of remarkable technological advance? Can we begin to talk about a new field of “molecular cardiology?”

The most impressive progress so far has been made in the elucidation of the molecular basis for Mendelian disorders that involve the cardiovascular system. Here, there is no difficulty in defining the seminal branch. The elegant series of experiments by Michael Brown and Joseph Goldstein14 on familial hypercholesterolemia were undoubtedly one of the most impressive examples of the application of modern cell and molecular biology to the study of human disease. The seeds had been sown by the recognition that this condition is characterized by a selective increase in the plasma level of one lipoprotein, designated low-density lipoprotein (LDL). Using cultured fibroblasts from homozygotes, Brown and Goldstein discovered the cell-surface LDL receptor and showed that familial hypercholesterolemia is caused by mutations in the genes specifying this protein. Later it was possible to purify the receptor protein, clone its cDNA and, by 1985, to isolate and characterize the particular gene involved. An analysis of the molecular pathology has disclosed that there are over 400 different mutant alleles responsible for hypercholesterolemia.
this condition, which can be classified into various subgroups depending on their effect on its complex functions, including recycling of the receptor. A great deal of progress has also been made in the analysis of other disorders of lipid metabolism, which have important implications for cardiovascular disease, particularly disorders of synthesis and secretion of lipoproteins, including the B apolipoproteins.15 As well as their intrinsic value in determining the molecular basis of important monogenic diseases, these studies are continuing to provide valuable insights into the pathogenesis of atheroma and, in particular, approaches to its management.

Studies of the molecular genetics of other Mendelian disorders, including hypertrophic and dilated cardiomyopathy, and arrhythmias such as the long QT syndrome, are providing extremely valuable information about the molecular pathogenesis and biochemistry of cardiac failure.16,17 Mutations of a variety of different genes have been implicated as the cause of familial cardiomyopathies (see, eg, reference 18), work that has also benefited from the use of animal models such as transgenic or knockout mice. Again, as well as their intrinsic interest, they have provided invaluable insights into some of the fundamental mechanisms of cardiac dysfunction. The rare Mendelian forms of hypertension or hypotension all appear to involve the renal pressure natriuresis mechanism that is implicated in essential hypertension, are providing new insights into the pathogenesis of atheroma and, in particular, approaches to its management.

In short, an analysis of Mendelian disorders involving the cardiovascular system at the molecular level has provided some valuable insights into both their pathogenesis, but also into disease mechanisms that may be active in the more common, multigenic forms of these conditions.

THE FUTURE

As we have progressed down the multiple trees, stems, and branches of the enormous forest of modern molecular genetics, it has become apparent that no medical discipline is an island and that we are entering a period of integrative biology in which extremely talented branches are generating what used to be viewed as individual trees. What is the future of cardiology in the post-genome era?

It has already been possible to produce databases that contain an annotated compendium of over 25,000 distinct cardiovascular-expressed genes.16 It appears that in many cases these genes form nonrandom clusters at particular chromosomal sites. Genetic linkage strategy has already been used to identify chromosomal loci linked to heart failure in mouse models. More recently, it has been possible, with the advent of microarray technology, to analyze many of the 25,000 or more genes that may be expressed in complex multifactorial conditions such as the failing heart. It seems likely that approaches of this kind will provide valuable information about the molecular pathophysiology of heart failure and other cardiovascular diseases and may, in the long term, offer new targets for therapy.

Much has also been made of the possibility of defining the genes involved in multigenic disorders like coronary artery disease, hypertension, diabetes, and other common killers of middle and old age. Since the genome is now plastered with linkage markers and single nucleotide polymorphisms (SNIPs), approaches using very large populations that have been carefully genotyped, combined with extensive linkage studies, may unveil some of the players in these complex diseases, that often reflect a variable degree of heritability combined with a large environmental component. While these approaches may bear fruit, at the moment they must be viewed with extreme caution, given the multiplicity of genes involved, the relatively low degree of heritability, and the extreme difficulty of defining human genotypes.

Another hope for postgenomic medicine is the individualization of therapy based on varying genetic response to therapeutic agents, a field that has attracted the formidable names of pharmacogenetics and pharmacogenomics.19,20 Of course, well-defined polymorphisms in the handling of drugs used in the treatment of cardiovascular disease, notably warfarin, have been known for many years and yet this knowledge is only now being applied in clinical practice. There is little doubt that polymorphisms of drug metabolism will be discovered more rapidly in the future, but whether this information becomes part of day-to-day clinical practice will depend on their frequency, the magnitude of their metabolic effects, the cost-effectiveness of testing for them, and the feasibility of carrying out these tests in a general hospital setting; much work is required before the era of personalized medicine is reached. In the long term, it may also be possible to identify individuals at partic-
ularly high risk for common cardiovascular diseases at a stage early enough so that, by environmental or other means, it may be feasible to reduce the likelihood of contracting the disease; this approach will require the development of a new specialty, genetic epidemiology.

At the moment it is impossible to anticipate how long all this will take, let alone how it will eventually affect day-to-day medical care. But one thing is sure: given the enormous biological complexity of sick people, genomic medicine, although it undoubtedly has enormous promise for the future, will not alter our clinical practice overnight.

REFERENCES


FURTHER READING


BLOSSOMS ON THE TREE OF CARDIOLOGY:
some predictions for the coming decade

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Medical history teaches us where we came from, where we stand in medicine at the present time, and in what direction we are marching. It is the compass that guides us into the future.
Sigerist H: "A History of Medicine"

The best of prophets of the future is the past.
Byron: Journal [January 28, 1821]
Past is prologue.
Shakespeare: “The Tempest”

This anniversary issue, which reviews the history of ten key areas of cardiology, documents how new understanding of cardiovascular medicine has narrowed the gap between the basic sciences and clinical practice. In the ancient world, when clinical observations were interpreted largely in a philosophical context, science had virtually no impact on patient care. Studies of pathological anatomy that began in the 16th century, along with Harvey’s description of the circulation in 1628, provided some explanations for cardiovascular disease, but these had virtually no clinical benefits for almost 300 years. It was not until the 20th century that invention of the electrocardiogram, developments in hemodynamic physiology, identification of the role of coronary disease in myocardial infarction, characterization of hypertension, discoveries in biochemistry and vascular biology, and other advances began to close the gap between bench and bedside. Practical applications included cardiac surgery, pharmacological agents tailored to correct pathophysiological abnormalities, risk factor modification, and new technologies for diagnosis and treatment. Basic science and clinical medicine moved even closer to one another in the late 1980s, when molecular biology made it possible to identify additional mechanisms of cardiovascular disease. Today, only a few years can elapse before a discovery identifies new ways to help the cardiac patient. The rapid pace at which we are now learning about cardiovascular disease and the increasing relevance of basic science to clinical practice continue historical processes described in this issue. This article projects these trajectories ahead to make a number of concrete predictions regarding cardiovascular medicine in 2016.

Keywords: hemodynamics; diagnosis; heart failure; hypertension; ischemic heart disease; atherosclerosis; electrophysiology; autonomic nervous system; surgery; genetics; molecular biology; prediction
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Dialogues Cardiovasc Med. 2006;11:157-167
This anniversary issue uses the analogy of a tree to trace the development of modern cardiology. Starting with the roots and trunk, each article describes the emergence of the major branches that support today’s rich foliage. In this concluding article, I use these contributions to draw lines from the past to the present and into the future to venture a few predictions as to which of today’s blossoms might yield the most luxuriant fruit.

Among the most remarkable features of the history told in this issue is the effectiveness with which cardiology has incorporated data and technologies from other fields of science. Looking back to the clinical observations that lie at the root of Western medicine, the initial effort was to identify specific syndromes. However, ancient medicine was based on a mixture of empiricism and philosophy with virtually no understanding of pathophysiology, so that these efforts had little success. Cardiology did not begin to advance until the 17th century, when increasing use of human dissection, coupled with Harvey’s description of the circulation, made it possible to identify the hemodynamic abnormalities associated with anatomi cal syndromes caused by rheumatic heart disease, then the major cause of cardiac death. However, more than 300 years were to pass before surgical treatment of these structural abnormalities became possible. Bacteriology, which emerged in the late 19th century, made it possible to identify the causes of infective endocarditis, and later of rheumatic fever. Advances in public health, notably improved sanitation, began to eliminate rheumatic heart disease in the early 20th century; these efforts were aided by the discovery of antibiotics, which also made it possible to prevent and treat infective endocarditis. Epidemiological data regarding the geographic distribution of atherosclerosis and its correlation with diet, smoking, diabetes, and hypertension, along with studies of lipid transport and metabolism, identified treatable risk factors that helped make it possible to reduce ischemic heart disease mortality more than 50% from its mid-20th-century peak. Studies of autonomic physiology led to advances in pharmacology that had a major impact on the treatment of hypertension, while discoveries in cardiac electrophysiology brought new understanding to the pathophysiology of arrhythmias. Newly discovered principles of physics came to be used for cardiac diagnosis at the beginning of the 20th century, when x-rays were used to image the heart and the string galvanometer to record the electrocardiogram. More recent applications of ultrasound, radioisotope decay, magnetic resonance, and other technologies, along with developments in electronics and computer science, have made this technology an essential feature of modern cardiology. Extending this list is not necessary to support my first—and most general—prediction, that cardiology will, over the next ten years, continue to incorporate new discoveries in science and technology to improve the diagnosis and treatment of heart disease. I cannot guess what these areas will be except to suggest that, as in the past, progress will come from unexpected directions.

HEMODYNAMICS

Michael Webb-Peploe’s article highlights the value of interventional approaches to coronary artery disease, and suggests that molecular interventions like gene therapy will add to their benefit. I am not, however, enthusiastic about the ability of any interventional approach to prolong survival in patients with chronic angina pectoris. Although the procedures used today are effective in controlling symptoms, the few properly designed studies carried out over the last 30 years failed to show much improvement in prognosis. It is unlikely today that any new bioengineering or molecular intervention, alone or in combination, could reduce mortality in patients with stable coronary disease simply because this syndrome is now so benign as to preclude a significant survival benefit from any therapy other than that which can slow or reverse the underlying disease in the arteries. It is not widely appreciated that 40-year-old Metropolitan Life Insurance Company statistics show that a prior myocardial infarction reduced the life expectancy of a “standard” 55-year-old life insurance applicant, which was then about 20 years, by only 4 to 5 years (Table I). The small impact of stable ischemic heart disease on prognosis was subsequently confirmed in an analysis of trials completed before 1990, which showed the life expectancy of a 55-year-old medically managed patient with 3-vessel disease, mild angina, and a normal ejection fraction to be more than 17 years; this is only 3 years less than that of a patient with mild angina and single-vessel disease, which, like that of the general population at that time, was more than 20 years (Table I). Even when associated with severe angina, 3-vessel disease reduced life expectancy less than 4 years. These small effects of stable coronary disease on survival were documented before the widespread use of safe and effective antihypertensive medications, precise blood glucose control in diabetics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, antithrombotic drugs, thrombolytic therapy, and other treatments now known to im-
prove prognosis in this condition. It is therefore likely that the adverse effect of stable angina on survival is now so minor that no surgical or interventional approach could prolong life significantly. I doubt, however, that anyone will measure this!

Current evidence does support the value of interventional approaches in acute myocardial infarction, so that I will predict, though with some trepidation, that intracoronary ad-
to adapt new knowledge from the physical sciences to produce better images of the heart and vasculature, I am unable to extend the story told by Arthur Hollman into the future. I suspect that by 2016 noninvasive imaging will allow us to hold a 3-di-

ministration of novel signaling molecules and other chemical medi-
dators at the time of primary an-
gioplasty will be found to improve prognosis in this group of patients. I am less enthusiastic about infusion of bone marrow and other types of stem cells as the risks seem likely to exceed the benefits, in part because these cells produce so many active compounds.

**DIAGNOSTIC CARDIOLOGY**

I am afraid that my crystal ball fails me here. Aside from my first prediction that cardiology will continue the fact, I believe it likely that they will do more harm than good because increased reliance on diagnostic technology is moving physicians from the bedside to the imaging center. As Hollman points out, a precise history and careful physical examination, rather than elegant images, remain the key to diagnosis and therapy for most cardiac patients. Furthermore, when physicians spend more time away from the bedside, they are less able to dispense what A. Conan Doyle called the healing touch... that magnetic thing which defies explanation or analysis, but which is a very evident fact none

**HEART FAILURE**

My article in this issue concludes that improved management of heart failure will be made possible by “additional new stems [that] are likely to emerge from unexpected places,” and that most of these will be in areas of molecular biology, which is already having a major impact on the diagnosis and classification of the familial cardiomyopathies (Table II, next page). I expect that by 2016 this and other new information will have begun to influence when and how these patients are treated, and I predict that carriers of some of the more dangerous cardiomyopathy gene abnormalities will be found to benefit from treatment with β-blockers, ACE inhibitors, and other therapy _before_ they become symptomatic.

I am tempted to predict success in efforts to find selective inhibitors of signaling pathways responsible for maladaptive hypertrophy and activa-
tors of pathways that lead to adap-
tive hypertrophy, but the history in this field is mixed. On the one hand, we have learned that many neuro-
humoral inhibitors (β-blockers, ACE inhibitors, aldosterone antagonists) can delay, and for a time even reverse, the adverse consequences of cardiac hypertrophy, but it should be remembered that these findings came as a surprise to many experts in this field. The complexity of the intertwined and overlapping cell signal transduction pathways that mediate maladaptive hypertrophy makes it difficult to predict the long-
term clinical effects of molecules designed to activate or inhibit spec-
cific protein kinases, phosphatases, and other signaling molecules, so that I am reluctant to predict much
success in these efforts by 2016, but I hope that I am wrong. I am even less optimistic about the potential benefits of gene therapy, largely because of problems that emerged when this approach was used to treat other diseases. I am also pessimistic about what I view as a generally overly enthusiastic view of stem cell therapy as it is used today. I am especially troubled by the lack of solid evidence that the infused cells, even were they to survive and flourish, become functionally integrated with the native cardiac myocytes by forming gap-junction connections.

One syndrome for which I will make a concrete prediction is “diastolic heart failure” (DHF). I share the widely held view that ejection fraction (EF) distinguishes DHF, where EF is usually normal, elevated, or only minimally depressed, from the more common “systolic heart failure” (SHF), where EF is low. Because EF is simply the ratio between stroke volume and end-diastolic volume, and because stroke volume (like cardiac output) is reduced in virtually every patient with heart failure (the notable exception being high-output failure), simple algebra tells us that the major distinction between SHF and DHF is whether or not end-diastolic volume is increased. As inhibition of progressive dilatation (remodeling) accounts for much of the benefit of therapy that prolongs survival in SHF, drugs that have proven to be effective in SHF should be of much less value in improving prognosis in DHF where, by definition, progressive dilatation does not play an important role. I would be less than honest if I did not admit that this view is supported by data from hypertensive patients, a population that is predisposed to develop DHF, in whom ACE inhibitors and β-blockers—which have a clear survival benefit in SHF—appear to be less effective in improving prognosis, after taking into account their ability to lower blood pressure.

There is also evidence that ACE inhibitors are less effective in delaying the onset of heart failure in hypertensive patients with a left ventricular ejection fraction (LVEF) >35% and no evidence of heart failure, but they are in asymptomatic patients with an LVEF <35% (Figure 1). Similarly, an angiotensin receptor blocker given to patients with DHF barely reduced the primary end point of cardiovascular death and hospital admission for heart failure, and had no significant effect on cardiovascular death, further more, the beneficial effects of these drugs appear to be less in DHF than in the overall population with heart failure (Figure 2).
A recent report that a stiffer titin isoform is expressed in DHF than in SHF, which is consistent with other evidence that these two types of heart failure are associated with different molecular abnormalities, gains additional significance because titin is not only an important determinant of diastolic stiffness, but along with other cytoskeletal proteins plays an important role in cell signaling. This finding, along with other data suggesting that the cytoskeleton plays an important role in determining the size, shape, and composition of the heart (see ref 4), leads me to predict that inhibition of maladaptive cytoskeletal signaling will emerge as a major target for new approaches to prevent progressive deterioration of failing hearts.

**HYPERTENSION**

Norman Sharpe's description of the evolution of our understanding of hypertension is remarkably congruent with that of heart failure. In both, clinical pathologists of the 19th century observed morphological abnormalities, in the blood vessels and heart, respectively, that throughout most of the 20th century came to be overshadowed by the hemodynamic abnormalities. Furthermore, the morphological abnormalities in patients with hypertension, like those with heart failure, occur when maladaptive proliferative signaling causes hypertrophy and other changes in the target organ, in this case the arterial wall. Although these morphological changes had not been forgotten, the focus of antihypertensive therapy shifted to dynamic abnormalities like vasoconstriction and fluid retention, so that most of the drugs now used to treat this condition were selected because of their vasodilator properties or ability to rid the body of salt and water.

Recently, however, it has become clear that hypertension, like heart failure, is a complex group of syndromes that are often caused by signaling abnormalities associated with polymorphisms and other molecular abnormalities (Table III, next page). Much remains to be learned about these abnormalities, but I suspect that by 2016 many hypertensive patients will be treated with novel drugs that act on these and other proliferative signaling systems.

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*Figure 1.* Effect of ACE inhibition on the development of heart failure in hypertensive patients with LVEF >35% (lower curves), based on data from reference 6, and in asymptomatic patients following myocardial infarction with LVEF <35% (upper curves), based on data from reference 7. Unlike the asymptomatic patients with ischemic heart disease and a low LVEF, who benefited from ACE inhibitors, hypertensive patients without a significant decrease in LVEF who received an ACE inhibitor were no less likely to develop heart failure than those who received a thiazide diuretic. Dashed lines: patients not receiving an ACE inhibitor; solid lines: patients given an ACE inhibitor.

*Abbreviations:* ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; LVEF, left ventricular ejection fraction; SOLVD-Prevention, Studies Of Left Ventricular Dysfunction, Prevention arm.

*Figure 2.* Effects of candesartan on the risk of cardiovascular death, heart failure hospitalization, or both, in symptomatic patients with heart failure. Above: Unadjusted risk ratios for all heart failure patients. Below: Unadjusted risk ratios for patients with left ventricular ejection fraction >40%. Based on data in references 8 and 9.

*Abbreviations:* CV, cardiovascular; EF, ejection fraction; HF, heart failure.
had been stated by several leading authors, but instead, as believed by others, to result from coronary artery occlusion. Although there seems no likelihood that we will see another paradigm shift of this magnitude in the foreseeable future, steady progress can be expected in our understanding of both the underlying atherosclerotic disease and the transformation of what is usually a smoldering, often benign, process in the coronary arteries into a rapidly moving conflagration (see below). In patients with pump failure following a large myocardial infarction, I anticipate that technological advances in monitoring and ventricular assist technology, rather than conceptual breakthroughs, will improve management. The mortality after acute myocardial infarction should also continue to improve because better detection of myocardial cell necrosis, by improving the diagnosis of small infarcts, will help identify patients at risk for sudden cardiac death.13

The most important unanswered question in ischemic heart disease research today is the identity of the factors that, by destabilizing atherosclerotic lesions in the coronary arteries, cause acute myocardial infarction. During the next decade I anticipate that the outlook for these patients will be improved by better understanding of the mediators of plaque vulnerability and rupture, which already include endothelial cell dysfunction and the actions of monocytes and macrophages, platelets, mast cells, proteolytic enzymes, phospholipases, cyclooxygenases, adhesion molecules, cytokines, mediators of apoptosis, and angiogenic and other peptide growth factors. These findings, coupled with well-documented benefits of drugs like ACE inhibitors and statins, along with the likelihood that polymorphisms influence individual susceptibility to plaque rupture, suggest that, as in other areas of cardiology, optimal therapy of ischemic heart disease will soon be individualized. I therefore expect that in 2016 drugs will be available to modify the specific pathophysiological processes that operate in some of these patients. I also predict that novel means will be found to identify patients with vulnerable plaques, and that the use of new imaging modalities to localize unstable lesions will play an important role in preventing and managing acute coronary syndromes.

ATHEROSCLEROSIS

I believe that, at least for the next 10 years, this will remain a “mature” field, by this I mean that while important progress will be made, there will be no shifts in direction as dramatic as those of the past 30 years when, as described by Anton Becker, atherosclerosis was recognized to be an inflammatory response to endothelial injury. As is true of other topics in this anniversary issue, many of the seminal observations in this field were stimulated by thoughtful examinations of human autopsy material. I vividly recall the pulmonary artery of a young woman with primary pulmonary hypertension whom I cared for in the 1960s, the pathologist pointed out that the endothelial surface of the main pulmonary artery exhibited atherosclerotic lesions as severe as those seen in the aortas of much older patients who had died of a myocardial infarction, and suggested that the atherosclerotic process must be the way that large arteries respond to various types of injury. It is not surprising, therefore, that most of the deleterious effects of the traditional “risk factors” have been found to reflect their ability to damage the vessel wall. Of course, no one 40 years ago could have predicted the impact of the many advances in

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**Table III.** Some signaling systems in which genetic abnormalities have been implicated in the pathogenesis of hypertension.


**ISCHEMIC HEART DISEASE**

It is difficult to conceive of a paradigm shift as dramatic as that which occurred less than 30 years ago, when, as described by Desmond Julian, acute myocardial infarction was demonstrated not to be a primary abnormality of the heart, as had been stated by several leading
signal transduction discussed in Becker’s article. I hope that I am not overly optimistic in predicting that, by 2016, better understanding of what converts a stable, and so benign, atherosclerotic lesion to a dangerous unstable lesion will have improved both prevention and treatment of acute myocardial infarction and related syndromes.

**ELECTROPHYSIOLOGY**

The article by Michael Rosen and Michiel Janse ends with a description of the electronic pacemakers and cardioverter-defibrillators that have revolutionized the management of clinical arrhythmias. Over the next decade, there is little doubt that the proven benefits of these and other devices will be enhanced by miniaturization and other improvements in electronics. It also seems likely that clinical use of antiarrhythmic drugs, which, a generation ago, were the mainstay of arrhythmia management, will continue to decline. Aside from molecules that interact specifically with membrane proteins, such as β-receptor blockers, there seems little future for drugs with what were once called “membrane-stabilizing” actions. Amiodarone, which represents the major exception to this generalization, will probably continue to be prescribed for patients at risk for dangerous arrhythmias who do not have a long life expectancy, but I believe that this drug is too toxic for use in the growing population with serious arrhythmias who can be expected to live for 5 or more years.

A promising branch of the arrhythmia tree that I predict will have a growing impact on prevention and management has emerged from rapid advances in the molecular biology of cardiac ion channels and related proteins. Identification of ion channel abnormalities that cause, or increase susceptibility to serious arrhythmias (Table IV) represents a promising area whose impact on patient care over the next decade will be largely to improve diagnosis. Evidence that polymorphisms in these and other proteins can modify the clinical manifestations of a given ion channel gene standard” for identifying patients at high risk of a dangerous arrhythmia will not be the ECG, 24-hour (“Holter”) monitor, indirect tests such as heart rate variability, late potentials, and T wave alternans, or even formal electrophysiological testing. Instead, a blood sample from a patient judged to be at risk of sudden cardiac death will be examined for gene mutation increases the complexity of this field. For these reasons, I predict that by 2016, patients suspected of being at high risk for sudden cardiac death will be screened for many of the potentially arrhythmogenic mutations and polymorphisms listed in Table IV; an updated list can be found on a database maintained by investigators of the Molecular Cardiology Laboratories of the IRCCS Fondazione Salvatore Maugeri, Pavia, Italy. All this leads me to predict that the “gold standard” for identifying patients at high risk of a dangerous arrhythmia will not be the ECG, 24-hour (“Holter”) monitor, indirect tests such as heart rate variability, late potentials, and T wave alternans, or even formal electrophysiological testing. Instead, a blood sample from a patient judged to be at risk of sudden cardiac death will be examined for gene mutation and polymorphisms that predispose to a lethal arrhythmia. It is already clear that that the nature of the molecular abnormality determines individual risk; for example, arrhythmic events are more frequent in patients with HERG channel mutations when the abnormality is in the pore region, and the prognosis of right ventricular dysplasia/cardiomyopathy is worse in patients who have a mutation in plakophilin-2. For this reason, it is safe to predict that identification...
of specific gene abnormalities will play an increasing role in determining which patient needs a pacemaker, a cardioverter-defibrillator, or a drug such as a β-adrenergic blocker. This information should help provide a rational basis for alerting carriers of some genes to the hazards of strenuous activity and the need to avoid drugs that interact with cardiac ion channels, such as anti-depressants that prolong the QT interval.

I am willing to offer better than 50-50 odds that by 2016 a few molecular causes of arrhythmia will become amenable to specific treatment. Gene therapy, while of potential benefit, has proven to be both difficult and dangerous, but the value of simpler approaches is suggested by evidence that the HERG mutations responsible for the type 2 long-QT syndrome often impair trafficking of this potassium channel protein to the plasma membrane.18 A practical value of this knowledge is suggested by the ability of a drug that interacts with an abnormal HERG protein to promote channel transport to the cell surface, which can “rescue” a model of the clinical abnormality.19

Another, quite different, group of patients at risk for a lethal arrhythmia, is found in the large and rapidly growing population with heart failure. In addition to reentry caused by fibrosis and increased heart size, electrical abnormalities associated with the molecular changes that accompany cardiac myocyte hypertrophy play a major role in causing sudden death in these patients. Most important is the depolarizing current that accompanies calcium efflux from the cytosol via the sodium/calcium exchanger, which is increased by the reversion to the fetal phenotype seen in cardiac myocytes from failing hearts.20 Although there is some rationale for trying to inhibit the sodium/calcium exchanger, thereby reducing the depolarizing currents that cause afterdepolarizations and triggered activity, I believe that success in this effort would represent a Pyrrhic victory, because the resulting calcium overload would accelerate myocardial cell death and so worsen prognosis in these patients. A potentially more promising approach would be to reverse the loss of sarcoplasmic reticulum that accompanies the reversion to the fetal phenotype; in fact, efforts are already under way to test this approach in patients with end-stage heart failure.21 I am afraid, however, that costs and risks will preclude this approach for this large population. For this reason, I predict that for the next decade implantable cardioverter-defibrillators will remain central to preventing arrhythmic deaths in these patients.

**AUTONOMIC BIOLOGY**

Gary Francis and Wilson Tang set the stage for developments in this field when they describe how, at the beginning of the 20th century, the autonomic nervous system was believed to consist of two opposing arms: sympathetic and parasympathetic. The simplicity of this early view is reminiscent of the atomic structure I was taught in the early 1940s (protons, electrons, neutrons, and for a bit of “spice” the newly discovered positron), but which has now been replaced by an increasing number of subatomic particles, forces, and other arcana. Similarly, a growing list of specialized autonomic nerves, receptors, and receptor subclasses, neurotransmitters, and other components has added a cacophony of new mediators, whose names are both logical and weird, to known autonomic signaling systems. We have become aware that peptides like endothelin, vasopressin, neuropeptide Y, adrenomedullin, leptin, ghrelin, cytokines, and growth factors; the arginine derivative agmatine; prostaglandins, which are synthesized from fatty acids; the steroid hormone aldosterone; and even nitric oxide, a free radical gas, have important effects on the heart and vascular system. We are also beginning to learn how interwoven networks of intracellular signal transduction systems can alter the clinical manifestations of cardiovascular disease when extracellular messengers modify both the reactivity and structure of the heart and blood vessels.

I cannot predict which of the known, not to mention “yet-to-be discovered” signaling systems will turn out to be important for cardiovascular disease, but I suspect that all will be found to have important actions in some individual patients. Clinical studies of drugs that modify these systems have already provided a number of important surprises, such as the improved prognosis in patients with heart failure who receive β-adrenergic and aldosterone blockers. Unfortunately, other surprises have been less pleasant, notably the excess mortality when patients with chronic heart failure are treated with inotropic drugs that increase cellular levels of cyclic AMP. It is too risky to try to speculate how modification of any of these systems will affect individuals with cardiovascular disease, but I feel safe in predicting that there will be additional surprises when therapies that modify these and other signaling systems are tested in humans.

**CARDIAC SURGERY**

There are several reasons why the remarkable success of cardiac surgery described by Robert Litwak is not likely to be repeated during the
The number of patients eligible for surgical repair of cardiac abnormalities is decreasing. The changing nature of heart disease, notably the rapid decline in rheumatic valvular disease, coupled with increasingly early repair of congenital malformations, has virtually eliminated the reservoir of cardiac abnormalities that are amenable to surgical correction in the adult population. Furthermore, a growing number of these patients can be treated using new percutaneous approaches. Finally, new knowledge of cell signaling, by adding to available therapeutic options, will reduce the need for surgical treatment, as is already apparent in the ability of statins and ACE inhibitors to slow progression of coronary artery disease and other complications of atherosclerosis.

Genetics and Molecular Biology

The concluding section of Sir David Weatherall’s article, headed “The Future,” highlights the importance of genetics and molecular biology for the future of cardiology. These descriptions of the role of genetic factors in the pathophysiology and clinical manifestations of disease, and the influence of genetic polymorphisms on the response of individual patients to specific therapy, are similar to predictions made in the present article. I have no doubt that the impact of genetics and molecular biology on patient care during the coming decade will be enormous.

I expect that growing recognition of individual responses to disease and drugs will dampen the current enthusiasm for “evidence-based medicine,” where the results of large randomized clinical trials dominate clinical decision-making. These trials, while invaluable in telling us how a given approach can be expected to operate in a population, are limited in their ability to tell us what will happen to an individual patient. I therefore expect the focus in patient care to shift back to the more traditionally “physiologically-based medicine” that views each patient as a unique entity. This change in emphasis would represent a paradigm shift of the magnitude described by Thomas Kuhn,22 as it would no longer be feasible to generate optimal diagnostic and therapeutic plans by viewing patients simply as members of a large database. Instead, optimal decision-making would require integration of a careful history, detailed physical examination, and thoughtful and selective use of laboratory data from each patient. I have italicized “selective” because, as noted by Weatherall, vast quantities of new genomic and proteomic data are being added to the large existing body of anatomical, biochemical, and physiological data as we move into the new era of individualized “postgenomic medicine.” Reliance on therapy directed to the needs of individual patients will also make it difficult to develop “blockbuster” drugs that are appropriate to deal with the diverse pathophysiology in large populations of patients.

Conclusions

The changes in cardiology predicted in this article can be expected to have a major impact on aspects of medicine other than diagnosis and treatment. Most important are medical economics and medical education, which are especially vulnerable to stresses that would occur if only a few of my predictions were correct. In fact, both are already experiencing severe stress because of the enormous progress, documented in this anniversary issue, that has occurred during the past decades. The cost of health care can be both increased and decreased by the advances I have anticipated in this article. An optimist might predict that these advances will lead to savings as it is now clear that careful outpatient management of heart failure reduces expenditures, largely by keeping these patients out of hospital. The optimist would also point out that genetic screening to determine an individual’s susceptibility to sudden death would be less expensive, and probably more accurate, than electrophysiological testing. The pessimist, on the other hand, might say that expenditures would be increased because physicians tend to overuse new tests, procedures, and treatments, of which there will be many. I cannot predict the future costs of health care delivery because these economics differ markedly in various countries, and because expenditures are heavily influenced by politics, which follow rules that are incomprehensible to most physicians, including myself.

The flood of new information that is now sweeping over cardiology poses a daunting challenge for medical education. Much as inflating a balloon separates the points on its surface, expansion of both basic and clinical knowledge is drawing preclinical and bedside teaching away from one other. This is a major reason why it has become increasingly difficult to identify teachers competent in both basic science and clinical medicine, which leads to the common complaint that medical students are taught basic science by professors who know little about the clinical problems relevant to their laboratory research, and clinical medicine by professors who know little about the basic sciences that can explain what is wrong with their patients. In the United States, this has led to a sea change in med-
ical education since the 1970s, when basic science professors were often physicians, and most full-time clinical teachers had at least some meaningful training in a research laboratory. Today, in contrast, most basic science teachers are molecular biologists with no clinical training, and few clinical teachers have had any research experience. Exposure of students to the scientific foundations of modern medicine is also being reduced by curricular changes that, at least in the United States, are increasing the time spent in courses and electives that highlight social aspects of medicine, at the cost of decreasing the time allocated to teaching the basic sciences.

Sadly, these considerations lead me to a final prediction, that economics and a shortage of appropriately educated physicians will deny many patients access to new knowledge. This prediction does not, however, describe a new situation; in 1964, my father wrote:

As far as application of new knowledge is concerned, no serious gap appears to exist between the laboratory and clinical research... instead there appear to be difficulties in bringing new information to the attention of the physician in daily practice. The gap thus appears to be between the medical center and the community hospital rather than between the laboratory and the physician in the medical center...

Looking back over the 50 years since my father wrote:

As we move toward 2016, current trends indicate that an increasing number of physicians will have had neither an adequate opportunity to learn the scientific foundations of modern medicine nor enough time away from revenue-generating activities to remain up to date in this rapidly changing profession. I am therefore afraid that ten years from now an increasing number of patients will not have access to the full benefits of the physiologically based approach to cardiovascular medicine that will be made possible by the advances described in this article.

REFERENCES

1. Friedberg CK.
The cardiologist evaluates myocardial revascularization. In: Russek HI, Zohman BL, eds. 

2. Wong JB, Sonnenberg FA, Salem DN, Pauker SG.

3. Doyle AC.
Behind the times. In: 

4. Katz AM.

Effects of ACE inhibitors, calcium antagonists, and other blood pressure-lowering drugs: results of prospectively designed overviews of randomized trials.

6. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).
Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic.

7. The SOLVD Investigators.
Effect of enalapril on mortality and the development of heart failure. I Asymptomatic patients with reduced left-ventricular ejection fractions.

Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial.

Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall Trial.

Myocardial structure and function differ in systolic and diastolic heart failure.

11. Granzier HL, Labelt S.
The giant protein titin. A major player in myocardial mechanics, signaling and disease.

Genetic determinants of blood pressure regulation.

The diagnostic and prognostic impact of the redefinition of acute myocardial infarction: lessons from the Global Registry of Acute Coronary Events (GRACE).
Am Heart J. 2006;151:654-660.
Common sodium channel promoter haplotype in Asian subjects underlies variability in cardiac conduction.
*Circulation*. 2006;113:338-344.


Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel.

Clinical features of arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in plakophilin-2.
*Circulation*. 2006;113:1641-1649.

Most LQT2 mutations reduce Kv11.1 (hERG) current by a class 2 (trafficking deficient) mechanism.

19. Gong Q, Anderson CL, January CT, Zhou Z.
Pharmacological rescue of trafficking defective HERG channels formed by coassembly of wild-type and long QT mutant N470D subunits.

20. Pogwizd SM, Bers DM.
Cellular basis of triggered arrhythmias in heart failure.

Genetic maneuvers to ameliorate ventricular function in heart failure: therapeutic potential and future implications.

22. Katz TS.