First Annual Irvine H. Page Lecture

A Page in the story of hypertension

Julius H. Comroe, Jr., M. D.*

For the past 5 to 6 years I have been spending much of my time looking backward to learn how great lifesaving advances in cardiovascular-pulmonary medicine and surgery of the past 30 years have come about. Did the cardiac surgeon of the late 1930s and early 1940s suddenly make a giant leap from sea level to the pinnacle (*Fig. 1A*)?[1] Or did he walk up the back of the mountain (*Fig. 1B*)—up steps laboriously carved out by hundreds or thousands of scientists over many generations, scientists in many disciplines working in many countries?

I am not going to give a history lecture. Historians would not rate me as one of them—because I am not really involved in excavations that prove that the Yellow Emperor of China actually wrote on the circulation of the blood in 2600 BC (4200 years before William Harvey). My main interest is finding whether discoveries came quickly or slowly and, in each case, why. What accelerated discovery? What held it back? What was the importance of chance, of discovery in related fields, of undirected work (knowledge for the sake of knowledge), of authoritarian pronouncements, of mission-oriented work, of contracts for store-bought research, and of commissions, task forces, or presidential panels? How often did commissions advance knowledge, how often did they retard progress? How important

Presented at The Cleveland Clinic Foundation, March 28, 1978.

* *Director, The National Pulmonary Faculty Training Center, University of California Medical Center, San Francisco, California.*

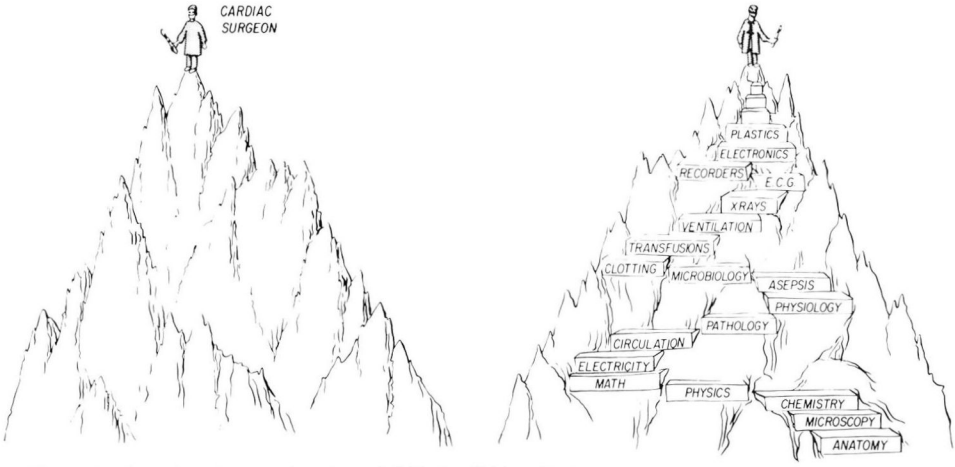

Fig. 1. A, One giant leap to the pinnacle? **B,** Or did he climb the steps up the back of the mountain?

was the character of individual scientists—for example, their persistence in the face of ridicule or indifference?

I am not going to give a lecture on hypertension, because it would be presumptuous of me to do so in Cleveland, but I will use part of the story of drug treatment of hypertension to illustrate how discoveries in medicine have really come about, and to wonder how they might have come more quickly.

First, let us look at the discovery of the blood pressure cuff and manometer. Today, you can walk into any discount drugstore and buy one for $15 to $20, complete with instructions for taking your own or anyone's blood pressure. It is logical to believe that such a simple device has been around forever but this is not so. The first good study (Janeway's) measuring blood pressure in a large series of patients by use of the new arm cuff was published when I was 1 year old.[2] Patients might have had high blood pressure since Cleopatra (indeed, she may have been an early cause of hypertension), but no one could have known about it for sure. A patient with hypertension must by definition have a higher blood pressure than one without hypertension, and, for the medical profession to diagnose hypertension, study its natural history, and determine the effect of treatment, it must have numbers. Physicians in the 19th century classified patients as having a hard pulse (signifying high blood pressure) or a soft pulse (signifying low blood pressure). At postmortem examination, pathologists saw left ventricles with very thick walls that must have been doing extra work, and from these thick walls they inferred the existence of high blood pressure in the patient before death.

One of the aspects of medical advance, or lack of it, that intrigues me is what I call lags between initial discovery and full clinical application. What harm is done by lags? Paul Beeson,[3] using the data of Franklin D. Roosevelt's personal physician, pointed out that when the world's most powerful statesman died in 1945 of malignant hypertension, his only medication was digitalis leaf, occasional use of aminophylline and phenobarbital, and sometimes dietary restriction of salt (*Fig. 2*). If the 1950 antihypertensive drugs had come in the mid-1940s, the course of world history might have changed con-

siderably. But that 10-year period pales into insignificance when I tell you that the lag between measurement of arterial blood pressure in the horse and arterial blood pressure in man was approximately 175 years!

Riva-Rocci[4] devised his arm cuff in 1896 for measuring systolic blood pressure in man. Korotkoff[5] modified this technique in 1905 so that he could also measure diastolic blood pressure. But an English clergyman, Stephen Hales,[6] measured arterial blood pressure in horses in 1720–1730. Why did a clergyman do this?. He was not a physician. He was not especially interested in medicine, or in the heart or circulation. He was interested in knowledge for the sake of knowledge; his was undirected research, not goal-directed and not mission-oriented. What he really wanted to learn was what makes sap rise from the bottom to the top of a tree. While pondering on sap and trees, he decided to measure the rise of sap in animals, i.e., the vertical height to which the heart could pump arterial blood. So, in the 1720s, 120 years before the discovery of general anesthesia, he tied a brass tube into a main artery of a horse, and using nature's accordion tubing (the flexible windpipe of a goose), he connected it to a long glass tube held vertically. How long a tube would he need? For a pressure of 200 mm Hg, he would need 200 mm x 13.6 (the specific gravity of mercury) or 2720 mm or 272 cm of tube, which is about 9 feet.

With this tube he learned many things. He learned of course how high the blood went up the tube, but he also saw it bounce up and down with systole and diastole, and he saw the effect of deep breathing, struggling, and of pain. He also removed bit by bit 17 quarts of blood and saw the horse's blood pressure fall from 8 feet 3 inches high to 2 feet 4

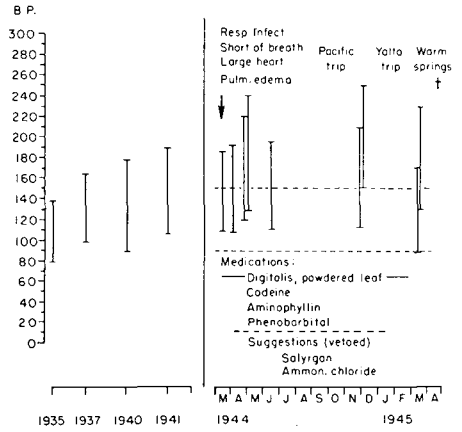

Fig. 2. Therapy of Roosevelt's malignant hypertension from 1944 to 1945.

inches. He measured the volume of the cavity of the left and right ventricles and the velocity of the ejection of blood from the heart. Not bad for a clergyman interested in botany!

But he really wanted to measure the rise of sap in plants. In 1720, quite by accident, he cut off a stem of a vine too close to its "bleeding" time. He bandaged it by tying a piece of bladder tightly over the cut stem, but he found that instead of stopping the oozing, the bladder became more and more tightly distended. He then realized that he could get actual numbers by attaching his long glass tubes designed to measure blood pressure to the cut stems and measuring how high the sap rose in them (*Fig. 3*). Serendipity? Yes, but as Hugh Walpole originally used the word, *not* to mean chance alone, but chance *and* sagacity (or as Claude Bernard said, "Chance favors the prepared mind.") So a clergyman made two great discoveries—one of fundamental importance to botany and one of fundamental importance to medicine and physiology. Hales taught us that great discoveries come in unexpected ways, and from unexpected professions and dis-

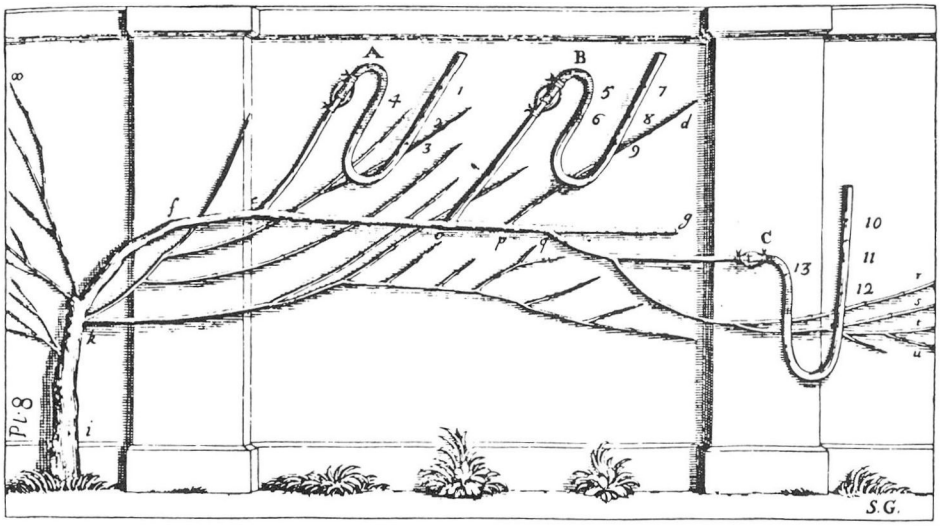

Fig. 3. Stephen Hales's method for measuring the pressure of sap in trees.

ciplines—and even without a task force or commission.

But we also learn that great discoveries are often ignored. So it was with the measurement of blood pressure. Hales's experiment did not lead to a great surge on the part of scientists to study the circulation. In fact, little further happened for about 100 years (1828) when a medical student, Poiseuille, decided that a 9-foot glass tube was a pretty inconvenient instrument for measuring blood pressure. He calculated that by placing mercury in a U-tube, he could reduce the tube length to 1/13.6 of 9 feet and have a manageable, portable instrument. His U-tube mercury manometer was used for the next 100 years in every student laboratory in Europe and America.

Why Poiseuille? Was he interested in blood pressure? No! He wanted to know where the resistance to blood flow was in the circulation and, especially, whether there was really a considerable resistance to flow through a normal aorta as all good physiologists claimed in 1828. For this he needed a good mercury manometer. He found blood pressure to be identical at the beginning and end of the aorta in a supine animal, and so proved that there was no measurable resistance in the aorta. Esoteric? Not clinically useful? Perhaps, but his research introduced a new method for studying the circulation still used today.

In 1847, Ludwig put a float atop the mercury column and added a horizontal lever that went up and down with the float and recorded blood pressure continuously on smoked paper attached to a rotating drum. This was the beginning of moving pictures of blood pressure.

As cardiovascular physiologists became more sophisticated, Poiseuille's mercury manometer became an unsatisfactory instrument for research (though it has always remained the standard for calibration). Mercury had weight and inertia, and a mercury manometer could not measure the systolic peak and the diastolic trough of blood pressure, but only the mean, and it could not follow the shape of pulse pressure curve that was needed to measure the dynamics of cardiac contraction.

Scores of new manometers were devised in the 19th century for use in animals and even a few for use in man. Some of those for man were simply impossible, some gave inconsistent numbers, and some yielded very consistent numbers but all were wrong.

Finally, in 1896, Riva-Rocci,[4] in Turin, learned how to make accurate and reproducible measurements of human systolic blood pressure (using a wide arm cuff). His goal was practical—to learn more about diagnosis, prognosis, and progression of disease. In 1905, Korotkoff of Leningrad (in a single-paragraph paper) told how to measure both systolic and diastolic pressures. Riva-Rocci's was a long paper and gave full credit to everyone who preceded him (a rare happening in those days). He even apologized for not having seen earlier Rabinowitz's modification of Basch's instrument:

> Not until my apparatus already had been completed did I become aware of the modification, my ignorance of it being the consequence of my unfortunate habit of not keeping up with the literature on a subject before I undertake new ventures. I hope the reader will forgive me on the score of the vastness and diffusion of the current literature on any given subject.[4(p1054)]

Note his dismay at being unable to keep abreast of the vast literature in 1896. At any rate, it took an Englishman, a Frenchman, a German, an Italian, and a Russian 172 years to go from the measurement of blood pressure in a horse to the measurement of blood pressure in man—to replace hard pulse and soft pulse with the numbers that at last permitted the study of hypertension to become a science.

It is interesting that George Crile, right here in hypertension city (and founder of The Cleveland Clinic Foundation), could have measured arterial blood pressure directly and continuously in man in the early 1900s, but did not. Scientists had just learned about human blood groups and, as a result, transfusions (formerly in dispute) came back into fashion. However, in 1906, there was no way to keep blood liquid or to store it; there was no heparin or citrate to serve as an anticoagulant. But Crile, a remarkable surgeon even then, performed many direct transfusions of blood from donor to recipient by stitching the artery of the first to the vein of the second. Sometimes he used metal tubes to make the connection and he could have used a Y- or a T-tube and attached a mercury manometer to the extra tube. Crile had no way of knowing how much blood the donor was losing to the recipient, but he could at least have known the donor's blood pressure continuously during hemorrhage (as Hales did 172 years earlier). But it would not have lasted long, because the specialty of "transfusionist" went out of business in 10 years. And, of course, it would not have helped in studying patients with chronic hypertension or in collecting large amounts of data on thousands of subjects (young and old, fat and thin, male and female) over a period of years, which was essential to learn the natural history of hypertension.

Janeway[2] studied the thousands between 1903 and 1912. Why did his study have to wait until the 1900s? I believe this is a classic instance of authorities in medicine holding back progress by their weighty pronouncements. In this case, the authorities were pathologists. Bright's full description of Bright's disease (glomerulonephritis) did not come until 1836.[7] His table of autopsy findings in 100 patients included 20 patients in whom the left ventricle was decidedly enlarged and its wall thickened—good

evidence that the ventricle had been overworked by its task of raising aortic pressure high enough to drive blood through the diseased and narrow renal vessels. Cohnheim[8] and Traube,[9] great German pathologists and authorities, pronounced that the hypertension was compensatory and therefore essential. So a hard pulse or a high blood pressure, when it occurred in the 19th century, was considered to be a *good* accompaniment of Bright's disease; it meant that a good heart was compensating for a bad kidney. And Soma Weiss, a great clinician in the early 1930s, stated that hypertension was a good response to a bad disease and meddling with it would cause renal and maybe cerebral ischemia.

But authority eventually begins to crumble. The crumbling here was a long process. It began in 1872 when Gull and Sutton[10] found healthy kidneys in patients with large, thick-walled left ventricles and suggested that the cause of left ventricular hypertension was disease of small blood vessels. And 2 years later, Mahomed[11] also recognized high blood pressure in patients with no kidney disease and said that Bright's disease and hypertension could be and usually were separate diseases.

But it took Janeway to establish hypertension as a disease and a very common one. Janeway became involved because he believed "that neither clinical studies of nearly a century nor experimental investigation of nearly half a century had succeeded in elucidating the real cause of hypertension." Why did Janeway succeed? In part, let me answer as my professor of obstetrics did when I, as a student, asked him why pregnancy lasted 9 months (not 8 or 10). He gave a succinct answer: "When an apple is ripe, it falls." The cuff made the time ripe for Janeway. Further, he and his father, between them, had a large private practice and did not need the cooperation of other physicians. They had 7872 patients between 1903 and 1912, and the younger Janeway measured blood pressure in each. He found that at one time or another, 11.1% had a systolic blood pressure of 165 mm Hg or more (he decided that a pressure greater than 160 mm Hg was pathologic) and he called this "hypertensive cardiovascular disease." He emphasized not only its frequency, but also its serious consequences—those who had symptoms associated with or due to hypertension lived on the average only 4 to 5 years thereafter. Incidentally, note that Janeway's research was conducted as part of a busy private practice.

But the wall of dogma did not come crashing down. Physicians in general were unimpressed. Even the great Osler was unimpressed. In the 1919 edition of his text (the last that he himself wrote), there was still no separate section entitled "hypertension"; he mentioned it under arteriosclerosis, as a cause of it. Cecil's first edition (1927) had no separate section on hypertension. The second edition (1930) did. It recommended as treatment: "physical and mental rest, physiotherapy, phenobarbital—[but] drugs are disappointing."

It is clear now, looking backward, that many more studies of the natural history of untreated hypertension were needed and especially data on the results of *not* treating hypertension, instead of speculation on the hazards of treating it. Physicians boasted of how long they had followed patients with very high blood pressure: Albutt had as a patient "a physician with an extremely 'hard' pulse who lived for 18 years (from 60 to 78 years of age)." Even Janeway wrote that he "had one patient with a systolic blood pressure of 280 for more than 10

years." So, you were well off if you had a good heart and very strong arteries. Unfortunately, ordinary hypertension or essential hypertension was also called benign hypertension, and it was not malignant until it was ready to do your patient in, and *then* you tried to do something about it.

For real progress, someone had to prove that you could lower blood pressure in a hypertensive patient without making him worse or without hastening his death. The first to do so were Rowntree and Adson,[12] neurosurgeons at the Mayo Clinic. They performed in 1925 a bilateral lumbar sympathectomy on a patient with severe hypertension. They wrote: "It occurred to us that relative freedom from vascular spasm might be obtained through removal of the vasoconstrictor influence of the sympathetic nervous system to the vessels of the leg." My retrospectroscope shows that the same thought occurred to Claude Bernard in 1851, and Bernard[13] duly recorded it. The same thought occurred to Brown-Séquard[14] in the same year, and he even wrote in English for the benefit of Americans. The same thought occurred to Gaskell[15] in 1886 in his classic study of the sympathetic nervous system. The same thought occurred to Leriche[16] in 1913 and was actually suggested in 1913 in the *Cleveland Medical Journal* by George Crile.[17] At any rate, without benefit of a medical library, Rowntree and Adson at the Mayo Clinic thought of it and performed a bilateral lumbar sympathectomy. The patient improved temporarily. "There was no change in volume or composition of urine; certainly the efficiency of the kidney was in no way impaired." In Adson's[18] next paper (1934), he gave a follow-up on this 1925 experience and mentioned that the "results on blood pressure and ultimate outcome were not significant."

The real impact finally came in 1934 when Page entered the hypertension story and shattered the century-old dogma. Who was Page? We need mention only a few historical data at this point.

1. First is the title of his first or second (or third) paper in 1923.[19] The title and opening sentence would have curled Senator Proxmire's hair, and if he had been on a peer review section of NIH judging a grant application on arbacia eggs and sand dollars, surely he would have axed the arbacia eggs as a ridiculous, ludicrous, and outrageous waste of the public's money. Maybe Page would have fooled him on the sand dollar (after all, dollars *are* dollars). But the arbacia-egg man was indeed the one, 10 to 12 years later, who put the treatment of hypertension on the right track for the first time. The lesson to be learned is to look at the man—and not the title of his project (most scientists change fields every 10 or 15 years anyway); look at the man and not the immediate application of his work. Look at the man: does he have new ideas? Does he have new convictions? Is he willing to buck authority to test his ideas? Page had both conviction and persistence.

2. A second bit of historical information about Page is that in 1934 he was working at the Rockefeller Institute—the most prestigious institute in the United States—and one that let its staff work on problems that the staff member thought were important. If most of the staff were working on infectious diseases and immunology but *one* wanted to work on blood pressure, or lipids, or atherosclerosis, or pressor materials, that was fine. A good scientist did not do what a committee directed, but what he himself thought was important. But they all got together at

lunch (clinicians and basic scientists) and shared their experiences and ideas; this was a true learning program.

3. Van Slyke was at the Rockefeller Institute and had devised a urea clearance test to measure renal blood flow. This was the golden age of renal physiology and, as a result, a respectable test of renal function was now available. Page rounded up six patients with hypertension.[20] He stated the goal of the study clearly: "The object of the present investigation was to compare the efficiency of [renal] excretion when the blood pressure was at a high level with that when it was reduced." He lowered blood pressure in all six patients; actually, *he* did it in four and in the other two it came down spontaneously. In two of his four, he used sodium thiocyanate; in one he used aqueous colloidal sulfur; in one a surgeon denervated one kidney. There was no significant change in urea clearance in any of the six patients when blood pressure was lowered. He concluded, "Abnormal elevation of blood pressure in these cases does not appear to assist in maintenance of renal efficiency. This evidence does not support the compensatory theory of the cause of hypertension in patients suffering from nephritis or essential hypertension." Since it is unlike Page not to speculate on why lowering systemic arterial blood pressure did not decrease renal function, it is reasonable to assume that he must have thought of autoregulation of the circulation at that moment; I suspect autoregulation was in his manuscript, and a journal editor deleted it as speculation and therefore unfit for a respectable journal to print.

At any rate, he opened wide the door for treatment of hypertension. Who rushed through it? One would have guessed, scientists in drug companies and cardiologists. But they had nothing to offer at that time. It was the neurosurgeons who rushed in: Page and Heuer,[21] Adson, Peet, Grimson, Smithwick, Zintel, and others. They did either partial sympathectomy, or subtotal sympathectomy, or total sympathectomy, or total sympathectomy with adrenalectomy! For 10 to 12 years, they dominated the treatment of hypertension. They have now vanished completely without a trace like the lost continent of Atlantis, but they served a useful purpose. They kept alive the knowledge that hypertension was amenable to treatment. This gave time for pharmacologists, drug companies, and cardiologists to catch up—instead of give up. It kept them actively working in the field. These catch-up years were the years when:

- Dale and Loewi won the Nobel prize for discovering the humoral transmission of nerve impulses, including those at the sympathetic ganglia and at the sympathetic nerve ending.
- Walter Cannon proposed the Law of Denervation.
- Ulf von Euler discovered norepinephrine as the final transmitter at sympathetic nerve endings.
- Ahlquist conceived of alpha and beta receptors in sympathetically innervated tissues.
- Earl Sutherland discovered cyclic AMP.
- Von Euler came across prostaglandins.
- Julius Axelrod worked out the biosynthesis and storage of norepinephrine.

During these years, research groups in university laboratories, hospital and institute laboratories, and in government and industry started intensive research that began to produce drugs that block the activity of the sympathetic

nervous system in many different chemical or anatomical sites. They came up with alpha methyldopa, guanethidine (the first report on it was by Page and Dustan),[22] propranolol, and reserpine. New drugs came from every direction—some (guanethidine, propranolol) were the result of rational design; some (like reserpine) the result of good luck; some (like thiazides) the result of rational design and good luck.

In 1934, another revolution in the story of hypertension occurred in Cleveland (now known as hypertension city). Harry Goldblatt, Professor of Pathology at Western Reserve University, found that experimental renal artery clamping resulted in higher arterial blood pressure.[23] As I mentioned earlier, Bright had observed that hypertension occurred in some patients with glomerulonephritis, but no one knew what caused the hypertension and cardiac enlargement. In 1924, Cash[24] produced experimental hypertension by decreasing kidney tissue by more than 50% and allowing a portion of the kidney to remain in situ without any arterial circulation. Goldblatt decided to do a clean-cut experiment and found that partial occlusion of one renal artery coupled with removal of the other kidney resulted in hypertension.

Goldblatt is often said to have *re*discovered the 1898 work of Tigerstedt and Bergman[25] in Stockholm without knowing of its existence. Actually, the experimental approaches of Tigerstedt and of Golblatt were quite different. Tigerstedt extracted kidneys and found a substance that raised blood pressure. He named it renin. In the kidney, he found it only in the cortex and in the renal venous blood, and he found it in the kidney even when denervated. Goldblatt on the other hand found that renal ischemia released a pressor substance from the kidney. In 1938, three groups, working independently, rediscovered Tigerstedt's renin. I do not know why others never reproduced his results between 1898 and 1938.

But the real milestone was 1940, when two chemists, working in Indianapolis, found that renin itself did not raise blood pressure. They found that renin was an enzyme that acted on a globulin in blood to form a pressor substance—the most potent known (angiotonin, now called angiotensin). The name of one chemist was Helmer. The other was a very clairvoyant, perceptive young physician who realized early on that chemistry was going to be of great importance to medicine. Clairvoyant, because after finishing medical school and a 2-year internship, he became director of the chemical division of the Kaiser Wilhelm Institute in Munich for 3 years (1928–1931) with major responsibility for the study of brain chemistry. Back in the United States in 1931 he had some successes and some disappointments in the chemical field. On the plus side, he wrote a classic monograph on the chemistry of the brain in 1937.[26] On the minus side, he tried hard but unsuccessfully to determine the chemical nature of "pressor" substances known or believed to be present in blood.

In 1939, at the Lilly Laboratory for Clinical Research, he and Helmer found the nature of Tigerstedt's extract and of the substance released from the Goldblatt kidney.[27] Incidentally, very shortly thereafter, Braun-Menendez and associates in Bueños Aires, independently discovered the same substance—except that they named it hypertensin instead of angiotonin. In one of the rare displays of statesmanship in science, in 1958, each agreed to give up half of his baby's name, and angiotonin-hypertensin be-

came angiotensin.

When Bumpus, Schwarz, and Page[28] synthesized it in 1957, angiotensin then really went center stage. The renal pressor substance, once thought to be of interest only in patients with hypertension due to renal artery obstruction (often found to be correctable surgically) is now known to be one of the most important physiological substances.

Long ago I gave up trying to keep track of the scientific literature on angiotensin—what it does, its physiology and pharmacology, its use in diagnosis, and the uses of angiotensin inhibitors. Now I cannot keep track of just the review articles. The discovery of the angiotensin system and subsequent work on it will be forever enshrined in a very special Hall of Fame for scientific discoveries that deserved the Nobel prize but have not yet got it. It did win 15 other awards, though.

Angiotensin began when Page was still in Indianapolis. In 1945, he moved to Cleveland. The problem of a pressor substance in blood had not been fully cleared up by the discovery of angiotensin because it became obvious that there were two or more distinct pressor substances in blood. Page believed it mandatory to identify these chemically, and get the matter neatly cleaned up. In 1948, the Cleveland group (Rapport, Green, Page, and McCubbin) not only found the pressor substance, but again hit the jackpot, because it turned out to be another naturally occurring substance of great physiological and medical importance: 5-HT, 5-OH tryptamine or serotonin.[29] They were looking for a needle in the haystack and found the needle plus the farmer's daughter. This new discovery became of great importance to many branches of medical science—biochemistry, physiology, and especially neurophysiology and neuropharmacology (Page called it "tenure for pharmacologists"), and a wide variety of clinical states. In his book on serotonin, Page[30] lists some possible clinical implications. Unfortunately, serotonin too is enshrined in that very special Hall of Fame along with angiotensin.

My title for this talk was "A Page in the Story of Hypertension." The total story of hypertension (to date) is the sum of many individual stories besides that of Page and his superb associates. One separate story is that of Sir Henry Dale and Otto Loewi, of von Euler, Axelrod, Sutherland, and Ahlquist. It includes learning of the synthesis, release, binding, and storage of norepinephrine—its action on receptors and the role of antihypertensive drugs acting on or through the sympathetic nervous system. Another individual story is of the discovery of carbonic anhydrase and carbonic anhydrase inhibitors, of the diuretic action of sulfonamides (which is a carbonic anhydrase inhibitor), and the synthesis of sulfa derivatives and analogues that led to chlorothiazide, not only a diuretic for treating congestive heart failure but also an antihypertensive drug. And there is the closely related sodium story, the story of vascular smooth muscle, and the relationship between hypertension and atherosclerosis—in many of which the Cleveland group have been important contributors. All have great importance and scientific merit.

But I keep coming back to a paragraph Edward Freis wrote to Robert Dripps in 1971:

> "At the time I came into the picture in 1946, the drug treatment of hypertension was considered to be a foolish procedure verging on charlatanism. A few of us dared to think that the cardiovascular damage was the result of the hypertension. Page and his

group were the first to witness reversal of the signs of malignant hypertension. This view was scorned for many years but it gave us a rationale and determination to pursue drug treatment."

I know that the title of my talk is "A Page in the Story of Hypertension" but I would like 2 minutes more to show you a few more Pages and 2 to 3 minutes more to summarize. There is also a Page[31] in the story of atherosclerosis, and a Page[32] in the story of research methods (which came at a time when research methods were being devised, modified, improved, and revised and it was helpful to have things in one volume). There is a Page[33] in the story of basic education of physicians; when the American Physiological Society decided to tell the story of physiology to physicians, there was unanimous opinion that volume one, number one had to be written by Page, and later he became Editor. There is also a Page[34] in the story of clinical education of physicians and patient care; physicians needed to learn many facets of medicine in plain English and Page talked to them through *Modern Medicine.* There is a Page[35] in the story of writing English instead of alphabet soup, and there is a Page[36] in the story of the education of the public, and a Page[37] in the story of medical statesmanship.

And now, 2 or 3 minutes to summarize. I have spent 5 years looking through the retrospectroscope. What have I learned? There is time to mention just a few matters:

1. Figure 1 asks the question, "How did the cardiac surgeon get to the top of the mountain?" The answer is that he went up the back of the mountain, up the steps. It has taken thousands of scientists, whose names are long forgotten, to carve the steps, and all the public knows is the name of the man who took the last step.

2. Of 663 key articles crucial to clinical advance in cardiovascular-pulmonary disease, 40.5%—at the time done—were unrelated to the clinical aspects (diagnosis, prevention, and treatment) of disease that they solved.[38]

3. Of 663 key articles, essential for clinical progress, almost two thirds dealt with basic mechanisms. The other one third dealt with clinical application, clinical proof, and development of instruments and procedures.

From this I conclude that if there is one absolutely essential element in medical advance, it is this: find a man or woman with intelligence, curiosity, creativity, judgment, dedication, persistence, perception, and vision, give him what he needs to do his work, and let him alone. But give him an exciting intellectual environment that includes clinicians in every specialty and superb basic scientists in many fields, and see to it that they talk to each other—maybe at lunch, maybe at seminars. This was the secret of success at the Rockefeller Institute and this was the secret of success at the Cleveland Clinic, and I think it is a good formula.

Irv—this is the story of your life . . .

References

1. Comroe JH Jr, Dripps RD: Ben Franklin and open heart surgery. Circ Res **35:** 661–669, 1974.
2. Janeway TC: A clinical study of hypertensive cardiovascular disease. Arch Intern Med **12:** 755–798, 1913.
3. Beeson PB: The ways of academic clinical medicine in America since World War II. The Cartwright Lecture. Man Med **1:** 65–79, 1975.
4. Riva-Rocci S: Un nuovo sfigmomanometro. Gazetta medica di Torino **47:** 981–996; 1001–1017, 1896. English trans, Foundations of Anesthesiology, v. 2. Faulconer A Jr, Keys TE, eds. Springfield, Ill, Thomas, 1965, pp 1043–1075.

5. Korotkoff NS: K voprosu metodokh uzsledovaniya kroyanovo devleniya. Voen Med Akad Izvestiia **11:** 365–367, 1905. English trans, Badger AS. Cardiovasc Res Cent Bull **5:** 57–74, 1967.
6. Hales S: Statical Essays, Containing Haemastaticks, v. 2. London, Innys and Manby, 1733, 361 pp.
7. Bright R: Cases and observations, illustrative of renal disease, accompanied with the secretion of albuminous urine. Guy's Hosp Rep **1:** 338–400, 1836.
8. Cohnheim JF: Vorlesungen ueber allgemeine Pathologie, 2 v. Berlin, Hirschwald, 1877–1880.
9. Traube L: Ueber den Zusammenhang von Herz und Nierenkrankheiten. Berlin, Hirschwald, 1856, p 59.
10. Gull WW, Sutton HG: Chronic Bright's disease with contracted kidney ("arteriocapillary fibrosis"). R Med Chir Soc Lond, Med-Chir Trans **55:** 273–326, 1872.
11. Mahomed FA: The etiology of Bright's disease and the pre-albuminuric stage. R Med Chir Soc Lond, Med-Chir Trans **57:** 197–228, 1874.
12. Rowntree LG, Adson AW: Bilateral lumbar sympathetic neurectomy in the treatment of malignant hypertension. JAMA **85:** 959–961, 1925.
13. Bernard C: Influence du grand sympathique sur la sensibilité et sur la calorification. C R Soc Biol **38:** 163–165, 1851.
14. Brown-Séquard CE: Experimental researches applied to physiology and pathology. I-III. Med Exam Philadelphia NS **8:** 481–497, 1852.
15. Gaskell WH: On the structure, distribution and function of the nerves which innervate the visceral and vascular system. J Physiol **7:** 1–80, 1886.
16. Leriche R: De l'élongation et de la section des nerfs périvasculaires dans certains syndromes douloureux d'origine artérielle et dans quelques troubles trophiques. Lyon Chir **10:** 378–382, 1913.
17. Crile GW: A note regarding the possible surgical control of the kinetic system. Cleveland Med J **12:** 828–829, 1913.
18. Adson AW, Brown GE: Malignant hypertension. Report of case treated by bilateral section of anterior spinal nerve roots from the sixth thoracic to the second lumbar, inclusive. JAMA **102:** 1115–1118, 1934.
19. Page IH: Asteriasterol—a new sterol from the starfish and the sterols of certain other marine echinoderms. J Biol Chem **57:** 471–476, 1923.
20. Page IH: The effect on renal efficiency of lowering arterial blood pressure in cases of essential hypertension and nephritis. J Clin Invest **13:** 909–915, 1934.
21. Page IH, Heuer GJ: A surgical treatment of essential hypertension. J Clin Invest **14:** 22–26, 1935.
22. Page IH, Dustan HP: A new, potent antihypertensive drug. Preliminary study of [2-(octahydro-1-azocinyl)-ethyl]-guanidine sulfate (guanethidine). JAMA **170:** 1265–1271, 1959.
23. Goldblatt H, Lynch J, Hanzal RF, et al: Studies on experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med **59:** 347–379, 1934.
24. Cash JR: A preliminary study of the blood-pressure following reduction of renal substance with a note on simultaneous changes in blood-chemistry and blood volume. Bull Johns Hopkins Hosp **35:** 168–180, 1924.
25. Tigerstedt R, Bergman PG: Niere und Kreislauf. Skand Arch Physiol **8:** 223–271, 1898.
26. Page IH: Chemistry of the Brain. Springfield, Ill, Thomas, 1937.
27. Page IH, Helmer OM: A crystalline pressor substance (angiotonin) resulting from the reaction between renin and renin-activator. J Exp Med **71:** 29–42, 1940.
28. Bumpus FM, Schwarz H, Page IH: Synthesis and pharmacology of the octapeptide angiotonin. Science **125:** 886–887, 1957.
29. Rapport MM, Green AA, Page IH: Crystalline serotonin. Science **108:** 329–330, 1948.
30. Page IH: Serotonin. Chicago, Year Book Medical Publishers, 1968.
31. Page IH, ed: Chemistry of Lipides as Related to Atherosclerosis; A Symposium. Springfield, Ill, Thomas, 1958.
32. Page IH, ed: Methods in Medical Research. Chicago, Year Book Publishers, 1949.
33. Page IH: Physiology for Physicians. American Physiological Society, 1963–1966; Physiology in Medicine, published periodically in the N Engl J Med 1967.
34. Page IH, ed: The 'two worlds' of hypertension. Modern Med **45** (12): 13–18, 1977.
35. Page IH: The birth and adolescence of serotonin. Reprinted in Speaking to the Doctor; his responsibilities and opportunities. Minneapolis, Proforum, 1972.
36. Page IH: Why must physicians educate the public? Modern Med **44** (19): 9–14, 1976.
37. Page IH: Personal communication, October

5, 1966.
38. Comroe JH Jr, Dripps RD: Scientific basis for the support of biomedical science. Science **192:** 105–111, 1976; The Top Ten Clinical Advances in Cardiovascular-Pulmonary Medicine and Surgery between 1945 and 1975; How They Came About. National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, 1977, 591 pp.