HYPERTENSION

Volume X

NEURAL AND RENAL MECHANISMS

Proceedings of the Council for
High Blood Pressure Research,
American Heart Association,
Cleveland, November 17-18, 1961

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From Bright Toward Light: The Story of Hypertension Research*

By George E. Wakerlin, M.D., Ph.D.

■ 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-

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ture 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 Haemostatics,* 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" (arterioles) 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 "arteriocapillary 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 Volhard 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 antimetabolite 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, pathophysiologic 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.

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Neural Factors Responsible for Cardiovascular Regulation

By Eric Neil, M.D., D.Sc.

■ The greatest medical discovery of all time —that of the circulation of the blood—was made by an Englishman, William Harvey,[1] in 1628. It is arguable that Harvey and his pupil, Richard Lower,[2] had a clearer picture in the seventeenth century of the problem of the circulation than have most physiologists today. Both Harvey and Lower (whose thesis "De Corde" written in 1669 was never translated into English but only into French) had a lucid appreciation of venous capacity. Lower introduced the term "venous tone" and extended the views of Harvey in showing how postural effects could profoundly modify the priming of the cardiac pump.

Yet another Englishman, Stephen Hales,[3] first measured in 1733 the systemic blood pressure in terms of the height of the column of blood (some eight feet) as registered in a glass tube connected by the windpipe of a goose to the severed femoral artery. Almost a hundred years elapsed before Poiseuille[4] who was then a clinical student, connected the arterial cannula to a mercury manometer; henceforth the blood pressure was measured in terms of millimeters of mercury. Carl Ludwig[5] in 1847 first graphically recorded the blood pressure on the kymographion by placing a float and writing point over the mercury.

The function of vasomotor nerves, adumbrated by Weber[6] and Stilling[7] although perhaps first demonstrated by Claude Bernard[8] in 1851, was most clearly expressed by Brown-Seguard[9] in Philadelphia in 1852. Claude Bernard, however, made the fundamental observation in 1858[10] that cervical spinal transection caused a profound fall of arterial blood pressure. Carl Ludwig and Elie de Cyon in 1866[11] discovered that the stimulation of the central end of the aortic nerve evoked systemic hypotension—a response which they interpreted correctly as a reflex inhibition of "centers" in the neuraxis, basing their views on the concepts of Marshall Hall (1837) as to the nature of a reflex arc. The site of the vasomotor center was determined in Leipzig by Ludwig's pupils Dittmar and Owsjannikow.[12, 13] The concept that this vasomotor center discharged tonically to the thoracolumbar sympathetic fibers, hence producing tonic vasoconstriction, arose from experimental results of Dittmar,[12] Ludwig and Thiry,[14] and others.

It is interesting to note that one discovery of the great physiologist Claude Bernard[10]—that the stimulation of the chorda tympani caused vasodilatation of the submaxillary gland—misdirected the efforts of physiologists in cardiovascular research for some 60 years. The idea arose that vasodilator nerves were widespread and that their activity exerted quantitatively significant effects on the circulatory system as a whole. An intensive search for such vasodilator nerves led to the discovery of the nervi erigentes by Conrad Eckhard[15] in 1863. The activity of these nerves, contributing as it does to reproductive function, might perhaps be considered a fundamental example of that of a vasomotor nerve, but even a Casanova could hardly be accused of altering his total peripheral resistance by their utilization in biological circumstances.

Ludwig did not believe that the depressor nerves—now known to arise from the aorta and its immediate branches and hence termed "aortic nerves"—were tonically active. He based his views on the fact that the section of both these nerves did not cause a rise in arterial blood pressure. Although Sewall and Steiner[16] contested this view, the reason for the continued stabilization of arterial blood pressure following bilateral aortic nerve section was not made clear until 1923, when Hering proved the existence of the carotid sinus nerves. Hering showed that the section

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of these nerves led to marked hypertension and fully understood that the two sinus nerves acted in conjunction with both aortic nerves as a functional entity. The term "Blutdruckzügler" of Hering[17] was opposed by Kahn[18] (later to lose his life in a concentration camp in Czechoslovakia), who named them more appropriately "Blutdruckregler." Samson Wright,[19] with his peculiar genius for descriptive writing, named them buffer nerves. Thanks to the work of Hering and particularly Heymans[20] and Koch,[21] the *modus operandi* of the buffer nerves was widely appreciated by the beginning of the 1930's.

The vascular arrangements of the carotid bifurcation lend themselves to the critical analysis of the carotid sinus baroreceptors (or mechanoreceptors). Most of our knowledge of the effects of such mechanoreceptor stimulation stems from experiments on the carotid sinus. A rise of intraluminal pressure in the sinus causes reflex inhibition of the vasomotor center (and hence dilatation of arterioles which lowers peripheral resistance and of veins which increases venous capacity) and reflex stimulation of the dorsal motor nucleus of the vagus which slows the heart. Conversely, section of the sinus nerves causes hypertension and tachycardia despite the presence of the vago-aortic nerves. Bronk and Stella[22] first showed the afferent impulse activity in the multi-fibers or single fibers of the carotid sinus nerve. Bursts of impulses occurred with each pulse, as indeed had been recorded 30 years previously by Köster and Tschermak[23] in the aortic nerve (1903).

The nerve endings in the carotid sinus and the aortic arch have been named pressoreceptors or baroreceptors but neither term is particularly felicitous. The sensory terminals are deformation receptors which are ordinarily stimulated by the distention of the artery occasioned by each systolic ejection of the heart. Thus if this distention is prevented, as by a plaster of Paris cast, surrounding the cartotid sinus, changes of intraluminal pressure in the sinus prove quite ineffective in provoking sinus reflexes (Hauss, Kreuziger, and Asteroth[24]). Abnormal types of deformation, such as external pressure on the sinus, tugging on the sinus and the topical application of vasoconstrictor drugs to the sinus wall, are also capable of evoking sinus reflex responses.

The deformation receptors or mechanoreceptors are responsive not only to the mean pressure which causes stretch of the arterial wall, but also to the rate of application and amplitude of variation of the stretch caused by the pulsatile changes of blood pressure. Ead, Green, and Neil[25] examined the effect of "damping" the arterial pulsations on the sensory discharge from the carotid mechanoreceptors and on the reflex effects on the blood pressure exerted by the carotid reflexogenic zones. They found that the normal pulsatile pressure provided in the systemic arterial system was more effective in promoting sinus reflex effects on the vasomotor supply of the arteries and veins than was a steady pressure of an even higher mean value. They concluded that a reduction of the pulsations in the systemic circuit, such as resulted from a weakened systolic ejection of the heart, particularly if this was coupled with tachycardia, would provide a lesser stimulus to the reflexogenic zones, with consequent escape of the vasomotor center from the ordinary degree of sino-aortic inhibition. They interpreted the maintenance of mean blood pressure during slow hemorrhage in this light, pointing out that the progressive vasoconstriction of skin and splanchnic areas thereby served to sustain the mean systemic pressure despite a continued deterioration of the cardiac output.

Heymans and Neil[26] suggested that a change in the biological characteristics of the vessel walls causing a reduced distention of the wall at each systolic pressure rise might explain the features of essential hypertension; McCubbin, Green, and Page[27] showed that the afferent activity in the sinus nerves of dogs subjected to sustained renal hypertension was indeed much less than might be expected from the study of sinus afferent impulse traffic in dogs, acutely subjected to drugs which tran-

siently yielded hypertension of a similar degree. Unfortunately McCubbin et al. did not attempt to differentiate whether the distensibility of the wall itself had changed in these renal hypertensive dogs, or whether adaptation and/or degeneration of some of the nerve endings had occurred. They did establish, however, that the sinus reflexes were still causing some degree of afferent inhibition of vasomotor discharge in these chronic-hypertensive dogs, for carotid occlusion still provoked a rise in blood pressure in their animals.

It is important to stress that these alterations of mechanoreceptor activity are secondary to chronic hypertension; there is no evidence whatever that such changes *initiate* the development of essential hypertension in man.

Cardiac receptors were first envisaged by von Bezold and Hirt[28] when they showed that the intravenous injection of veratrine caused vasodilatation, bradycardia and apnea. It was shown that vagal section prevented the effect, and von Bezold believed that the drug stimulated cardiac vagal receptors. Many years passed before Adolf Jarisch of Innsbruck again championed this proposal and, both by his own work and by collaboration with electrophysiologists, succeeded in proving his hypothesis. Amann and Schaefer[29] first showed the existence of atrial receptors. Paintal[30] defined two types of atrial receptors: (a) type A which discharges during atrial systole and during the venous filling of the atrium, and (b) type B which discharges only during venous filling of the atrium. Both types of receptor are found in each atrium. Paintal[31] also proved that ventricular receptors which discharge briefly during isometric contraction of the ventricle are stimulated by veratrine, as indeed are the atrial receptors. The Bezold-Jarisch reflex is produced by the pharmacological stimulation of these receptors, which normally seem to act as deformation receptors or "proprioceptors" of the circulation, as repeatedly argued by Jarisch.[32] These receptors seem to exert a tonic restraint on the circulation, qualitatively similar to that effected by the arterial mechanoreceptors. Thus the prevention, or rather minimization, of venous filling of the right atrium markedly lessens the discharge of receptors situated in the right atrium (Neil and Joels[33]). Conversely, increased venous filling profoundly increases their discharge. It is my experience that sudden alterations of venous return may completely alter the timing of the impulse salvoes of atrial receptors so that an "A" receptor may betray discharge characteristics of a "B" receptor and vice versa. Langrehr[34] has reached some similar conclusions. Although these atrial receptors were described histologically by Nonidez[35] as the receptors of the Bainbridge reflex, such is not the case. Experiments by Aviado and his colleagues[36] have shown that increased venous filling of the right atrium causes bradycardia and hypotension, not tachycardia, thus again providing evidence that these cardiac receptors act in the same general manner in provoking vasomotor and cardiac restraint as do the arterial mechanoreceptors.

We are still ignorant of the quantitative effects produced by these various circulatory reflexes on (a) arteries, veins, and heart, and (b) different parallel vascular circuits. It is attractive to suppose that the right atrial receptors might cause more profound effects on venous capacity, thereby minimizing the danger of overloading the right heart, whereas perhaps the arterial and left ventricular receptors may exert preponderant effects on arteriolar resistance. We now see as through a glass darkly, and much more evidence is required of such reflex effects.

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Discussion

Dr. Freis: Do you have any evidence that the atrial receptors do in fact have more effect on capacity vessels in other parts of the circulation?

Dr. Neil: It is suggestive but not convincing; at least it does not convince me. By giving small doses of veratrine into the right atrium (the timing is important here), right atrial discharge may be provoked and circulatory responses occur in the hind limb isovolumetric preparation which seem to predominate on the venous side.

Dr. Hamilton: I always feel puzzled as to why a constrictor drug ectopically applied to the carotid sinus, making it smaller in size, causes it to generate the same sort of impulses as it would if it were distended by high arterial pressure. Can it be that the contraction of the smooth muscle cells tightens the elastic fibers of the sinus wall, thereby stimulating the receptor to generate its specific impulses?

Dr. Neil: The so-called circular muscle of the arterial wall, at least, is a helix. When you apply these drugs to the carotid sinus, what you get is a pulling of the sinus itself, where the muscle is actually very eccentric in the wall. Epinephrine causes increased impulse activity even after the sinus is ligated and opened, when there is zero intraluminal pressure; you see that epinephrine applied locally affects the receptors indirectly, causing enormous stimulation.

Dr. Page: Can you give us any idea of the power of cardiac receptors versus the carotid sinus nerves?

Dr. Neil: We cannot for this reason: all the cardiac receptors cannot be excluded without destroying a preponderance of the cardiac efferents themselves. A change in the cardiac impulse discharge would be much more effective in slowing the heart than would sinus effects. A reservation might be that if you have an arteriosclerotic sinus wall you can provoke tremendous bradycardia by external digital stimulation. The best way of stimulating cardiac receptors is by the use of tiny doses of veratrine, a procedure that doesn't disturb the animal's thoracic anatomy, but there nevertheless must be a very big reflex inhibition of the sympathetic discharge to both arteriole and vein. As evidenced by results of electroneurography, this inhibition secondarily leads to hypotension and changes of cardiac output and rate, which in turn cause sino-aortic reflexes. And the fact that, even if you block the motor vagal effects with atropine, or rather minimize them, you still get hypotension, suggests a marked inhibition of vasoconstrictor discharge to the vasculature. It is also extraordinarily difficult to activate cardiac receptor reflexes without involving pulmonary mechanoreceptors, because of the secondary effects on pulmonary arterial pressure.

Dr. Ogden: In hypertension of long standing, the mechanoreceptors appear to go out of business. Is there any indication as to how soon they go out of business, whether it is reversible and whether they stay that way indefinitely?

Dr. Neil: I am sorry if I implied they went out of business. I said their activity was reduced. I am sure both Dr. Page and Dr. McCubbin would testify to this—they remain in business at least within the time course of their experiments. You can still provoke reflexes consequent upon a temporary interruption of their activities, such as by carotid occlusion. As far as I know, the Green, McCubbin, Page paper is the only evidence which we have in this respect. I don't know whether Dr. Page and Dr. McCubbin may know of other people who have repeated it. All I know is that some Russians have reported a similar sort of thing and that there is a degeneration of the nerve endings. There, of course, they are on a very good wicket. You have to explain something somehow. How they count those endings defeats me, having looked at them myself. I am sure Dr. McCubbin or Dr. Page could contribute more effectively than I.