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History of hypertension treatment

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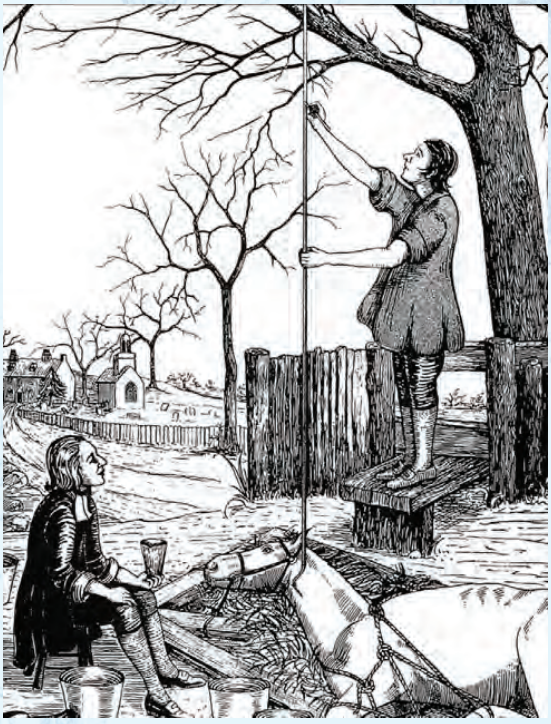
The first attempt to measure blood pressure (BP) took place in 1733, when Sir Stephen Hales introduced a brass pipe connected to a glass tube into a horse's leg artery and observed the rise of the blood column. Sir Hales, born in 1677, was a fellow at Cambridge University. His main interests were natural history and astronomy. He apparently conducted his first experiments on animals around 1708. In 1718, he was elected to the Royal Society, which encouraged his work. In 1727, he published his first textbook, *Vegetable Staticks*, and 6 years later the second volume, *Haemostatics* (or *Volume II of the Statical Essays*), in which he described the first experiments on BP measurements.[1] One of the most famous was conducted in 1714 on an old mare, which was otherwise to be killed as unfit for service. With the horse in the lateral decubitus position, he inserted a brass pipe with a 1/7-inch bore into its carotid artery and connected it to an excised goose windpipe, connected to a glass tube 12.75 feet high (Figure 1.1). After releasing the artery ligature, blood spurted to a height 9.5 feet above the level of the left ventricle, rising rhythmically with the heart contraction. Thus, Hales was the first to measure

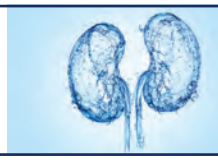
Figure 1.1. *Hales measuring blood pressure in an old mare. https://www.researchgate.net/figure/Stephen-Hales-measuring-blood-pressure-in-a-horse-1705_fig5_235774227*



and describe BP, and also the first to recognize the concepts of cardiac output and peripheral resistance.[2] He temporarily stopped his studies on circulation, resuming them some years later, when he also dedicated his time to the study of the left ventricle. Although his findings had a great scientific impact at that time, their importance was not fully recognized, even by himself.[3] Indeed, almost a century had to pass before other studies on the measurement of BP developed. The contribution of Poiseuille, a French physician, was certainly fundamental. In his doctoral thesis in 1828, he discussed the use of a mercury manometer for accurate pressure measurement, earning the gold medal of the Royal Academy of Medicine. His idea was a manometer connected to a cannula filled with potassium carbonate (an anticoagulant). Insertion of the cannula into an artery in experimental animals gave a measurement of the BP. Cannulating small arteries of about 2 mm in diameter, he also demonstrated that the pressure is maintained in small vessels.

Twenty years later, in 1847, Carl Ludwig, a professor of comparative anatomy, added to Poiseuille's manometer a kymograph that could record clinical data. He connected a float to a mercury column and a pen to the float as well as a recording cylinder. This was a sensational invention, but had the inconvenience of being invasive, because it required that an artery be punctured. In 1855, Karl von Vierordt, a German physiologist, hypothesized a noninvasive method, based on measuring the pressure that would be needed to cause the pulsation in an artery to cease, by connecting a weight to the lever of a sphygmograph. The idea was improved by the French physiologist Etienne Jules Marey and then by the physician Samuel S. Karl Basch, who built an inflatable rubber bag filled with water and connected it to a mercury-filled manometer bulb, from which a hollow column ran up. Pulsing the bag until the pulsation distal to the point of application ceased enabled the measurement of systolic blood pressure (SBP) with greater accuracy. French cardiologist Pierre C. Potain replaced water with air compression and added a second bulb and a portable aneroid manometer. BP measurements became increasingly accurate, although there was some initial reluctance to accept such instruments because, as the *British Medical Journal* wrote, they could lead to a reduction in the physicians' clinical acuity.[1]

A turning point came in 1890 thanks to the Italian Scipione Riva-Rocci, who published the results of his studies in two papers entitled "A new sphygmomanometer" in the *Gazzetta Medica di Torino*.[1] Riva-Rocci's sphygmomanometer consisted of a rubber bag surrounded by a nonexpandable material, wrapped around the entire circumference of an arm and inflated with air thanks to a rubber bulb. The pressure was increased until the palpation of the radial artery ceased and registered with a mercury manometer. The slow decrease in the pressure let the mercury column fall, and the point at which the pulse reappeared was taken as SBP. This method was easy



to apply, accurate, and noninvasive. It had just one defect: The cuff was too narrow (only 5 cm wide), leading to a less accurate measurement. In 1901, the German pathologist Heinrich Von Recklinghausen replaced the pressure cuff with one that was 12 cm wide. He also invented an oscillotonometer to measure diastolic blood pressure (DBP). The pulsation of an artery caused oscillations that transited to a larger one, which defined SBP, to a small one, which indicated DBP. Last but not least, the Russian empire surgeon Nikolai S. Korotkov deserves a mention because he invented the auscultatory method. He assumed that in normal conditions a perfectly constricted artery does not emit any sound. As the mercury in the column drops, the reappearance of the first tone indicates that part of the pulse wave of the blood passed under the sleeve, thus revealing SBP. As the mercury fell even more, other tones could be heard. The last tone one heard corresponds to DBP.[1]

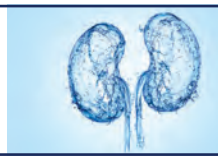
Renin discovery and the Goldblatt model

One of the milestones in the pathophysiological bases of hypertension was the discovery of renin. It was 1898 when Professor Robert Tigerstedt, a noted physiologist at the Karolinska Institute, and his student, Per Bergman, found that a substance produced in the kidneys passed into the blood and caused BP to increase. Their interest and hypothesis in renal pressor substances took inspiration from previous scientists, particularly from the studies of Richard Bright, Carl Ludwig, and Charles Brown-Séquard. Bright (1789-1858) was the first who suggested a link between kidney disease and hypertension, noting that people dying with contracted kidneys showed signs of cardiac hypertrophy and a full pulse. Brown-Séquard (1817-1894) was among the first who theorized that organs produce substances released into the blood that were not only waste products, but also "chemical messengers" with specific effects on other organs. Based on Brown-Séquard's experiments, Tigerstedt and Bergman homogenized fresh rabbit kidney in saline, centrifuged the material, and then injected the supernatant fluid into other rabbits. These rabbits showed an increase in BP, assessed with the kymographic method. The two scientists demonstrated that this substance was not present in urine; it was present in renal venous blood, but not in arterial blood; and it had a potent hypertensive action even in small quantity. They called it "renin."[4] The importance of renin was not recognized, even from its discoverer, until the pathologist Harry Goldblatt, in the 1930s, reawakened an interest in a substance that could act as a pressor agent, released from the kidneys in case of impaired renal circulation. Using animal models, he provided the bases for research that would lead to the discovery of the renin-angiotensin BP control system and, later, to the design of enzyme inhibitors for the treatment of hypertension.[5, 6]

Goldblatt's hypothesis that decreased blood flow and poor oxygen supply to the kidney could trigger hypertension was born after noting a narrowing of the renal vessels in patients who had died of hypertension. Goldblatt confirmed this hypothesis after clamping the major renal arteries of dogs bilaterally and recording a persistent rise in BP. Clamping other vessels such the splenic or the femoral had no effects on BP, thus demonstrating the kidney specificity of the substance. These brilliant achievements were first published in 1934 in the *Journal of Experimental Medicine*.

In 1936, two independent groups of researchers described the presence of a new compound in the renal veins of ischemic kidneys. One group was led by Dr. Eduardo Braun-Menendez from the University of Buenos Aires; the other one was the group of Irvin H. Page, from Eli-Lilly Laboratories in Indianapolis. With different and pretty simultaneous experiments based on animal models, they both demonstrated the existence of a substance, enzymatically activated by renin, which was the real culprit responsible for the BP elevation.[4] Braun-Menendez and colleagues published their work in a book in 1943. At the same time, Page's group tested a similar hypothesis by purifying renin extracts, noticing that it had no effect on increasing BP. They later suggested that renin was not the pressor agent. The substance was first named "hypertensin" in Buenos Aires and "angiotonin" in the United States. Braun-Menendez's results were presented in a conference at the University of Michigan and then published in a supplement of *Circulation*. It was clear that the two groups had discovered the same molecule, so they agreed to convert the name of the active compound into "angiotensin," the renin substrate of renin to "angiotensinogen," and the enzyme that degrades the peptide to "angiotensinase."[7]

In 1953, biochemist Leonard Skeggs and his group from Cleveland University discovered the two forms of angiotensin. In an attempt to purify angiotensin, they revealed not one but two pressor molecules, naming them "hypertensin I" and "hypertensin II," the latter of which was the real culprit of hypertension. They prepared renin with fresh hog kidneys and then injected it into horse blood. A first substance, hypertensin I, was converted into a second one, hypertensin II, by the action of a plasma enzyme that was activated by chloride ions. Similar results were obtained with human materials. Skeggs and colleagues concluded that in animals and humans there are two forms of hypertensin, the conversion from the former to the latter is enzymatic, and the necessary enzyme is present in human and horse plasma.[8] These findings intuitively led to the idea that an excessive secretion of renin must be necessary to induce hypertension. However, Laragh *et al.*[9] disproved this hypothesis. Indeed, they demonstrated that hypertension recognized multiple, complex interrelated mechanisms. In the following decades, the role of renin has been defined much better. Evaluating renin activity has been proposed as a screening test for patients with hypertension.



The role of the central nervous system

In the subsequent decades, the actors of the renin-angiotensin system (RAS) have been characterized gradually. Experiments using specific inhibitors of renin, angiotensin-converting enzyme (ACE), and angiotensin II, all of which block the system or compete for an effector site, have provided the basis for medical treatment of hypertension.[10] Angiotensin levels are dependent on renin levels, which in turn are directly controlled by angiotensin II, and indirectly on the effects of angiotensin on blood volume, BP, and sodium balance.

Studies have also concentrated on the nervous system. Adrenergic and cholinergic fibers run close to both vascular and tubular components of the juxtaglomerular system. Electrical stimulation of renal fibers induces a rapid increase in renin release and concomitant renal vasoconstriction. The electrical stimulation of the central nervous system, particularly in the mesencephalic pressor area or the medulla near the obex, also increases renin secretion in animal models. After renal sympathectomy, there is a decrease in basal renin levels, an abolished response to electrical central stimulation, and a decreased response to sodium depletion. Over the years, the mechanisms and the molecules influencing renin levels have been identified. Researchers have elucidated the role of sodium and potassium levels on the renin increase, the suppressive action of antidiuretic hormone, and the aldosterone-mediated feedback.

Anti-hypertensive drugs

In the 1940s, a few medications for the treatment of hypertension became available, although there was no consensus regarding the optimal BP values. The general thought was that BP <200/100 mmHg did not need to be treated. The textbook *Cardiology* from W. Evans (1948) defined hypertension as SBP ≥180 mmHg and/or DBP ≥110 mmHg on three consecutive examinations, and in the presence of evidence of cardiac hypertrophy.[11] The idea that only symptomatic hypertension is a disease and should be treated continued to spread in the 1950s, as shown in the first edition of *Principles of Internal Medicine* by Harrison.[12]

The case of President Franklin Delano Roosevelt is a clear example of the natural history of untreated hypertension. Despite reported values of 160/100 mmHg since the age of 54 years, he did not receive therapy. He developed heart failure symptoms and episodes of pulmonary edema, signs of left ventricular hypertrophy, and proteinuria. The cardiologist Howard G. Bruenn decided to try therapy with digitalis, in addition to a low-salt diet and other lifestyle changes including reduction in

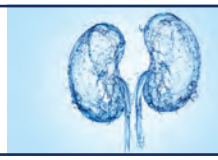
alcohol and smoking and limitation of the President's workday to 4 hours to relieve his stress. Roosevelt's health continued to worsen progressively as his BP continued to rise, and it is not surprising that his illness weakened his mental capacity and thus impacted his political role. On April 12, 1945, at the age of 63, Roosevelt suddenly died for an occipital hemorrhagic stroke while he was sitting for a portrait, immediately after saying he was experiencing a terrible headache. A BP of >300/190 mmHg was recorded. Nevertheless, his physician Dr. McIntire said his death "came out of clear sky," and his death shocked the entire world, which pictured him to be in excellent shape, when it was clear that his health had been declining for many years.[13, 14]

President Roosevelt is not the only famous example of the dangers related to uncontrolled hypertensive disease. The Yalta Conference, one of the most important of the past century, hosted three of the most influential men of the modern era: Roosevelt, Winston Churchill, and Joseph Stalin (Figure 1.2). Within two decades, all of them had died of stroke or its complications.

In those times, the absence of scientific evidence and remedies to lower BP led to an intuitive and nonscientific idea that hypertension could be managed with good organ perfusion spread. In his textbook *Heart Disease*, the cardiology pioneer Paul Dudley White (1886-1973) wrote that "The treatment of hypertension itself is a difficult and almost hopeless task in the present state of our knowledge, and in fact for aught we know, hypertension may be an important compensatory mechanism which should not be tampered with, even where is certain that we could control it."[15] In 1931, Professor John Hay wrote in the *British Medical Journal*, "There is a danger that patients may take the variations in their blood pressure too seriously," and also "The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it."

Between 1940 and 1960, several molecules were introduced but most of them had severe side effects, which made them poorly tolerated. The first one tested to treat hypertension was sodium thiocyanate, at the beginning of 1900, but it was rapidly abandoned because of its toxicity.[16] The antimalarial pentaquine, the herb *Veratrum virides*, molecules acting on the sympathetic nervous system (*i.e.*, phenoxybenzamine, hexamethonium, pentolinium, mecamylamine, and guanethidine), and others like reserpine and rauwolfia had a similar fate. Hydralazine was

Figure 1.2. *"The Big Three": W. Churchill, President F.D. Roosevelt and J. Stalin at the Yalta Conference, 1945.*



introduced in 1949: It could reduce BP but also induced headache and tachycardia. Thus, researchers experimented with combinations of drugs in an attempt to reduce the side effects of high doses of a single agent. It is important to underline that most of these molecules were initially tested on animals and then in humans, but not in scientific trials. Moreover, the etiopathogenesis and consequences of untreated hypertension were not yet fully understood, and it was unclear whether mild-to-moderate hypertension needed to be treated or whether its treatment would have any morbidity or mortality benefits.

A big step in scientific research came in 1957 with Freis *et al.*[17] from Washington University. As previous animal experiments demonstrated increased urinary excretion of sodium, potassium, and chloride after oral administration of chlorothiazide, they decided to test this drug on 10 untreated patients with hypertension under carefully controlled conditions. The patients were hospitalized, and their salt intake was reduced and standardized to stabilize BP. Chlorothiazide was administered for 1 week, demonstrating a consistent BP reduction in all the patients, with an average reduction of 18.7% and 13.9% in SBP and DBP, respectively. Increased diuresis and weight loss were reported; some patients experienced transient nausea and weakness during the first months. In subjects with signs of postural hypotension, chlorothiazide exaggerated it, but it did not cause postural hypotension. No other significant adverse reactions were reported. Then the molecule was tested in a multiple-drug regimen in 73 patients who were receiving hydralazine, reserpine, ganglionic blocking agents, or *Veratrum* alkaloids, and in five patients who had previously undergone dorsolumbar splanchnicectomy. Both groups showed a >20% decrease in BP at an average follow-up of 3.5 months. Chlorothiazide was also administered in 15 normotensive patients, hospitalized for extracardiac diseases (pneumoniae, osteoarthritis, diabetes mellitus, and peptic ulcers) under the same conditions (salt-controlled diet): this subgroup did not show a >10% BP decline. Serum levels of sodium, potassium, and chloride were assessed and monitored, showing a tendency to decrease but without falling below the normal range. Symptoms of congestive heart failure improved. There were no significant electrocardiographic changes. Freis *et al.*[17] concluded their report with a hypothetical mechanism of action of chlorothiazide, which was supposed to be related to a salt-depleting effect. They also underlined that their follow-up was too short to determine definitively the safety and the absence of delayed toxicity of this new antihypertensive agent.

In the same period, acetazolamide and later osmotic diuretics were discovered.[18-21] Among loop diuretics, the first compounds tested were furosemide and bumetanide, both sulfonamide derivatives. Ethacrynic acid was found to not have sulfonamide moiety; thus, it could be used in case of sulfonamide allergy.[22] Today, diuretics are recommended as a first-line therapy in hypertension, according to the most recent European Guidelines.[23]

The history of mineralocorticoid-receptor antagonists (MRAs) began between the 1940s and 1950s as some scientists tried to identify inhibitors of aldosterone activity. Among them, the independent groups of Selye, Kagawa, and Liddle deserve a mention because they described the role of aldosterone in inducing nephrosclerosis and cardiac fibrosis, and their work led to launch spironolactone as a diuretic for the management of edematous conditions, primary aldosteronism, and essential hypertension. Later potassium canrenoate, canrenone, and more recently eplerenone were introduced in clinical practice.[24] In the following decades, several trials were conducted to explore the efficacy of MRAs in several diseases, mainly heart failure. MRAs are actually recommended in resistant hypertension, when the first line therapy cannot effectively control BP.[23] The 2015 PATHWAY-2 randomized controlled trial (RCT) (ClinicalTrials.gov Identifier: NCT02369081), a four-way crossover trial conducted on 335 patients with resistant hypertension that compared the use of spironolactone *versus* bisoprolol, doxazosin, or placebo, demonstrated the superiority of spironolactone over the others. The 2012 ReHOT trial found that clonidine was not superior to spironolactone in patients with true resistant hypertension, but the overall BP control was lower, suggesting spironolactone is preferable in those subjects. The meta-analysis of a subsequent RCT (ClinicalTrials.gov Identifier: NCT01643434) confirmed those findings.

β-blockers were discovered in the early 1960s.[6] They have been shown to effectively treat angina and cardiac arrhythmias, their original purpose, as well as several other conditions including hypertension.[25] The first β-blocker was propranolol, introduced in 1964 by Sir James Black (1924-2010), a Scottish pharmacologist awarded the Nobel Prize for Medicine in 1988, who was searching for a treatment able to reduce oxygen consumption in the event of an angina attack, by "stopping the effects of adrenaline on the heart." His studies were guided by the experiments conducted by Raymond P. Ahlquist on the adrenoceptor subtypes.[26] Practolol was released in 1966 from the team at Imperial Chemical Industries, with the aim to eliminate the bronchoconstriction effect of propranolol. In 1973, new cardioselective β-blockers were developed (*i.e.*, atenolol and metoprolol), and they soon replaced practolol. Third-generation β-blockers (the "vasodilating β-blockers" carvedilol, labetalol, and nebivolol)[25] came a few years later. β-blockers were included in the first clinical trial a decade after Black's works.

The Medical Research Council (MRC) trial was the first to test the efficacy of propranolol compared with thiazide and placebo in an initial cohort of 1,849 patients with mild hypertension. The study ran from 1973 to 1977 and the results were published in 1985, 20 years after the discovery of propranolol, with data on more than 17,000 subjects with an average follow up of 5 years. The conclusions were that the active treatment reduced strokes rate but not coronary events; moreover, β-blockers