The story of hypertension research is largely the story of men and women whose contributions have moved our knowledge of hypertension from total darkness into a clearing penumbra. Of course, the story does not begin with Richard Bright, one of the great physicians of Guy's Hospital. Indeed, its beginnings are lost in the mists of ancient times since many facets of medical observation and research have contributed to our knowledge of hypertension. To a lesser degree, the same is true of research in the physical sciences and even the social sciences and humanities.

The Edwin Smith Surgical Papyrus is believed to include writings of the Egyptian physician, Imhotep, (3000 B.C.) who later became the Egyptian demigod of medicine. The papyrus contains the sage observation that "the pulse is an index of the heart and of the condition of the patient."

In The Yellow Emperor's Classic of Internal Medicine, we find the following answers to the plain questions of the Yellow Emperor of China, 2600 B.C.:

"The blood current flows continuously in a circle and never stops."

"When the heart pulse beats vigorously and the strokes are markedly prolonged, the corresponding illness . . . makes the patient unable to speak."

If too much salt is used in foods, the pulse hardens . . ."

More than 4,000 years elapsed before William Harvey proved the circulation of the blood; still later, the sequence of hypertension, cerebral hemorrhage, and aphasia was recognized; and now the role of the sodium ion in hypertension is under scrutiny.

In the 16th and 17th centuries B.C., several Egyptian papyri not only counseled examination of the pulse, but also direct auscultation of the heart as the source of the pulse.

Choun-You-J, a Chinese physician of 200 B.C., wrote prophetically, "When the pulse, upon depressing, is very firm and upon superficial palpation tight, then the disease has its seat in the kidney."

Greco-Roman medical writings contain many references to apoplexy and to hemiplegia, although hypertension as a cause was, of course, completely unknown.

Then followed the period of the dark and middle ages during which advances in knowledge, including those related to the heart and circulation, were minimal.

17th Century

The epoch-making discovery of William Harvey, which also established the scientific method in the study of medicine, was the sine qua non for later blood pressure and hypertension studies. Although his famous book was not published until 1628, his lec-
nature notes for 1616 contain convincing experimental proof of the circulation of the blood. In 1658 Johann Wepfer, a physician of Basel, reported necropsies on four patients who died of apoplexy due to cerebral hemorrhage. He noted that if any illness "deserves investigation for the sake of more accurate knowledge . . . it is apoplexy . . ." In 1694 Giorgio Baglivi of Rome reported the necropsy which he performed on the body of the famous Italian physiologist and anatomist, Marcello Malpighi of Bologna, who, among other important findings, discovered the capillaries and contributed to our knowledge of the structure and function of the kidney. The necropsy indicated that Malpighi's fatal apoplexy was due to cerebral hemorrhage, probably secondary to renal hypertension since Baglivi stated, "The left kidney was free from any inflammation; the right, on the contrary, was observed to be almost half as small as the left; the pelvis of the latter was so greatly dilated . . . ."

18th Century

The studies of Stephen Hales were by far the most significant contribution of the 18th century toward hypertension research. Hales was curate of the Parish of Teddington in Middlesex to the south of London and a brilliant student of nature. In 1733 he published his famous Statical Essays: Containing Hae-mostatics, in which he reported experimental proof that flowing blood exerts a pressure on the walls of the blood vessels. He also showed that the circulation obeys other hydrostatic laws. One of the most widely known experiments in biology is his measurement of the blood pressure in the femoral artery of a horse. Hales not only measured systolic arterial pressure, but also pulmonary pressure, venous pressure, and the effect of hemorrhage on arterial pressure. He understood the distinction between end and lateral pressures. He also measured blood volume, calculated the velocity of flow in the arteries, and determined that the "capillary arteries" (arteri-oles) were the site of the chief peripheral resistance. The last observation, of course, is basic to the modern concept of the pathophysiology of hypertension.

In addition to his interest in the circulation, Hales was active in public health matters; he obtained a supply of pure water for his parish and devised ventilation systems for hospitals and prisons.

After Hales, the Parish of Teddington remained obscure for 200 years until its curate attained brief note in 1937 by officiating at the marriage of the Duke and Duchess of Windsor.

19th Century

During the 19th century, practical laboratory and clinical methods of measuring blood pressure were devised, hypertension was recognized as a clinical entity, and differentiation of primary and secondary hypertensions was initiated.

As a senior medical student in Paris in 1828, Jean Poiseuille devised the mercury manometer for measuring blood pressure and demonstrated respiratory blood pressure waves. Later, he enunciated Poiseuille's Law and devised the plethysmograph. He also showed that the pressures may be the same in different arteries of an animal and that arterial pressures are approximately the same for different-sized hearts and animals. Poiseuille used sodium carbonate as an anticoagulant in his pressure measuring system.

In 1833 Jules Hérisson of Paris modified the mercury manometer of Poiseuille by sealing the end of a mercury-containing glass tube with a thin membrane which rested on the artery, and thereby obtained crude readings of the blood pressure of intact arteries in man. Although subsequent improvements were made in the Hérisson instrument, for the next 50 years or more main reliance was placed on palpation of the pulse or on pulse tracing for estimating arterial pressure in man, and/or deduction of hypertension from the presence of cardiac hypertrophy in the absence of valvular lesions.

In 1847 Carl Ludwig of Marburg added a float to the mercury manometer of Poiseuille and recorded blood pressure on a revolving
kymograph. This became the classic method of recording blood pressure in the experimental laboratory for 100 years and is still used by some today. Ludwig and his many postgraduate students made other significant contributions to cardiovascular-renal physiology during the remainder of the 19th century.

In 1880 Samuel von Basch of Vienna described a semipractical clinical sphygmomanometer which measured the systolic pressure of the radial artery. He reported readings on 17 patients and found the pressure raised in two patients with cardiac hypertrophy. During the next 10 years, he made more than 100,000 blood pressure determinations and observed many patients with hypertension. Other physicians made some use of his sphygmomanometer during this period.

However, the first clinically acceptable sphygmomanometer was designed by Scipione Riva-Rocci of Turin in 1896. This measured systolic pressure by obliterating the brachial artery with an inflatable rubber cuff.

While methods for the measurement and recording of blood pressure were being refined during the 19th century, our knowledge of blood pressure regulation and of changes in blood pressure associated with disease was notably advanced.

Although induration of the kidneys with oliguria, hematuria, and edema had been described by physicians for more than 1,000 years, it remained for Richard Bright, in 1827, to associate the clinical findings of albuminuria, hardness and fullness of the pulse, edema, and hypertrophy of the left ventricle with the pathologic finding of sclerosing, contracted kidneys. He emphasized the absence of valvular disease in relation to the cardiac hypertrophy associated with contracted kidneys, gave us a better understanding of diseases of the kidney, particularly nephritis, and differentiated renal from cardiac edema.

In 1836 Bright first proposed that the quality of the blood was changed to cause an increase in the resistance of flow through the "minute and capillary circulation," thereby originating the concept of arterial hypertension with the kidney as the cause. His Reports of Medical Cases and his Tabular View of the Morbid Appearance in 100 Cases Connected with Albuminous Urine summarizes his controlled observations on patients with chronic disorders of the kidney. Bright pioneered investigation of disease at the bedside and to this day glomerulonephritis is not infrequently referred to as Bright's disease.

In 1852 Claude Bernard of Paris discovered vasoconstrictor nerve fibers and in 1858 vasodilator fibers.

In 1872 William Gull and Henry Sutton of London ascribed chronic Bright's disease to primary generalized "arterio-capillary fibrosis," which they believed produced left ventricular hypertrophy and contracted kidneys.

In 1874 Frederick Mahomed, Resident Medical Officer of the London Fever Hospital, who died of typhoid at 35, first recognized the condition later called essential hypertension which he termed the "pre-albuminuric stage of Bright's disease," and proposed the view that hypertension can give rise to renal vascular changes.

In 1893 Henri Huchard of Paris and T. Clifford Allbutt of London noted the frequency of hypertension and recognized that it can occur in the absence of morphologic changes in the kidneys and arteries. In 1895 Allbutt addressed the Hunterian Society on "Senile Plethora or High Arterial Pressure in Elderly Persons" and emphasized that renal disease was not a necessary prelude to hypertension and that hypertension and arteriosclerosis were independent, though frequently associated, diseases. He was the first to use the terms, hyperpiesis and hyperpiesia.

20th Century

As all of you are aware, the 20th century has witnessed tremendous advances in our knowledge of hypertension, importantly as a consequence of the efforts of many of the physicians and laymen attending this meeting. Numerous advances have been made in methodology for blood pressure measurement and circulatory studies, the most significant of the former being the auscultatory method of
Nikolai Korotkoff and the membrane manometer of William Hamilton.

In 1905 Korotkoff, a 31-year-old privatdozent in the Imperial Medical Academy of St. Petersburg, reported on the auscultatory method of determining systolic and diastolic blood pressures, now the standard clinical procedure in all parts of the world. Korotkoff's excellent defense of his method against the adverse criticisms of superiors and colleagues is well worth reading. Nevertheless, during the same year the British Medical Journal argued that by sphygmomanometry "we pauperize our senses and weaken clinical acuity."

Thirty years after the work of Korotkoff, the membrane manometer of Hamilton of Augusta, Georgia, enabled corroboration of the reliability of the Korotkoff technique of blood pressure measurement.

Although electronic techniques now permit the monitoring and telemetering of blood pressure, we are still in need of a practical method of continuous blood pressure recording in normally active individuals.

At the beginning of the 20th century there were three schools of thought with reference to the pathogenesis of essential or primary hypertension: followers of Bright maintained that essential hypertension was due to renal disease; followers of Gull and Sutton, to widespread vascular disease; and followers of Huchard and Allbutt, to generalized vasoconstriction unrelated to renal disease. The third view became increasingly ascendant, and essential or primary hypertension is still defined as high blood pressure of unknown cause. In the meantime, a number of hypertensions of known cause have been separated from essential hypertension, the most recent being that of primary aldosteronism.

In 1904 Theodore Janeway, then of New York City, first used the terms "essential hypertension" and "hypertensive vascular disease." In the same year, two French interns, Leo Ambard and Eugene Beaujard, published their experiments on sodium chloride depletion and repletion in patients with hypertension. They interpreted their results as favoring the view that essential hypertension is due to chloride retention.

In 1914 Frans Vollhard and Theodor Fahr of Mannheim differentiated the malignant phase of essential hypertension. They also classified Bright's disease into (a) degenerative diseases (nephroses), (b) inflammatory diseases (nephritides), and (c) arteriosclerotic diseases (scleroses).

Although experimental and clinical research on hypertension continued throughout the remainder of the first quarter of the present century, the next important advance did not come until 1929 when Eberhard Koch and Heinz Mies of Cologne, following the work of their preceptor, Heinrich Hering, produced the first persistent experimental hypertension (in rabbits). This was accomplished by section of the carotid sinus and aortic depressor nerves. However, buffer nerve hypertension did not serve as an effective stimulus to investigators, partly because the debuffering technique not infrequently produced intermittent or temporary hypertension, but more importantly because the hypertension involves increased cardiac output and heart rate, which are found in the hypertension of pheochromocytoma but not in essential or primary hypertension. Subsequent modification of the debuffering technique has enabled more consistent production of buffer nerve hypertension in rabbits and dogs, and this experimental hypertension is deserving of further investigation.

A most potent stimulus to hypertension research came in 1934 when Harry Goldblatt and associates of Cleveland published their work on experimental renal hypertension by constriction of the renal arteries of dogs. Goldblatt cited evidence for the resemblance between experimental renal and essential hypertensions. He further reported that severe constriction of the renal arteries led to a condition in dogs resembling malignant hypertension in man. Experimental renal hypertension was soon confirmed and produced in other species, including the rat and the mon-
key. In these two species unilateral renal manipulation was frequently sufficient to produce persistent hypertension and similarly, in the human, persistent hypertension may occur as a result of unilateral renal involvement.

Goldblatt's finding led to resurrection of the work of Robert Tigerstedt and P. G. Bergman of Stockholm demonstrating the presence of renin in the kidney. In the concluding paragraph of their paper published in 1898, these Swedish investigators modestly pointed out that they did not wish to formulate a new hypothesis about the interconnection between renal diseases and cardiac hypertrophy, but wanted to draw attention to the possible importance of the blood-pressure-raising substance formed in the kidney.

As previously mentioned, the discovery of experimental renal hypertension by Goldblatt stimulated a significant expansion of hypertension research. Indeed it may be said that Goldblatt's contribution produced a chain reaction which is still in effect. Since 1934, Goldblatt and collaborators have continued to contribute most significantly to the pathogenesis, pathophysiology and pathology of experimental renal and clinical hypertensions.

In 1940 Irvine Page and co-workers, now of Cleveland, and Eduardo Braun-Menendez and collaborators of Buenos Aires simultaneously demonstrated that renin is a proteolytic enzyme which acts on an alpha-2-globulin of the plasma to produce the pressor polypeptide, angiotensin, so named by Page and Braun-Menendez shortly before the untimely death of the latter in 1958. Page and his associates and Braun-Menendez and colleagues continued their outstanding contributions to hypertension research, as have many other able investigators of the United States, England, Germany, France, and other countries to the present day.

The status of renin in the pathogenesis of experimental renal hypertension and the status of the kidney and renin in the pathogenesis of essential or primary hypertension have varied widely during the 20th century. Several nonconfirmatory and confirmatory reports appeared in the decade following the work of Tigerstedt and Bergman, and then renin remained dormant for 20 years. In the 1930's, renin was frequently assumed to be the pathogenetic agent in experimental renal hypertension, and during that period some uncritical clinicians referred to renin as the pathogenetic agent of essential hypertension. The latter view, however, was not supported by scientific evidence. During the 1940's, renin lost most of its status as the pathogenetic agent of experimental renal hypertension, and the relation of the kidney and renin to the pathogenesis of essential or primary hypertension hung by a gossamer thread. However, a few investigators offered findings during this period which prevented total discard of renin in relation to hypertension. In recent years, the renin-angiotensin system has undergone a scientific revival. Indeed, the structure of angiotensin was recently determined by two groups in Cleveland and one in London, and shortly thereafter angiotensin was simultaneously synthesized at the Cleveland Clinic and at Ciba in Basel. If the strenuous search for an antiminbilete to angiotensin now under way proves successful, we should have an answer to the 63-year-old question of the pathogenetic significance of renin in hypertension.

Other experimental hypertensions, corresponding more or less to clinical hypertensions of known cause, have been produced by various procedures during the past 20 years, including cerebromedullary ischemia, administration of adrenocortical steroids, adrenal enucleation, administration of anterior pituitary extract and of somatotrophic hormone, exhibition of sodium chloride, constriction of the thoracic aorta, and curiously enough, the administration of licorice.

Renoprival hypertension has also had much study in recent years, particularly in the United States and England. Blast-whistle stimulation produces hypertension in rats, which persists only as long as application of the stimulus is continued. The production of
chronic experimental hypertension in monkeys and apes by reflex conditioning and/or prolonged stress has recently been reported from Russia, but I am not convinced by available data.

Among the many factors relating to the pathogenesis of experimental and clinical hypertensions now under active investigation, the following may yield important information: heredity; stress and the anterior pituitary-adrenal cortex axis; the central and sympathetic nervous system; catecholamines, aminoxidase, and methyltransferase; pressoreceptors and buffer nerve reflexes; the juxtaglomerular apparatus, renin, and regulation of the renal circulation; the blood pressure regulatory function or vasodepressor hormone of the kidney; adrenal cortical hormones and their inter-relations with renin, the anterior pituitary, and the buffer nerves; the sodium ion and its relation to membrane potentials; other facets of electrolyte and water metabolism; and contractile mechanisms of arteriolar smooth muscle.

From such studies most probably will one day come the key to the etiology and pathogenesis of essential hypertension and the secondary hypertensions.

Part of the difficulty in determining the etiology and pathogenesis of essential hypertension no doubt rests in the probability that essential hypertension is still a generic classification. Although our increasing knowledge of secondary hypertensions has measurably improved chances of cure for patients with such hypertensions, including clinical renal hypertension, present-day therapies of primary or essential hypertension are necessarily based on empiricism or, at best, pathophysiological considerations. These therapies have proved effective in prolonging the lives of patients with malignant hypertension, and in relieving the symptoms and probably prolonging the lives of patients with essential hypertension. Nevertheless, investigators still have a tremendous obligation to solve the etiology and pathogenesis of primary and secondary hypertensions. Only when this has been achieved will therapies become specific, preventive, and curative for millions of patients with hypertension.

The American Foundation for High Blood Pressure (later a Council of the American Heart Association) early pointed the way toward more adequate financial support of hypertension research, following its organization in 1945 under the leadership of Alva Bradley of Cleveland and Irvine Page. The Foundation thereby stimulated hypertension research support by the Association, its affiliates and chapters; the National Heart Institute and other government agencies; the Hartford Foundation; the Life Insurance Medical Research Fund; the pharmaceutical industry; and other groups who have since contributed millions of dollars.

The master clock of hypertension research seems to be set in terms of centuries since Harvey, Hales, and Bright made their great contributions in 1628, 1733, and 1827, respectively. Whether Goldblatt's contribution of 1934 will definitely take its place with this galaxy depends upon the results of future investigations. In any event, let us hope that the complete conquest of hypertension will come prior to 2034.

General References
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