Progress in Hypertension Research

1900–2000

Jacques Genest

Abstract—The author reviews the various factors (sodium, aldosterone, renin-angiotensin system, and norepinephrine; each of these factors being influenced by others) involved in the mechanism of human hypertension. A coherent picture is emerging, with the final pathway of these mechanisms converging on the renin-angiotensin system in the presence of a positive sodium balance and responsible for arteriolar resistance and responsiveness to pressor agents. This would correspond to the labile phase of hypertension, which leads with time to arteriolar restructuring and the increased media/lumen ratio, as demonstrated by Schiffrin and coworkers, and which can revert to normal structure with the administration of antihypertensive drugs such as converting-enzyme inhibitors, calcium-blocking drugs, and antagonists of the angiotensin II type 1 receptor. The author also presents the experience obtained in the Hypertension Clinic of the Clinical Research Institute of Montréal, which has been in existence since 1953; this experience is based on the observation of senior observers (clinical scientists, clinicians, and nurses) that the blood pressure of hypertensive patients can be controlled to normal levels in almost all cases for years and decades with a proper combination of the present antihypertensive drugs. (Hypertension. 2001;38:e13-e18.)

Key Words: sodium ■ aldosterone ■ renin-angiotensin system ■ norepinephrine

The extensive financial support given to the study of hypertension from the point of view of its mechanisms and management is based on its high incidence (≈25% of the population has blood pressure [BP] >140/90 mm Hg); the markedly decreased life expectancy, because of severe complications, if it is not treated; and the fact it is one of the largest healthcare expenditures.

In this presentation, we will deal with (1) the physiopathological molecular biology and genetic mechanism hypertension and (2) its modern management, which is one of the major advances in modern therapeutics.

Mechanisms of Hypertension

In our view of the mechanisms of essential hypertension (EH), there are 3 major landmarks. First in 1904, Ambard in France reported the BP lowering effect of a low-salt diet in hypertensive patients. Allen confirmed this in the period of 1918 to 1922. Later in the mid 1940s, similar observations were reported in patients on the rice-fruit diet of Kempner, who found this effect by serendipity. Dole, Dahl, and Cotzias showed conclusively in 1951 that this diet had a low-sodium content and that BP in patients with EH was often a function of the amount of salt ingested. Many others confirmed that hypertension could be corrected by a diet containing <230 mg of sodium per day to levels ≤140/90 mm Hg in 35% to 50% of patients with EH.

Second in 1934, Goldblatt and coworkers produced hypertension in dogs by narrowing 1 or 2 renal arteries by means of silver clamps. They attributed this effect to a substance that Tigersted and Bergman in 1898 called renin and to the pressor effects of crude renal extracts. This led to the renal experimental model of hypertension and a flurry of work in this field. It was quickly established that purified renin had no pressor effect by itself and acted on a plasma globulin called angiotensinogen (452 amino acids) to liberate the first 10 amino acids, thus yielding angiotensin (Ang) I, again an inactive substance. Renin is present principally in the juxtaglomerular cells of kidneys and, as demonstrated by Ganten and others, in the adrenals, brain, and many extrarenal tissues. The work of Skeggs demonstrated that the active pressor substance Ang II (an 8AA peptide) is liberated from Ang I by a converting enzyme, which released His 9–Leu 10 from Ang I in the presence of chloride ions. Ang III, a des-aspartyl heptapeptide of Ang II, has only 25% of the pressor activity of Ang II, but the major route goes directly from renin to Ang II. Since the 1940s, this enzymatic cascade became known as the renin-angiotensin system, with Ang II being the most important pressor substance. The kidney was thus probably implicated in the pathogenesis of hypertension.

These findings formed the basis and starting point of our working hypothesis in 1945 that there were in EH at least 2
important factors involved: the renin-angiotensin system from the kidney and a dysregulation of sodium. It was generally believed that the key factor involved in the renal regulation of sodium was most probably of adrenal origin. In this search, Tait and Simpson succeeded in 1952 in isolating aldosterone from the amorphous fraction of adrenal extracts; Wettstein and associates at Ciba in Basle chemically characterized aldosterone in 1953.

Since these major contributions, many other pieces of evidence linked sodium to hypertension. Among them, some of the most important are (1) the effectiveness of a low-sodium (<230 mg/d) or rice-fruit diet in 35% to 50% of hypertensive patients with a decreased arteriolar responsiveness to norepinephrine and Ang II; (2) the effectiveness of natriuretic agents alone or in potentiating the effects of other anti-hypertensive drugs; (3) the absence of hypertension in populations on low-sodium or very low-sodium diets; (4) the prolonged pressure response to cross-transfusion of blood from a renal hypertensive rabbit to a high salt-fed rabbit in contrast to the absence of any effect in rabbits fed a normal diet; (5) the increase of sodium concentration in red blood cells, leukocytes, and lymphocytes in patients with EH; and (6) the production of hypertension in a strain of rats on high sodium intake (Dahl rats).

Many observations showed a relation between aldosterone and hypertension: (1) a mean increase in urinary excretion of the 3-oxo conjugate metabolite in patients with EH, and (2) an increase in plasma aldosterone in 2-month-old spontaneously hypertensive rats (SHR) and a significantly enhanced response to adrenocorticotropic hormone compared with that of control rats (this latter finding was also observed in hypertensive patients). In human hypertensive patients compared with control subjects, there is (3) a blunted aldosterone response to severe sodium restriction or depletion; (4) a lesser suppression of aldosterone secretion rate, urinary secretion, and plasma levels on a high sodium intake (300 mmol/L per day); (4) an exaggerated plasma aldosterone increase in response to Ang II infusions; and (5) a marked increase in digital vascular reactivity in hypertensive patients when pretreated with aldosterone (1 mg IM for 3 days).

Third, with the finding that aldosterone was the key adrenal steroid involved in the renal regulation of sodium excretion, the search began for a connection between pressor substances (norepinephrine, Ang II, and others) and aldosterone secretion and salt. It was here that in 1959, our group made the key contribution that Ang II is the major stimulant of aldosterone production, whereas other pressor agents such as norepinephrine and phenylephrine, for example, were without any effect at infusion rates inducing similar increases in BP. These findings first reported in October 1959, and in early 1960 they were confirmed by Laragh and by the groups of Davis, Ganong, and Mulrow.1,2

Now, at last, we could integrate the renin-angiotensin system with the adrenal secretion of aldosterone and the renal regulation of sodium, which is now expressed as the renin-angiotensin-aldosterone-sodium (RAAS) system, to which so many researchers have devoted long and intensive efforts to clarify its various aspects and their relationships with other factors and to establish its fundamental role in human hypertension.

The role of the nervous system is mainly linked to the vasoconstrictor activity of norepinephrine, a major pressor substance liberated by the sympathetic nervous system and shown to be dependent on the sodium balance, being much less vasoactive under severe restriction or depletion and enhanced by high salt intake and aldosterone. The same vasoactivity dependence on salt balance was shown for Ang II. The norepinephrine plasma concentration in patients with EH is similar in most studies to that of normal subjects in the same age group. In addition, renin secretion is increased by infusions of norepinephrine, so that a relationship could be established between the sympathetic nervous system and the RAAS system.

Clinical experience during the past 50 years has taught me that the role of the nervous system (ie, of stress) is the single most frequent aggravating factor in patients with established EH. But it is not the causal factor, except for brief periods and under conditions of acute and severe stress. Such stress can provoke a marked rise of BP for days, weeks, and even months, sometimes culminating in complications of a cerebrovascular or coronary nature. The resolution of such stresses is accompanied by a return of the BP to normal levels or, in already hypertensive patients, to more a mildly elevated state. Experimentally, normalization of BP in normotensive subjects or animals occurs rapidly after cessation of prolonged pressor infusions of norepinephrine.

In the past 50 years, there has been much debate among researchers as to the respective part exercised by the components in a closed system made of a pump (heart), arteries of progressively decreased diameter, and blood volume. It was demonstrated that at times and in special conditions, an increased cardiac output (eg, thyrotoxicosis) or increased blood volume (eg, polycythemia) could be incriminated in these forms of hypertension. But it is now generally accepted that the key factor involved in EH is the increased peripheral resistance of the precapillary arterioles to the flow of blood ejected by the heart. It is at this level that the RAAS system plays a major role.

A major concern of many researchers has been to determine whether the structural changes in the precapillary arterioles were the cause of the increased BP or a consequence of it. It has been our view that the primary event in the early and labile phase of hypertension is an increased toxicity or stiffness and responsiveness of these small arterioles to the pressor activity of Ang II and norepinephrine as a consequence of an increased renal tubular reabsorption of sodium because of excessive sodium intake or of genetic mutation. This leads in the long term to structural changes (increased media width and media/lumen ratio) and a state of established hypertension. (This aspect was examined in great details in Genest3).

Many factors counteract the elevation of BP and the impaired sodium excretion by the kidney. They are the atrial natriuretic factor, vasopressin, bradikinin, NO, kallikrein, medullipin, and others. The role of endothelin, a potent vasoconstrictor produced by vascular endothelial cells, remains to be elucidated, as well as the interplay of all these
factors at the level of the precapillary arterioles—the site of the increased peripheral resistance (Figure 1). But it is now more widely accepted that the hypertensive process expresses itself through the common final pathway of the RAAS system. A confirmation was recently provided by the work of Schiffrin and his group on the regression of the structural arteriolar changes in human EH after the chronic administration of antihypertensive drugs interfering with this system (see Management of Human Hypertension below).

Now, after what might be called the physiopathological era, many researchers in the past few years have concentrated their efforts to elucidate the genetic factors involved in hypertension. In this field, Lifton’s group at Yale has been at the forefront of research in elucidating some of the genetic disorders in the rare mendelian, monogenetic forms of hypertension. As recently stated by Lifton, “molecular genetic studies have now identified mutations in 8 genes that cause mendelian forms of hypertension and 9 genes that cause mendelian forms of hypotension. As recently stated by Lifton, “molecular genetic studies have now identified mutations in 8 genes that cause mendelian forms of hypertension and 9 genes that cause mendelian forms of hypotension (such as in Bartter syndrome). The mutated gene products in all cases act by altering the tubular sodium reabsorption”.

Some examples include the following.

**Syndrome of Glucocorticoid-Remediable Aldosteronism**

The syndrome of glucocorticoid-remediable aldosteronism was described in 1966 by the group of Laidlaw, who showed high aldosterone levels suppressed renin activity and hypokalemia and significantly increased urinary excretion of 18-oxo-cortisol and 18-OH-cortisol. Ectopic aldosterone secretion occurs in these cases in the adrenal fascicular zone under the stimulation of adrenocorticotropic hormone (ACTH). Lifton and his group have shown that it is due to a chimeric gene, a crossover of aldosterone synthase, and 11-β-hydroxylase genes and that it encodes a protein with aldosterone synthase activity regulated by ACTH. Administration of cortisol suppressed the secretion of ACTH and consequently of aldosterone, and spironolactone corrects the excessive renal sodium reabsorption and the hypertension. It has been strongly recommended that hypertensive children with a family history of hypertension and suppressed plasma renin levels should be screened for GRA.

**Syndrome of Mineralocorticoid Excess**

The hypertension syndrome of “mineralocorticoid excess” with low levels of renin and aldosterone and with hypokalemia is associated with an absence in 11-β-hydroxysteroid dehydrogenase, which normally converts cortisol to cortisone, a steroid incapable of activating the mineralocorticoid receptor. This deficiency is responsible for the excessive unmetabolized cortisol, which exerts its mineralocorticoid activity and subsequently increases renal sodium reabsorption. A similar 11-β-hydroxysteroid dehydrogenase deficiency is seen in patients with hypertension caused by high licorice ingestion, because of its content in glycyrrhetinic acid, and possibly with patients with Cushing’s syndrome.

**Suppression of Plasma Renin Activity and Aldosterone**

Another extremely rare hypertensive condition, first described by Liddle, consists of suppression of plasma renin activity and aldosterone, and responds to the administration of amiloride and triamterene, 2 inhibitors of the epithelial sodium channel (ENaC). Mutations in the β- or γ-subunits of ENaC gene (on chromosome 16) were found to be responsible for the increased renal sodium reabsorption.

Such studies strongly suggest that the renin-angiotensin-aldosterone-sodium system and the renal mineralocorticoid receptor are the final pathways of hypertension process (Figure 2). It is a confirmation of the starting hypothesis of our own research work back in 1948 that sodium and the kidneys through its renin-angiotensin system were intimately involved in the basic mechanism of hypertension.

Despite these impressive advances in understanding the molecular basis for some of the rare monogenic forms, study of populations of patients with EH in whom the disease is known to result from the actions of multiple genes has been frustrating. As a result, there does not exist a predictive genetic test for hypertension risk in humans. Many excellent scientists are studying the genetics of hypertension and
end-organ damage in animal models, and this work has the potential to identify new genes and new intervention targets in the future. With the advent of the sequence of the entire human genome, we can expect the pace of research on the genetics of EH to pick up dramatically over the next few years.

Efforts are being made in several laboratories throughout the world to unravel the genes responsible for EH, using predominantly linkage and association studies for testing for candidate genes. Similar efforts are made for the experimental types of hypertension, such as the Dahl rats and the SHR, in which some suspect overexpression of the renin gene. Despite the great advances made in the past 50 to 60 years, fundamental questions remain. First, how does the RAAS system exert its effect at the arteriolar level and how do we unravel the complex interplay of the many factors (including neurogenic) influencing myogenic tone and contractile response to vasoconstricting and vasodilating agents in the ionic (sodium, potassium, magnesium, and calcium) environment of the precapillary arteriolar cells. Second, the fine tuning of the final sodium excretion in EH must be elucidated. The integration of the key factors involved (1) the mineralocorticoid receptors, their genetic mutations, and the sodium exchange and transport systems; (2) the major hormonal factor, ie, the RAAS system and the interplay of others such as atrial natriuretic factor, endothelin, NO, local prostaglandins, and kinins; (3) the reflex pressor sensors in the atria and pulmonary reamins in the carotid sinus and the aorta arch and in the glomerular afferent artery, especially in relation to the role of the sympathetic nervous system and the release of norepinephrine; and (4) blood flow and renal perfusion pressure, including the glomerular filtration rate, the medullary blood flow, and the peritubular capillary hydrostatic pressure.

Management of Human Hypertension
The advances made in the management of human hypertension are even more impressive because of their importance in the lives of patients, their productivity, and the significantly decreased incidence of hypertensive complications and reduction of expenditures in the healthcare system.

Despite severe criticisms and shortcomings of the large clinical trials, since the first one done by Freis in 1967 and 1970 (there have been ≈15 more such large trials since), on the effects of specific antihypertensive drugs (several now used infrequently or not at all) on the mortality and morbidity of hypertension, they nevertheless demonstrated conclusively that even a small reduction of BP resulted in a significant decrease in the incidence of the severe complications such as cerebral hemorrhage, atherothrombotic stroke, myocardial infarction, congestive heart failure, and renal failure. But the major aim of these large trials was not the management of the individual patients with EH and the control of their BP to normal. This aspect has been left to the practicing physician.

Despite all the efforts and the extensive educational programs and the fact that there is a 25% incidence of EH in North Americans, it remains a fact that only 16% (Canada) to 27% (USA) of patients are well controlled with BP, 140/90 mm Hg. These findings contrast greatly when they are compared with the successful management of almost all hypertensive patients in specialized clinics with the antihypertensive drugs now available (see below). The success seen in these clinics indicates the importance for patients with moderate to severe EH to be managed by clinicians with a long experience in the field and who are best equipped because of their knowledge of the disease and of the pharmacology of these drugs. Numerous guidelines have been proposed for a more effective management by the practicing physicians.

There are many such hypertension clinics in university hospitals and in medical centers such as Mayo Clinic, Cleveland Clinic, and Oschner Clinic. But I would like to describe briefly the organization and results obtained at our own clinic at the Clinical Research Institute of Montreal and at the University of Montreal Hôtel-Dieu Hospital since 1953.

Our clinic was held once a week and then twice a week for several years, with 6 to 8 senior physicians and clinical scientists with a large experience in the field and with 4 or 5
specialized nurses who were trained in checking compliance to drugs and diet and in inquiring about their emotional and social aspects and were available at all times during the day for calls from patients. The clinical group also included a dietitian and the active collaboration of cardiologists, nephrologists, endocrinologists, ophthalmologists, a vascular surgeon, a radiologist, urologists, and a pathologist. This clinic was a division of our Hypertension Group, which also had the control of a large section of the hospital clinical investigation unit, where patients could be investigated in full, and of research laboratories, which were under the same scientific direction. These laboratories provided the biochemical support for the determination of plasma renin activity, Ang II, steroids (aldosterone, cortisol, and others and their metabolites, progesterone, dehydroepiandrosterone) and catecholamines (norepinephrine, epinephrine, dopamine, and their metabolites). The whole constituted the Multidisciplinary Research Group on Hypertension supported for the past 3 decades by a Group Grant from the Medical Research Council of Canada (now the Canadian Institutes for Health Research). At the clinic, there was an average of 350 to 400 new patients referred per year and 700 to 1100 patients followed every year, for 3500 to 7000 patients visits per year.

I am firmly convinced on the basis of our experience that in “using what we know” about hypertension physiopathology (Lenfant et al.), >95% of patients with EH—whatever the initial level of their BP—can be controlled to normal levels for years and for more than a decade with the existing drugs with no or minimal side effects and with greatly improved quality of life provided that (1) these patients were thoroughly evaluated and secondary causes of hypertension were eliminated (renovascular, primary reninism, primary aldosteronism, unilateral renal atrophy glucocorticoid remediable aldosteronism [all associated with an overactive RAAS system], Cushing syndrome, pheochromocytoma, coartation of the aorta, contraceptive pills, licorice), and (2) a judicious combination of antihypertensive drugs is used. Such combinations used since the 1960s permit a lower dosage of each drug and decrease the incidence of side effects.

One quite important aspect of such a clinic, besides the pharmacological expertise and clinical competence of the physicians, is the atmosphere provided by a personnel quick to smile and provide help, especially a staff of highly intelligent nurses actively participating and interested in their work. A consequence is a harmonious atmosphere and a close rapport with patients, who in return easily confide to the nurses about worries (such as family or work) and their emotional stresses. Compliance is easier to verify, and the patient becomes a friend and does not feel like he is a number!

The 5 groups of drugs most commonly prescribed at the present for the control of hypertension, are (1) the thiazide diuretics (1958), which occupy a central place in the modern treatment of hypertension; (2) the β-blockers (1970s), which block norepinephrine release and decrease renin production; (3) the calcium-channel blockers (1979), which decrease the entry of calcium in arterioles; (4) the inhibitors of the converting enzyme (1977), which block the conversion of Ang I into Ang II, the effector component of the renin cascade; and (5) recently in the 1990s, the Ang II type 1 receptor antagonists. Other drugs such as α-methyldopa, clonidine, hydralazine, and spironolactone can be added and may be quite beneficial in certain cases of hypertension. A new group of vasopeptidase inhibitors (specifically of neutral endopeptidases and ACE) is under intensive study at present.

Since 1953, we have made a systematic recommendation to all our patients to follow a diet without added salt (at the table or of salted food such as chips, salted peanuts, salted popcorn, soy sauce, bouillons, and frozen dinners), a diet restricted to about 3 to 4 grams of salt per day and with low animal fat (little or no butter, cream, mayonnaise, egg yolk, or cheese and elimination of meat fat and rich desserts). Such a diet was easy to follow and was recommended at the time on the basis of the work of Ahrens, Beveridge, Kinsell, and Mustard and their groups, who demonstrated in the 1950s the dietary link of animal fats to plasma cholesterol and platelet aggregation. It was also in line with the old observations of the effects of salt restriction by Ambard (1904), Allen (1918–1922), Kempner (1945), Dole (1946), and many others. It is important to recall that >60% of hypertensive people are salt sensitive and that dietary sodium restriction to 10 mmol/d was shown to lower BP to normal levels in 35% to 50% of hypertensive patients.

The effective management of most hypertensive patients implies more than the mere prescription of antihypertensive drugs and often requires important changes in lifestyle. Factors other than the genetic and physiopathological are frequently involved in the severity of hypertension and must be corrected and prevented. These factors are related to overeating (obesity); to excessive intake of salt, of “rich” foods, and of alcohol; and to the innumerable stresses of modern daily life. Their “management” by the patients requires self-discipline (or self-control), willpower, moderation, and a better adaptation or attitude toward various stresses—all qualities judged essential for a right way of life by the great Greek and Roman scholars of the Stoic School of Cicero and Seneca and by the great religions. It also implies (1) the acquisition of a greater degree of serenity, for which transcendental meditation can also be of help in decreasing the level of mental tension under which we live; and (2) daily moderate exercise such as walking, swimming, and cycling.

Finally, I must point to an additional advantage for our clinic in the management of our patients. We were greatly helped in our clinic by the healthcare system in Canada, which is free, ie, no direct cost to the patients for doctor visits, consultations, and tests (biochemical, hormonal, radiological, imaging, nuclear medicine, and others). In addition, at least in Quebec, a compulsory government drug insurance plan provides drugs at a greatly reduced cost or for free above a maximal contribution of $750.00 (Can).

Many studies in the past 20 years and the data from the National Center for Health Statistics (1999) have confirmed the marked decrease in the mortality rate from stroke and coronary heart disease by >65% and 53%, respectively. In our clinic, we have encountered in the past 15 years no case of cerebral hemorrhage, malignant hypertension, or advanced renal failure, thanks to the various education programs and the efficacy of new drugs. Severe complications, when they
occurred, were the consequence not of the hypertension itself but of atherosclerosis (atherothrombotic stroke and coronary thrombosis). Is it necessary also to emphasize how much quality of life is improved in patients with BP controlled to normal levels who are free of the anxieties of possible and severe hypertensive complications?

The recent work of Schiffrin and his group is of special interest. Following the observations of Mulvany on arterioles and vascular remodeling, Schiffrin has demonstrated, in patients with mild EH and with BP controlled to normal levels by antihypertensive drugs for 1 or 2 years, a regression of the structural changes, ie, a decrease of the media thickness and media/lumen ratio to normal and of the excess collagen deposition. This structural normalization occurs after the administration of Ang II type 1 receptor antagonists, inhibitors of ACE, and calcium-channel blockers but not with β-blockers, despite a similar decrease of BP to normal levels (Figure 3). These results suggest that the arteriolar structural changes are the result of the increased BP and not its cause.

The very great and rapid advancement of our knowledge of the mechanisms of hypertension and the effective management of the individual hypertensive patient are in my view two of the great accomplishments of modern medicine and a major contribution to public health. It is the result of close collaboration between clinical scientists, expert clinicians, and researchers in universities, research institutes, and pharmaceutical industry.

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References

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