

HYPERTENSION: from a mare in Cambridgeshire to the South-American pit viper

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The soil and seeds of hypertension are those provided by an understanding of the circulation originating from William Harvey's work in the early 1600s. The truncal position historically is accorded to the British scientist and curate, Stephen Hales, who first measured blood pressure in animals directly in the 1730s. The development of instrumentation for indirect blood pressure measurement progressed through the late 1800s, culminating in Nikolai Korotkoff's auscultatory method reported in 1905. Once the trunk of measurement was established, the first branches representing early understanding of blood pressure and disease sprouted by the early 20th century. However, blooming of these branches to establish the broad canopy representing our modern understanding of the pathophysiology of blood pressure has continued to the present.

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.

Keywords: hypertension; pathophysiology; blood pressure measurement; genetics; renin-angiotensin system; ACE inhibitor

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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



Figure 1. Stephen Hales (1677-1761) circa 1759. Copyright © National Portrait Gallery. Art by Dmitry Krymov.

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 in to 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*.¹ 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 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, 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).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. Hales' 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 hydrodynamometer in the early 1800s by Poiseuille allowed reduction of the pressure column

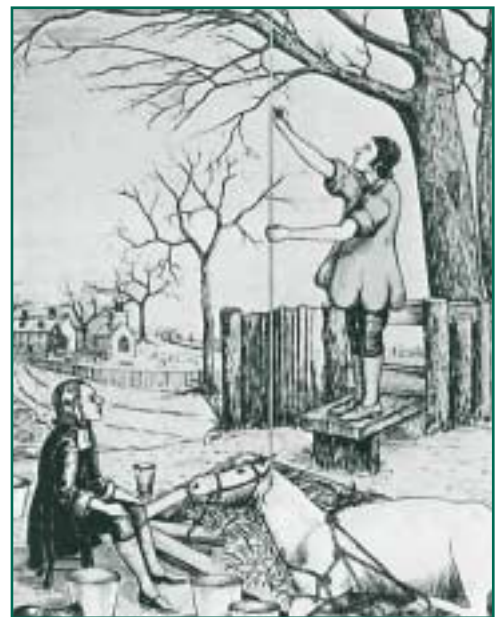


Figure 2. Stephen Hales and assistant measuring the jugular venous pressure in a horse.

Reproduced from reference 2: Lyons AS, Petrucelli RJ. *Medicine, an Illustrated History*. New York, NY: Abradale Press. Copyright © 1987, Abradale Press / Harry N. Abrams, Inc, Publisher.

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 1896.³ 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 distinc-



Figure 3. Nikolai Korotkoff (1874-1920). Copyright © Russian Military Academy.

tion 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,⁵ 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 sys-

tematically 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 children'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 1836⁷ 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 1852.⁸ 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

1872⁹ 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 1874.¹⁰ 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,¹¹ 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.

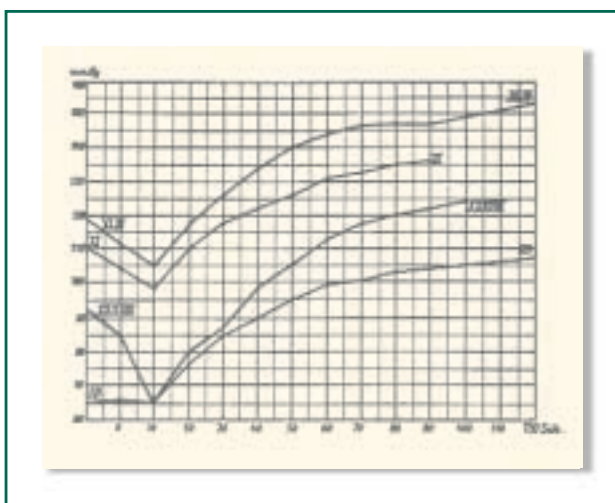
BRANCHES BLOOMING: TOWARD A MODERN UNDERSTANDING OF THE PATHOPHYSIOLOGY OF BLOOD PRESSURE

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*).¹² 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.

Figure 4. The time course of pressure elevation following injection of renin in rabbits.

Reproduced from reference 12: Tigerstedt R, Bergman PG. *Niere und Kreislauf*. Skand Arch Physiol. 1898; 7-8:223-271. All rights reserved.



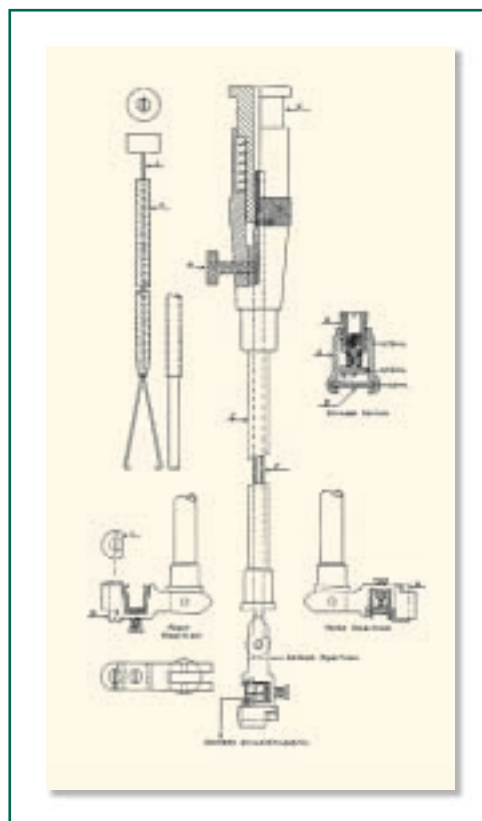
The connection of this sequence of renin production causing increased vascular resistance was also provisionally linked to cardiac hypertrophy. However, the biochemical findings of Tigerstedt and Bergman were not replicated and it was to be more than thirty years before the renin-angiotensin-aldosterone 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

Figure 5. The Goldblatt clamp used to produce renal ischemia in dogs.

Reproduced from reference 16: Goldblatt H, Lynch J, Hanzal RF, Summerville WW. The production of persistent elevation of systolic blood pressure by means of renal ischemia. *J Exp Med*. 1934;59:347-378. Copyright © 1934, Rockefeller University Press.



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:

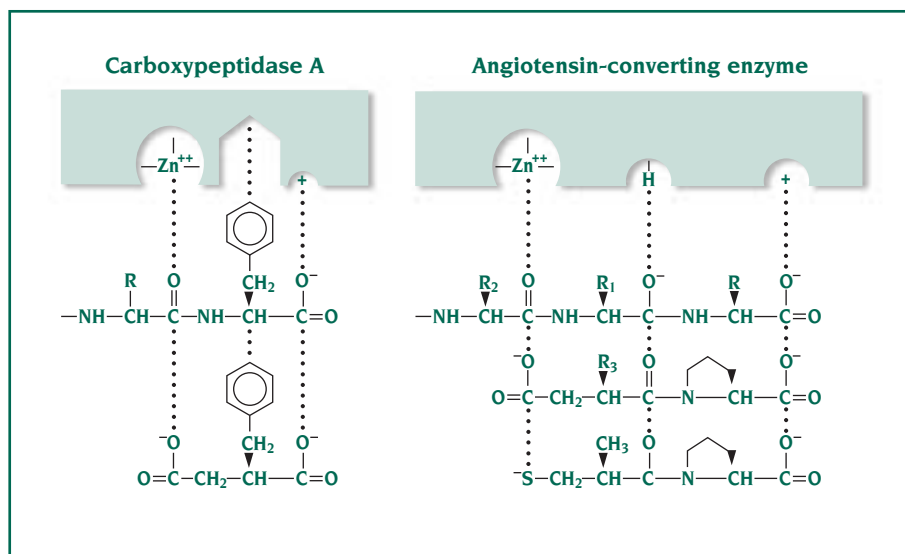
The pressor and vasoconstrictor properties of the venous blood from kidneys in acute ischemia, extracts of which contain a pressor substance (hypertensin) which is also formed in vitro when blood proteins are incubated with renin. Experiments indicate that renin is an enzyme, blood pseudoglobulins the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



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

Reproduced from reference 24: Ondetti MA, Rubin B, Cushman DW. Design of specific inhibitors of angiotensin-converting-enzyme: new class of orally active anti-hypertensive agents. *Science*. 1977;196:441-444. Copyright © 1977, American Society for the Advancement of Science.



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,²⁰ and the work of Elliott and Peart from London who similarly reported the amino acid sequences of bovine hypertensin.²¹ 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.²²

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*.²³ 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-convert-

ing 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.²⁴ 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).²⁴ 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 1961.²⁵ This view was amplified by Kolff's group from Cleveland who in 1964 proposed both renal and renovascular components for renal hypertension.²⁶ 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-

ponent was removed by bilateral nephrectomy, the resultant renoprival hypertension responded easily to salt and water restriction. A successful kidney homotransplant then converted the renoprival 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%.²⁷ 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 pressure was a continuous variable and not a familial dominant characteristic as believed by Platt. Pickering concurred with Page's mosaic theory that essential hypertension was multifactorial, resulting "from a constellation of facets, one or even none being more or less dominant."

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 uniformly 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 hypertension²⁸ 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 concept 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 flourishes. New and broader insights into hypertension causation in modern societies alter the hue of some parts, pharmacogenomics and improved 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 celebrating discovery.

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