Pathophysiology of Hypertension – the Mosaic Theory and Beyond

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Abstract

Dr. Irvine Page proposed the Mosaic Theory of Hypertension in the 1940s advocating that hypertension is the result of many factors that interact to raise blood pressure and cause end-organ damage. Over the years, Dr. Page modified his paradigm, and new concepts regarding oxidative stress, inflammation, genetics, sodium homeostasis and the microbiome have arisen that allow further refinements of the Mosaic Theory. A constant feature of this approach to understanding hypertension is that the various nodes are interdependent, and that these almost certainly vary between experimental models and between individuals with hypertension. This review discusses these new concepts and provides an introduction to other reviews in this compendium of Circulation Research.

Introduction: The state of clinical hypertension in 2021:

According to the 2017 guidelines of the American Heart Association, almost one half of the adult population in the United States has hypertension,[1] and the Global Burden of Disease study ranks elevated systolic pressure as the leading cause of lost years of quality life.[2] Despite advances in medical therapy, hypertension remains a major risk factor for stroke, heart failure, renal failure, atherosclerosis and we now recognize dementia. In large part this

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is because almost one half of individuals with hypertension are not aware that they have this disease, and hypertension is not adequately treated in about one half of those in whom the diagnosis is made.[3]

Clinical hypertension can be grouped into two broad categories. Primary (or essential) hypertension represents between 85 to 95% of human cases and has an unidentified etiology. In contrast, secondary hypertension is caused by identifiable underlying conditions, including renal artery stenosis, pheochromocytoma, adrenal adenoma or single gene mutations. Historically, most patients were screened for secondary causes. However, it is now clear that this is not cost effective and that in the absence of compelling clinical findings (abdominal bruit, hypokalemia, clinical symptoms of a pheochromocytoma) or a pressing need to improve treatment (drug resistant hypertension) patients are generally treated without such an evaluation.

Pathophysiological/historical concepts:

The elusive nature of primary hypertension and the precise mechanisms underlying an elevation of blood pressure, even in cases of secondary hypertension and in models of experimental hypertension, have remained a focus of debate and research for more than a century. Beginning with seminal observations by Robert Tigerstedt,[4] Franz Volhard,[5, 6] and subsequently refined and elegantly published by Goldblatt,[7] it became apparent that the ischemic or underperfused kidney releases a substance or substances that can raise the blood pressure in recipient animals. These early findings set the groundwork for Irvine Page and Braun Menendez in 1939 to report their discovery of a potent vasoconstrictor and pro-hypertensive agent isolated from renal extracts that they named hypertensin and angiotonin, respectively.[8, 9] They ultimately agreed to call it angiotensin.[10]

Irvine Page is among the most prominent pioneers of hypertension research and is notable for his enduring contributions. In his initial experimental observations with Oscar Helmer, he discovered that when preparations of renin were exposed to plasma containing what he termed "renin activator" a pressor substance was formed that could raise blood pressure up to 300 mmHg. He named this substance "angiotonin".[11] It would have been easy to assume that this elevation of blood pressure was entirely due to intense vasoconstriction. However, his further observations suggested this was an inadequate explanation. In a classic paper in 1949, he summarized evidence that hypertension could be mediated by the central nervous system, cardiovascular factors, endocrine factors and perturbations of renal function.[12] He provided evidence that the hypertension induced by acute injections of "angiotonin" could be reversed by ganglionic blockade with tetraethylammonium. In a subsequent study, Dr. Page and colleagues reported that low rates of angiotensin II infusion had minimal or no effect on blood pressure in the first hours after starting the infusion, but increased blood pressure by 30 mmHg 24 hours later,[13] suggesting the importance of mechanisms beyond immediate vasoconstriction. His discovery of this "slow pressor" response to angiotensin was, in itself, a major contribution to the field and has given subsequent investigators a valuable model of human hypertension. He reported further that these infusions of low dose angiotensin II caused the blood pressure to become highly labile, such that minimal environmental stimulation would cause enormous increases in pressure, accompanied by

increases in heart rate. These increases in blood pressure were exacerbated by tyramine (that releases norepinephrine from nerve terminals) and were blocked by guanethidine (that prevents norepinephrine release). Page concluded from these highly insightful studies that "angiotensin causes hypertension by an indirect action mediated by the central nervous system, an action independent of its vasoconstrictor action".[13] He observed that renin was not elevated in the chronic phase of many cases of human hypertension and surmised that human hypertension has complex origins, and therefore presumably was multifactorial. In his 1949 paper, he chose to describe this multifactorial nature by the term "Mosaic", pointing out that "… many mechanisms are more or less involved. Elevated blood pressure is the resultant of multiple forces acting on the variety of tissues which compose the circulatory apparatus." In a subsequent review, Dr. Page presented a now iconic octagonal diagram (Figure 1A), that has been modified and often reproduced to illustrate his concept that hypertension is caused by multiple factors, including neural and chemical perturbations, alterations of vascular caliber and elastance, cardiovascular reactivity, blood volume and viscosity.[14] Dr. Page subsequently revised the Mosaic Theory to include more general terms (Figure 1B),[15] however the principle of his Mosaic Theory has prevailed to the present day. [16, 17] It is fascinating to ponder that the factors composing his Mosaic Theory reflect an ongoing central discussion about the importance of the kidney (volume and cardiac output), the vasculature (elastance, vascular caliber and reactivity) and the central nervous system (reactivity and neural). In the past two decades, there have been numerous refinements of our understanding of the nodes in Figure 1A and 1B, and entirely new concepts. In this review we will begin by considering time honored topics: the roles of the kidney, the vasculature and the central nervous system and a prevailing effect of aldosterone in hypertension. We will then discuss new concepts that have emerged in the past two decades that Dr. Page did not consider in his writings, but likely influence every node in the Mosaic diagram. Many of these topics are covered in greater depth by other articles in this compendium.

The role of the kidney and body fluid volumes in hypertension:

The kidney is an important node in Dr. Page's Mosaic Theory. Figure 1A refers to volume and cardiac output. Cardiac output is the product of heart rate and cardiac stroke volume. Stroke volume is dependent on venous return and is governed in large part by the kidneys and their modulation of volume homeostasis. Guyton built on these early concepts of Irvine Page to elaborate a complex mathematic model of the dynamic interactions between many of these Mosaic components.[18] The model predicted that the renal pressure natriuresis mechanism regulated the body fluids and thereby exerted a primary role in setting the level of blood pressure, while the central nervous system and vascular function, amongst others, provided important modulation. The critical role of the kidney has been illustrated repeatedly by studies in which the kidneys of hypertensive animals raise blood pressure, or permit hypertension, when transplanted into normal animals, dating to seminal work by Fasciola et al.[19] Dahl et al performed cross transplantation of kidneys between salt sensitive and salt resistant rats and showed that hypertension followed the kidney.[20] Moreover, the transplant of kidneys from normotensive donors into patients with renal failure from hypertensive nephrosclerosis has led in some cases to a slow reversal of their hypertension

and some of the accompanying organ damage.[21] Crowley et al subsequently reported that transplantation of kidneys from mice lacking the angiotensin type 1 receptor protected wild type recipient mice from angiotensin II-induced hypertension, while transplantation of wild type kidneys into AT1R ko mice restored their ability to develop hypertension upon angiotensin II infusion.[22] This refinement relates a critical component of hypertension from angiotensin II to activation of its principal receptor within the kidneys, and provides further mechanisms extending the theories of Page and Guyton.

The kidney has at least 4 major roles in hypertension. One is the production of renin, an aspartic protease that cleaves angiotensinogen to angiotensin I, which in turn is acted on by the angiotensin I-converting enzyme to generate angiotensin II. Renin is the rate-limiting step for activation of the circulating renin-angiotensin system (RAS) and its synthesis and secretion by the kidney is tightly regulated.[23] Renin is initially synthesized as the inactive precursor pro-renin, which is converted to active renin upon binding to the pro-renin receptor (PRR). Under normal conditions, renin is produced almost exclusively by specialized juxtaglomerular cells of the afferent arteriole. It is released in response to a reductions in perfusion pressure or delivery of sodium chloride to macula densa cells, or by an increase in sympathetic stimulation.[24] Prolonged stimulation of the renal sympathetic nerves transforms a subset of vascular smooth muscle cells into renin producing cells in the afferent arteriole. This transformation is governed by the transcription factor SRY-related HMG-box gene (Sox)-6.[25] Principal cells of the collecting duct also can produce renin. This is mediated in part by a loss of nitric oxide production in various pathophysiological conditions.[26] While renin is normally released almost exclusively from the juxtaglomerular apparatus of the kidney, the proximal tubules can become an important site of renin production during oxidative stress or in response to increased glomerular protein filtration.[27] Drs. Gomez and Sequeira-Lopez will discuss these and other features of renin biology in their review of this compendium.

Mice lacking the PRR in the collecting duct have a reduced hypertensive response to angiotensin II infusion, in part due to reduced sodium resorption in this segment.[28] Direct actions of renin per se in clinical settings remain controversial. Treatment with the direct renin antagonist Aliskiren paradoxically worsened outcomes in humans with heart failure,[29] and a recent meta-analysis reported no improvement in outcomes in hypertension and a lower certainty of blood pressure reduction for Aliskiren than for ACE inhibition.[30] However, these disappointing reports may reflect pharmacokinetic defects of Aliskiren.[31] Moreover, renin is a dual purpose enzyme that both metabolizes angiotensinogen and acts as a complement C3 convertase.[32, 33] It has long been known that circulating levels of C3 predict the subsequent development of hypertension,[34] likely by promoting innate and adaptive immune responses.[35] Therefore, a role may yet emerge for improved direct renin inhibitors in the treatment of hypertension and for reducing complement C3 activation.

A second major role of the kidney in hypertension is to reset or alter the pressure diuresis and natriuresis. As originally described by Guyton and co-workers, a rise in blood pressure causes a brisk diuresis and natriuresis, thereby returning blood pressure towards normal values. Guyton defined the relationship between blood pressure with sodium and water excretion as the pressure-natriuresis curve and reasoned that there must be a rightward

resetting of this curve for hypertension to be sustained.[36] While the mechanisms for pressure natriuresis and its resetting are multifactorial, substantial evidence implicates increases in renal interstitial pressure and alterations of the sodium transporters such as the sodium hydrogen exchanger 3 (NHE3) and the sodium–phosphate cotransporter isoform 2 in the proximal tubule.[37] Acute hypertension retracts these from the luminal cell membrane to the base of the apical microvilli in the proximal tubule where they cannot participate in sodium reabsorption. Likewise, an increase in BP can relocate the thiazide-sensitive sodium chloride co-transporter in the distal tubule. However, during chronic hypertension, these transporters are translocated to the apical microvilli, where they enhance sodium reabsorption and likely sustain hypertension.[38] The sodium glucose linked transporter type 2 (SGLT2) in the proximal tubule is also upregulated by angiotensin II acting on AT1 receptors during renovascular hypertension[39] where it is functionally linked to NHE3 via the microtubule-associated protein 3[40] to enhance proximal Na^+ reabsorption during ROS stimulation.[41] Perfusion of an SGLT2 inhibitor into the proximal tubule inhibits Na^+:H^+ exchange.[42] Since NHE3 transports more Na^+ than SGLT2, this functional interaction between the two is likely to contribute to the surprisingly robust 27% inhibition of proximal Na^+ and fluid reabsorption by the SGLT2 inhibitor dapagliflozin in diabetic rats.[43] This may underlie the reported effects of SGLT2 inhibitors to reduce the plasma volume in heart failure and the blood pressure in hypertension.[44,45] Multiple other sodium transport mechanisms are similarly affected as has been expertly reviewed elsewhere.[38]

Shifts in transporter location and function can be mediated by angiotensin II, inflammatory cytokines, loss of nitric oxide and adrenergic stimulation. It is important to note that shifts in pressure natriuresis are often not reflected by overt changes in renal function as measured by usual clinical parameters such as blood urea nitrogen, creatinine or creatinine clearance. Moreover, renal Na^+ retention in hypertension is not usually accompanied by overt signs of fluid overload.

A third, recently recognized role of the kidney in hypertension is to modulate systemic sympathetic tone by generating reflex signals via renal afferent nerves. Approximately 90% of renal nerves are efferent nerves sending sympathetic signals to the kidney, thereby enhancing tubular sodium resorption, renin release and vasomotor tone depending on the intensity of nerve traffic.[46] However, a smaller proportion of renal nerves are afferents that generate signals from within the kidney and transmit them to the brainstem where they can initiate reflexes that promote increases in efferent SNS tone and induce hypertension.[47] More than 20 years ago, Campese and colleagues reported that the hypertension in rats with 5/6 nephrectomy was reduced markedly after severing renal afferent nerve traffic by bilateral spinal dorsal rhizotomy.[48] This was accompanied by a marked reduction in norepinephrine turnover in the posterior and lateral hypothalamus. In a subsequent study, this group reported that injection of a small bolus of phenol into one pole of the kidney also increased renal afferent nerve activity and norepinephrine production by the posterior hypothalamus led to hypertension. These events were abrogated by renal denervation, suggesting that excitation of renal afferent nerves played a critical role. These findings are in keeping with other observations that the hypertension associated with cyclosporine administration in renal allograft recipients is in part mediated by afferent nerve activation.[49] More recently, it has been recognized that the renal afferent nerves have a special role in salt-dependent

hypertension. Banek et al reported that renal deafferentation reduced hypertension in rats with DOCA-salt hypertension.[50] The ability of renal afferent nerves to initiate an increase in global sympathetic outflow might explain the pleiotropic effects of renal denervation.[51] In angiotensin II-induced hypertension, renal efferent, rather than afferent nerves seem to have a predominant role.[52, 53]

Although the precise sites in the kidney where afferent nerves are activated remains undefined, recent studies have thrown light on some of the underlying mechanisms. A high salt diet in the context of both acute[54] or chronic[47] causes the expected reduction in the circulating RAS but paradoxically activates the intrarenal RAS via increased ROS and activates renal afferent nerve traffic to reflexly increase blood pressure.

A fourth important role of the kidney in hypertension is to serve as a site of immune activation. As discussed below, angiotensin II-induced hypertension activates antigen presenting dendritic cells in the kidney that migrate to secondary lymphoid organs to activate T cells which in turn return back to the kidney.[53] This process is blocked by renal denervation, suggesting that efferent renal nerves promote neoantigen formation in the kidney in hypertension. Single cell sequencing has shown that the kidney, as opposed to blood vessels or the spleen, accumulates T cells with an oligoclonal T cell receptor population, supporting the role of the kidney in antigen formation.[55]

The role of the vasculature in hypertension:

Several of the nodes in Dr. Page's Mosaic diagram refer to potential vascular mechanisms, including vascular caliber, reactivity, elasticity and indirectly, cardiac output. Systemic vascular resistance is almost uniformly enhanced in adults with hypertension, and many common agents used for the treatment of hypertension are vasodilators. Historically, Guyton proposed that in response to an initial expansion of blood volume and elevation of cardiac output, "systemic autoregulation" caused vasoconstriction and a further increase in blood pressure.[56] This leads to additional pressure natriuresis and returned the blood volume to normal, but at the expense of sustained hypertension. Somewhat in keeping with this scenario, Fagard and Staessen reported an increased cardiac output in hypertensive individuals less than 25 years of age but a normal cardiac output in older subjects.[57] In addition to systemic autoregulation, that is a physiological response, it is now clear that there are long-term pathophysiological manifestations of hypertension that increase vascular tone and resistance. In the following paragraphs we will review some new observations about how vascular function is altered and contributes to hypertension. We will attempt to relate these to older concepts embodied in Page's Mosaic theory.

There are at least 4 vascular perturbations that occur in and contribute to hypertension. The first is an enhanced milieu of vasoconstrictor hormones including angiotensin II, catecholamines and vasopressin, coupled with alterations in vascular function that promote vasoconstriction and diminish vasodilatation. Studies of isolated vessels have demonstrated that both conduit vessels and arterioles from hypertensive animals display enhanced vasoconstriction to a variety of agents. Of particular interest are genes that modulate G-protein coupled receptor (GPCR) signaling, including the regulators of G protein signaling

(RGS) proteins, that induce GTP hydrolysis to terminate G-protein signaling. The RGS proteins 1 and 2 are linked to GPCRs that enhance responses to vasoconstrictors including thromboxane, angiotensin II and norepinephrine. Almost 20 years ago, Heximer et al showed that mice lacking RGS2, expressed predominantly in vascular smooth muscle, develop baseline hypertension that is dependent on the angiotensin type 1 receptor.[58] Additional studies showed that vascular smooth muscle cells from these mice displayed augmented calcium transients, with delayed declines to baseline following agonist stimulation. A key role for RGS2 was highlighted in subsequent work showing that RGS2 in the renal vasculature was critical for promoting hypertension.[59] More recently, Patel et al defined an important role of RGS1 in vascular control in atherosclerotic ApoE deficient mice where the knockout of RGS1 evoked a marked increase in blood pressure and vasoconstriction to phenylephrine, thromboxane and angiotensin II.[60] Bone marrow transplant studies demonstrated that this phenotype was not mediated by hematopoietic cells. Rather, these investigators showed that mRNA expression of RGS1 is attenuated by chronic angiotensin II infusion and suggested that hypertension leads to a loss of this important modulatory pathway. In contrast, RGS5 seems to have modest to no effects on blood pressure by itself but activates RhoA stress fiber formation and a contractile phenotype of vascular smooth muscle.[61] RhoA is a critical activator of Rho Kinase that targets contractile proteins including the myosin light chain in vascular smooth muscle to promote vasoconstriction.[62] Endothelial Rho kinase phosphorylates NO synthase on threonine 495 to inhibit NO production, which also increases vasoconstriction.[63] The Rho kinase inhibitor Fasudil is approved for use in Japan and China for the treatment of cerebral vasospasm and pulmonary hypertension and has blood pressure lowering effects in genetic and salt induced forms of experimental hypertension.[64]

Hypertension is also associated with impaired vasodilatation. For many years it has been recognized that endothelium-dependent vasodilatation and nitric oxide signaling are reduced in hypertension, as recently reviewed.[65] There are fundamental differences in the mechanisms underlying endothelium-dependent vasodilatation between larger conduit arteries, branch arteries and resistance arterioles. Larger vessels predominantly employ nitric oxide while smaller arteries and arterioles are also modulated by endothelium-dependent hyperpolarization and vasodilator prostaglandins. In larger vessels, defects in NO synthesis and bioavailability include loss of critical co-factors for NO synthase including L-arginine and tetrahydrobiopterin,[66, 67] inhibition of NOS activity by ADMA and oxidative inactivation of NO.[68] It should be stressed that alterations of NO production extend beyond the vasculature and have implications for renal and CNS dysfunction in hypertension. In smaller arteries and arterioles endothelium-dependent vasodilatation is mediated by hyperpolarization, but the factors responsible for this have largely defied identification. In the past decade, there has been increasing interest the role of direct communications or gap junctions that permit transmission of signals between the endothelium and vascular smooth muscle cells. Early studies using intracellular labeling showed polarized unidirectional movement of fluorescent dyes from the endothelium to adjacent smooth muscle cells.[69] These dyes were shown to traverse myoendothelial junctions (MEJs) that were subsequently identified as holes in the internal elastic membrane lying between the endothelium and vascular smooth muscle. MEJs are particularly common in smaller arterioles,[70] and are sites

of signaling events and signaling molecules, including calcium pulsars, the inositol 3 phosphate receptor and calcium sensitive potassium channels.[71] Endothelium-dependent hyperpolarization is transmitted via MEJs directly to vascular smooth muscle cells. MEJs also facilitate the transfer of nitric oxide generated by NOS that is expressed at these junctions. The NO travels from the endothelium to the vascular smooth muscle where it regulates connexin43 to modulate the permeability of the MEJs.[72] MEJs also contains hemoglobin alpha, that controls the passage of NO from the endothelium to the vascular smooth muscle cells in a redox-dependent fashion.[73] Intriguingly, a peptide mimic that disrupts the binding of NO to hemoglobin alpha lowers blood pressure abruptly in wild type animals and reverses experimental hypertension caused by angiotensin II infusion.[74] Importantly, the density of MEJs is reduced and their local IP$_3$-stimulated calcium signals are blunted in mesenteric arterioles of Spontaneously Hypertensive Rats, indicating that these signaling loci are deficient in hypertensive resistance vessels.[75] In keeping with this, mice lacking the MEJ component Connexin40 exhibit hypertension and reduced endothelium-dependent vasodilatation in response to the potassium channel activator SKA-31. Likewise, endothelial specific expression of a mutant Connexin40, that causes electrical impairment of gap junctions, leads to exercise-induced hypertension.[76] Recently it has been shown that chronic sympathetic stimulation in the setting of hypertension due to experimental chronic kidney disease decreases the expression of Connexin43, leading to disruption of MEJ function and enhanced vasoconstriction.[77] These various lines of evidence strongly support a role of MEJs in modulation of microvascular tone and abnormalities thereof in hypertension.

Perturbations of both microvascular and large vessel structure represent a second vascular contribution to hypertension. More than 60 years ago, Folkow et al proposed that vascular smooth muscle hypertrophy and concomitant narrowing of the arteriolar lumen increases systemic vascular resistance.[78] This phenomenon has been detected in the retinal arterioles by fundoscopic examination in clinical hypertension[79] where a reduced arteriole to venule ratio increases the odds of developing hypertension. This indicates that arteriolar remodeling can precede, and possibly predispose, to hypertension.[80] The application of artificial intelligence and machine learning methods to quantitate parameters of retinal arterial morphology have further demonstrated that retinal artery morphology correlates with cardiovascular outcomes.[81] There are multifactorial mechanisms of arteriolar remodeling in hypertension.[82] These include the direct hypertrophic/growth-promoting actions of angiotensin II and catecholamines, oxidative signaling,[83] and inflammatory cytokines released by immune cells. Many of these enhance the expression or activity of matrix metalloproteinases that promote cell migration, hypertrophy and reorganization.

A related alteration of vascular function that likely contributes to hypertension is stiffening of large conduit arteries, and in particular the proximal aorta, via mechanisms that continue to be investigated. A healthy aorta distends during systole and recoils in diastole. This leads to a reduction in the systolic pressure while maintaining diastolic pressure and perfusion. The aorta stiffens in common conditions, including aging, diabetes, obesity and tobacco use, thereby reducing this critical Windkessel function.[84–87] Increased pulse wave velocity, reflecting aortic stiffening, has been reported in population studies to precede hypertension by several years and is a harbinger of stroke, myocardial infarction, and renal failure.[88]

Aortic stiffening can be both a cause and a consequence of hypertension. It develops well before the onset of hypertension in spontaneously hypertensive rats,[89] in diet-induced obesity,[90] and in two models of chronic vascular oxidative stress.[91] In contrast, Wolinsky reported that aortic collagen increases following the onset of Goldblatt hypertension,[92] and we found that experimental hypertension in mice causes aortic stiffening. Mechanical stretch of cultured aortic murine fibroblasts increases their expression of collagens I, III and V. Wu et al found that aortic stiffening occurs before blood pressure elevation in two models of chronic vascular oxidative stress.[91] It is thus likely that aortic stiffening and hypertension act in concert, with one leading to the other in a feed-forward fashion.[93]

While the mechanisms by which aortic stiffening causes end organ damage are not completely understood, a consequence is enhanced propagation of pressure into the microcirculation, leading to barotrauma in target organs, in part via increasing cyclical stretch of microvascular endothelial cells. Indeed, in an elegant analysis of the components of the pulse wave, an increased forward pressure wave was associated with an increased risk for incident cardiovascular disease.[94] Drs. Boutouyrie, Chowienczyk and Mitchell discuss vascular stiffening in greater detail in their review of this issue.

A fourth role of the vasculature in hypertension is to serve as a source and target of immune activation. This is in part mediated by a cross talk between the endothelium and immune cells that is covered in depth in the section on immune mechanisms below.

Finally, there is an impaired vessel wall defense against thrombosis in hypertension that has been related to increased endothelial expression of tissue factor and the vascular cell adhesion molecule 1. This enhances platelet-dependent leukocyte adhesion and is driven by thrombin factor XI and the platelet Factor XI receptor.[95] Inhibition of Factor XI in angiotensin-infused rats and mice prevents platelet thrombin formation, vascular leukocyte infiltration, endothelial dysfunction, and hypertension. Further studies of the mechanisms that activate thrombosis in hypertension may provide insight into stroke, atherosclerosis and end organ damage. Drs. Webb, Eguchi and Tostes cover the role of the vasculature in greater depth in their review.

The central nervous system in hypertension:

Dr. Page's revised diagram (Figure 1B) included the term "neural". Indeed Page demonstrated that angiotensin II caused hypertension predominantly by sympathetic neural activation.[13] Measures of muscle sympathetic nerve activity, norepinephrine spillover and heart rate variability have suggested that humans with hypertension commonly have increased sympathetic outflow and enhanced catecholamine mediated vasoconstriction.[96] Angiotensin II and ROS in the brain stem nuclei enhance vascular resistance by in part by inhibition of the microvascular endothelium-dependent hyperpolarizing factor that normally reduces vascular tone.[77] In keeping with these central vascular effects, ganglionic blockade acutely lowers blood pressure in humans with hypertension to a variable extent,[97] particularly in those who are obese.[98]

The many mechanisms whereby sympathetic tone modulates hypertension include enhanced vasoconstriction and vascular remodeling, renal renin production via beta 1 adrenergic receptors in the juxtaglomerular apparatus and enhanced renal sodium resorption and inflammation.

The central pathways involved in hypertension have been reviewed elsewhere.[99] An important initiating site is the laminal terminalis, located anterior to the 3rd ventricle, which contains the subfornical organ (SFO), the median preoptic eminence and the organum vasculosum of the lamina terminalis (OVLT). The SFO and OVLT are circumventricular organs that have a poorly formed blood brain barrier that permit blood born angiotensin II and sodium to activate neuronal firing. Indeed, the OVLT is responsive to even modest increases in sodium to initiate salt-sensitive hypertension.[100] Xiao et al recently identified a role of the prostaglandin EP3 receptor in this response, leading to a cascade of ROS production in renal arterioles, isoLG accumulation in dendritic cells and immune activation, [101] thereby providing a contemporary example of the mosaic interaction between neural regulation, vasculature and inflammation.

In addition to efferent signals promoting hypertension, there is ample evidence that afferent pathways are likewise involved. In addition to renal afferent activation, discussed above, afferent nerves from adipose tissue are triggered by a high fat diet to reflexively increase BP and insulin resistance.[102] Another source of afferent nerve stimulation is the heart. Infusion of saline into cardiac transplant recipients with no evidence of cardiac dysfunction failed to reduce their sympathetic nervous system activity, arginine vasopressin levels or their renin, angiotensin and aldosterone levels and led to hypertension.[103, 104] This hypertensive response was linked to a failure to suppress angiotensin II during blood volume expansion and was prevented by angiotensin converting enzyme inhibition.[105]

A summary of some of the roles and perturbations of renal, vascular, endocrine and neural control in hypertension are depicted in figure 2. These are organ specific features of the Mosaic Theory and hypertension pathophysiology that remain the focus of ongoing research. In the past 2 decades new factors and phenomena have emerged that likely affect the mosaic factor in a global fashion. These include oxidative signaling, inflammation and the microbiome. In addition, a new role of sodium has been identified. These are briefly considered in the following paragraphs.

Aldosterone, the mineralocorticoid receptor and their ubiquitous role in the Mosaic Theory:

A major development since the initial Mosaic theory is the evolving understanding of aldosterone in hypertension. Aldosterone is produced by the zona granulosa cells of the adrenal gland in response to angiotensin II and elevations of extracellular potassium. Until recently, the sole effect of aldosterone was thought to enhance sodium reabsorption in the collecting duct and aldosterone blockade was felt to predominantly promote diuresis. It has become obvious that the mineralocorticoid receptor (MR) is expressed in numerous organs and cells, including the heart, blood vessels, immune cells and in the brain. Studies using cre-lox technology have shown important roles of many of these extra-renal sites in

hypertension. As an example, mice with vascular smooth muscle deletion of MR have decreased blood pressure with aging and their vessels exhibit diminished vascular myogenic tone, agonist-dependent contraction, vascular superoxide production and expression and L-type calcium channel activity.[106] Likewise, Jia et al showed that endothelial cell MR deficiency prevents aortic stiffening caused by feeding a western diet, and established a role for the endothelial MR receptor in modulating endothelial sodium channel activation, oxidative stress and endothelial nitric oxide synthase activation.[107] Sun et al used Cre-Lox technology to eliminate the MR in all T cells and showed that this abrogated T cell interferon gamma production and the hypertension caused by chronic infusion of ang II. These authors showed that the MR interacted with other transcription factors to mediate IFNγ production and that its deletion from T cells attenuated fibrosis in the aorta and kidneys, reduced albuminuria and preserved endothelium-dependent vasodilatation. A role for the MR in macrophage activation has been reviewed elsewhere.[108]

These myriad effects of the MR receptor are important because at least 5% of all cases of hypertension are due to primary hyperaldosteronism and this is likely much higher among those with resistant hypertension. Brown et al recently reported that urinary aldosterone levels (in the sodium loaded state) parallel the severity of hypertension across all subjects,[109] suggesting that hyperaldosteronism is much more prevalent than previously considered, even among those without severe hypertension.

The role of ROS in hypertension:

It was first observed in the 1990s that scavenging superoxide could lower blood pressure in rats with hypertension due to chronic ang II infusion and in spontaneously hypertensive rats. [110–113] It has subsequently been recognized that several enzymatic sources of ROS are activated in tissues of hypertensive animals and humans, including the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, the mitochondria and uncoupled NO synthase. ROS likely contribute to almost each node of Dr. Page's diagram. Superoxide and other related ROS can oxidatively inactivate nitric oxide and oxidize tetrahydrobiopterin, a critical co-factor for NO synthase.[114, 115] ROS can also enhance vasoconstriction and thereby alter vascular caliber and reactivity. ROS are important for vascular stiffening and for remodeling of microarterioles.[83, 116] In the kidney ROS enhance renal sodium reabsorption,[117] and thus enhance volume and cardiac output. They have also been implicated in activation of matrix metalloproteinases and thus promote tissue remodeling.[118] ROS likewise increase neuronal firing in critical brain centers, including the subfornical organ,[119, 120] and brain stem centers, [121] thus altering neural control.

Griendling et al showed in the 1990s that angiotensin II could stimulate superoxide production in cultured vascular smooth muscle cells and in vivo by activating an enzyme similar to the phagocytic NADPH oxidase.[113, 122] The catalytic subunit of the NADPH oxidase is Nox2 and homologs of this are activated in vascular smooth muscle cells, the endothelium, renal tubular cells and in the central nervous system in hypertensive animal models. There is clearly an interaction of ROS derived from the NADPH oxidase and with other enzymatic sources, such that ROS from one can trigger ROS production by others in a feed-forward fashion.

While early studies emphasized the role of oxidative stress in vascular cells, the kidney and its vasculature develop oxidative stress with increased NADPH oxidase and reduced SOD activity both during angiotensin II infusion and during high salt intake. High salt intake enhances renal expression of NADPH oxidase and NOX2 and reduces SOD1 and SOD2,[123] whereas angiotensin II infusion increases renal NADPH/p22[phox] and reduces SOD 3 expression.[124] Renal ROS can activate renal afferent nerves,[125] and increase renal and circulating levels of asymmetric dimethyl arginine (ADMA),[126] by reducing its metabolism by dimethylarginine dimethylaminohydrolase and increasing its generation by protein arginine methyltransferase.[66] Thus, an increase in circulating ADMA is one means whereby ROS in the kidney may enhance peripheral vasoconstriction. ADMA inhibits endothelial function and flow-mediated vasodilation and activation of the SNS during high salt intake could contribute to the failure of salt-sensitive subjects to reduce their peripheral vascular resistance during increases in cardiac output evoked by a high salt intake. In the kidney, the proximal tubular cells take up oxidatively modified albumin that induces a robust local activation of the RAS via NADPH oxidase, protein kinase C, nuclear factor kappa beta NF-κB and activator protein-1 (AP-1).[27] These together increase proximal tubular angiotensin II that initiates renal inflammation and fibrosis. This proximal tubule ROS pathway provides a potential link between hypertension, systemic oxidative stress and proteinuria and the activation of the intrarenal RAS. These events damage the kidney and can thereby perpetuate salt-sensitivity and worsening hypertension.

Of interest is an emerging role of the mitochondria as a source of ROS in hypertension. Recent studies suggest that aging and hypertension reduce the function of Sirtuin3 (Sirt3), a histone deacetylase that modulates the acetylation status of SOD2. Mice lacking Sirt3 are protected against hypertension and its associated vascular disfunction in response to angiotensin II infusion, and this is prevented by mitochondrial-targeted antioxidants, including mitoTempol and mitoEbselen.[127] These alterations of the mitochondria in hypertension likely have myriad effects on cellular metabolism and function that contribute to the pathophysiology of hypertension through yet undefined mechanisms.

Therapeutically, scavenging ROS is not clinically employed, and there is evidence that high dose vitamin antioxidants can be harmful, possibly because ROS can have important signaling function.[128] Targeted scavenging of ROS using agents like mitoTempol, or treatment with agents that inhibit untoward activation of ROS forming enzymes are viable future options. Indeed, one of the major benefits of angiotensin II blockade might be due to inhibition of ROS formation. This topic is reviewed in depth in this compendium by Drs. Griendling and Touyz.

Inflammatory and immune mechanisms in hypertension:

It has been recognized for more than 50 years that inflammatory cells accumulate in the kidney and blood vessels of hypertensive humans and animals with experimental hypertension. It is now recognized that virtually every type of immune cell, including those of innate and adaptive immunity, contribute to hypertension. These transmigrate into the interstitium of the kidney and blood vessels where they release potent cytokines, ROS and metalloproteinases that modulate renal and vascular function and structure. It is likely that

these mediators affect virtually every node of Dr. Page's Mosaic diagram. A notable example is the cytokine interleukin 17A (IL-17A) produced by a subset of T cells, innate lymphocytes, histiocytes and renal tubular cells. IL-17A affects renal tubular handling of sodium and seems to modulate pressure natriuresis.[129] This cytokine stimulates vascular superoxide production,[130] causes inhibitory phosphorylation of the endothelial NOS,[131] and therefore reduces the caliber of blood vessels. Over the long term IL-17A promotes vascular fibrosis and impairs vascular elasticity.[132] In contrast, regulatory T cells and anti-inflammatory cytokines such as IL-10 have antihypertensive effects mediated , in part by counteracting IL-17A.[133, 134]

The manner by which immune cells are activated in hypertension is a matter of ongoing investigation. Accumulating data suggest that ROS in antigen presenting cells promote oxidation of fatty acids to form highly reactive isolevuglandin (isoLG) products that covalently modify protein lysines.[135] These altered proteins are antigenic and activate both CD8$^+$ and CD4$^+$ T cells.

There is substantial evidence that sympathetic outflow promotes immune activation in hypertension. Lesions of the forebrain that prevent sympathetic outflow reduce T cell activation,[119, 136] while manipulations that increase sympathetic outflow promote T cell activation.[137] Recent data suggest that renal sympathetic tone modulates trafficking of immune cells to and from the kidney and the homing of memory T cells to the bone marrow, where they can be reactivated upon future hypertensive challenges.[53, 138] In the vasculature, T cells accumulate in the perivascular fat and adventitia of larger vessels in hypertension, likely via expression of chemokines such as RANTES and MCP-1.[139, 140] This adventitial inflammatory response likely triggers collagen deposition, described above. There is also an immune reflex, whereby local tissue signals trigger a vagally mediated anti-inflammatory response.[141] This reflex seems to be miswired to promote inflammation in prehypertensive animals.[142]

Hypertension is associated with endothelial activation. It has long been recognized that the activated endothelium promotes rolling, adhesion and transmigration of leukocytes. As monocytes transmigrate the endothelium, they are transformed into inflammatory macrophages and dendritic cells that emerge as activated monocytes with enhanced potential to produce cytokines and activate T cells.[143, 144] Endothelial cell stretch, oxidative stress and loss of nitric oxide in hypertension can all enhance endothelial/leukocyte interaction and increase the endothelial activation of monocytes. Human monocytes activated in this way by the endothelium produce copious quantities of IL-6, IL-23, IL-1β and stimulate autologous T cells potently.[145] In addition, endothelial transmigration likely promotes myeloid cell accumulation in the corticomedullary junction of the kidney, where supraphysiological levels of sodium may provide a stimulus to activate monocytes.[146]

This vascular/immune cross talk again reflects the mosaic nature of hypertension, whereby a primary perturbation, in this case of endothelial (vascular) function, in turn generates mediators that promote inflammation that likely affects multiple other organs and cells. In this compendium, Drs. Madhur, Kirabo and colleagues provide an in-depth review that discusses more fully the role of inflammation in hypertension.

Genetic influences:

Genetic alterations are atop Dr. Page's revised Mosaic diagram (Figure 1B). Several single gene mutations, including those responsible for Liddle's syndrome, pseudohyperaldosteronism, aldosterone producing adenomas, glucocorticoid remedial hypertension and missense mutations of the mineralocorticoid receptor have been identified to be responsible for highly heritable Mendelian forms of hypertension.[147] While these single gene mutations have provided insight into the pathogenesis of hypertension, they are rare and do not explain the high prevalence of familial hypertension commonly observed in the clinic. In contrast, single nucleotide polymorphisms (SNPs) that often occur in non-protein coding regions of the genome and usually do not alter protein function are common. Genome wide association studies in the last decade have identified more than 1000 SNPs that associate with hypertension.[148] While individual SNPs have small effects on blood pressure, when multiple SNPS are analyzed as a polygenic risk score (PRS), they can account for as much as 13 mmHg of blood pressure variability. Vaura et al recently showed such a PRS is predictive of early onset hypertension in a progressive fashion, such that those with the highest 2.5% of PRS have an almost 3-fold risk of developing hypertension, while a low PRS is protective.[149] Refinements of the PRS promise to contribute to our future understanding and treatment of hypertension. The genetics in hypertension will be reviewed in detail by Dr. Caufield a subsequent section of this compendium.

Novel concepts related to salt and sodium intake:

Dr. Page's revised Mosaic Diagram (Figure 1B) included the environment, which includes diet, and in particular salt intake. There are numerous large epidemiological studies linking high levels of dietary sodium intake with risk for hypertension.[150] Conversely, reducing dietary salt or administration of diuretic agents such as thiazides are effective treatments for elevated blood pressure.[151, 152] In human populations, sodium-sensitivity, defined as an exaggerated change in blood pressure in response to extremes of dietary salt intake, is a relatively common phenotype associated with increased risk for hypertension and cardiovascular events.[153] The blood pressure of about one quarter of normal subjects and one half of hypertensive increases with salt intake.[154] While salt-sensitive hypertension entails a renal defect in salt excretion, the increase in BP with salt intake is caused by increased peripheral resistance that requires a communication between the kidneys and the peripheral vasculature. Indeed, enhanced vasoconstriction and endothelial dysfunction,[155] rather than a primary increase in renal Na^+ retention, can initiate salt-sensitive hypertension.[156] Salt-sensitive subjects are unable to increase peripheral vascular resistance appropriately during a low salt intake,[157] or to reduce their peripheral vascular resistance during a high salt intake,[158] thereby causing their blood pressure to be unusually dependent on salt intake. There is an accompanying failure of salt-sensitive subjects to suppress the SNS during salt loading,[159] accompanied by an increase in circulating ADMA during salt loading only in salt-sensitive subjects.[158]

Classic Guytonian models suggest that a defect in sodium excretion by the kidney is the primary basis for hypertension, with impaired elimination of sodium during high salt feeding leading directly to expanded extracellular fluid volume promoting increased blood pressure.

[18] Studies in recent years indicate that the impact of dietary sodium intake upon blood pressure is complex, beyond the simple construct of intra-vascular volume expansion balanced by excretory functions of the kidney. For example, it is now apparent that during high salt feeding, sodium accumulates in the interstitium of the skin and other tissues where it may be stored at hypertonic concentrations in complexes with proteoglycans, acting as a reservoir and buffering the impact of sodium accumulation on intravascular volume and blood pressure.[160] This interstitial sodium storage can be visualized and quantified in humans using ^{23}Na MRI.[161] Accumulation of sodium in tissues increases with high salt intake or aging, and has been associated with hypertension and increased cardiovascular risk.[162] In the sub-dermal space, sodium can also stimulate macrophages, triggering expression of TonEBP, a transcription factor regulating the expression of osmo-protective genes including vascular endothelial growth factor (VEGF)-C, a potent inducer of lymphangiogenesis.[160] It has been suggested that these immunomodulatory actions of salt deposited in skin may have evolved to subserve a barrier function to prevent invasion by micro-organisms, but in the modern world where dietary salt is ubiquitous, this may now be a maladaptive response.[163] Other recent studies indicate that very high levels of sodium intake can trigger archetypal metabolic changes aimed at conserving water, with a side effect of raising blood pressure.[164]

Elevated concentrations of tissue sodium can also activate immune cells that contribute to hypertension. Modest elevations of sodium can stimulate T cells to produce the cytokine IL-17A,[165, 166] which as mentioned above, promotes vascular remodeling, endothelial dysfunction and renal sodium retention. Sodium entry via an amiloride sensitive sodium channel can also drive dendritic cell activation,[167] and promotes transformation of human monocytes to a dendritic cell-like phenotype that produce cytokines like IL-6, TNFα and IL-1β.[146] Upon entry of sodium into myeloid cells calcium activation of the NADPH oxidase ensues leading to ROS formation and the generation of isoLG adducts, which as discussed above act as neoantigens in these cells.

In both T cells and myeloid cells, the effect of sodium is mediated by the serum glucocorticoid kinase-1 (SGK1). Wu et al. showed that high-salt feeding stimulated Th17 cells in the central nervous system and mesenteric lymph nodes and exacerbated experimental allergic encephalitis (EAE), a model of multiple sclerosis mediated by IL-17A.[165] Interestingly, mice with T cell SGK1 deficiency exhibited reduced EAE incidence and severity that was not exacerbated by high-salt feeding. Norlander et al showed that deletion of SGK1 in T cells blunts the hypertensive response to angiotensin II and DOCA-salt challenge in mice and abrogates renal and vascular inflammation in these models.[168] In this study, a T cell sodium-potassium-2 chloride cotransporter 1 was found to mediate the salt-induced increase in SGK1 and the IL-23 receptor (IL-23R), which in turn promoted IL-17A production. Likewise, deletion of this kinase specifically in antigen presenting cells markedly reduces renal inflammation and hypertension in a salt sensitive model of hypertension.[169] In this myeloid cell subset, SGK1 promotes assembly of the alpha and gamma subunits of the epithelial sodium channel, which further promotes sodium entry. These studies suggest that diuretic agents previously thought to act only on the kidney might prove useful in reducing salt-driven inflammation in hypertension.

The microbiome as an emerging modulator of blood pressure:

Along with effects on fluid homeostasis and immune activation, sodium as a dietary constituent may promote hypertension by modifying gut microbiota.[170] Indeed, a number of recent studies have highlighted the potential of the microbiome to influence blood pressure. [171–173] Advances in unbiased sequencing techniques have allowed precise identification and assessment of commensural bacterial species in the gut that cannot be cultured, transforming understanding of the role of the microbiome in health and disease. Such studies have provided evidence for contributions of the microbiome in the pathogenesis of a number of diseases, including hypertension.[174, 175] This work has also identified conditioning effects of diet and drugs on the composition of the gut microbiota and highlighted the potential of these disturbances to affect host responses including blood pressure regulation.

In healthy individuals, the gut microbiome is typically in a stable state of eubiosis and in relative equilibrium with the surrounding community.[176] By contrast, significant alteration in the microbiome (dysbiosis) has been observed in range of disorders including hypertension. For example, in humans with hypertension and pre-hypertension, characteristic alterations in the microbiome have been observed.[177, 178] Dysbiosis has also been seen in experimental models of hypertension such as Dahl salt-sensitive and spontaneously hypertensive rats,[179, 180] and in mice chronically administered angiotensin II or DOCA + high salt diet.[181] Fecal transfer from hypertensive mice to germ free mice sensitizes the latter to hypertension, providing strong evidence for a role of the microbiome. [178] In hypertension, alterations in the gut microbiome have been associated with inflammation, structural changes in the intestinal wall, and enhanced gut permeability.[182] Altered intestinal permeability may facilitate egress of mediators such as microbial products, hormones, and immune cells into the circulation where they can impact peripheral and central BP control mechanisms.

Along with associations between hypertension and gut dysbiosis, there is a direct relationship between diet and the composition of gut microbiota with potential to affect propensity for hypertension. For example, increased dietary salt intake causes significant alterations in the composition of microbiota and has been associated with accumulation of pro-inflammatory TH_{17} cells discussed above.[170] Sodium is not the only dietary constituent with potential to impact blood pressure through effects on the microbiome. Multiple studies have shown that diets enriched in fruit, vegetables, and fiber can lower blood pressure and reduce risk for hypertension.[183] Moreover, dietary fiber increases bacterial populations in the gut responsible for generating short-chain fatty acids (SCFAs) through fermentation.[184] In the human circulation, SCFAs are almost exclusively of microbial origin,[185] and have been implicated as a key pathway whereby microbiota influence host physiology,[186] perhaps through a family of nutrient-sensing GCPRs expressed in vascular smooth muscle cells, the autonomic nervous system and renal juxtaglomerular cells influencing renin release.[171, 187] Thus, the gut microbiome can influence blood pressure control through pathways affecting many of Page's Mosaic components, raising the possibility that pre- and pro-biotics, antibiotics, and specific dietary formulations could be used to modify gut microbiome and its metabolites to prevent and treat hypertension. The potential impact of the microbiome in hypertension will be reviewed by Drs. Muller and Luft.

Summary:

These considerations of the Mosaic Theory and beyond reflect the prescient nature of Dr. Page's original concept, depicted in Figures 1A and 1B, which is notable for the interdependence of the various components, such that a change in one can almost certainly perturb the others. As research has evolved, a newer Mosaic diagram could be constructed as shown in figure 3, emphasizing the interplay of factors like inflammation, oxidative stress, the microbiome with alterations of renal, neural and vascular function. It should be stressed that the role of these and other factors almost certainly vary from one hypertensive human to the next or upon the experimental model studied. Importantly, another factor that should be considered is that blood pressure elevation can influence hypertension by initially causing baroreflex activation and pressure natriuresis (to lower blood pressure) and ultimately by producing pathophysiological effects that progressively raise blood pressure in a feed-forward fashion. These features of the Mosaic Theory will undoubtedly guide hypertension research in the foreseeable future.

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Non-standard abbreviations and acronyms:

ACE	angiotensin I-converting enzyme
ADMA	asymmetric dimethyl arginine
AP-1	activator protein-1
ApoE	apolipoprotein E
AT1R	angiotensin type 1 receptor
BP	blood pressure
CNS	central nervous system
DOCA	Deoxycorticosterone acetate
EAE	experimental allergic encephalitis
EP3	E prostanoid receptor type 3
GPCR	G-protein coupled receptor
IL	interleukin
isoLG	isolevuglandin
MCP1	monocyte chemoattractant protein 1

MEJ	myoendothelial junction
MR	mineralocorticoid receptor
NADPH	nicotinamide adenine dinucleotide phosphate
Na$^+$:H$^+$	sodium:hydrogen
^{23}Na MRI	magnetic resonance imaging of the ^{23}sodium isotope
NHE3	Sodium hydrogen exchanger 3
NO	nitric oxide
NOS	nitric oxide synthase
Nox	NADPH oxidase catalytic subunit
OVLT	organum vasculosum of the lateral terminalis
PRR	pro-renin receptor
PRS	polygenic risk score
RAS	renin angiotensin system
RANTES	Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted
RhoA	rat sarcoma virus homologous protein A
RGS	regulator of G protein signaling
ROS	reactive oxygen species
SCFAs	short-chain fatty acids
SFO	subfornical organ
SGK1	serum glucocorticoid kinase 1
SGLT2	sodium glucose linked transporter type 2
Sirt3	sirtuin3
SNPs	single nucleotide polymorphisms
SNS	sympathetic nervous system
SOD	superoxide dismutase
Sox6	SRY-related HMG-box gene 6
TonEBP	Tonicity-responsive enhancer binding protein
TNFα	tumor necrosis factor alpha

| VEGF | vascular endothelial growth factor |

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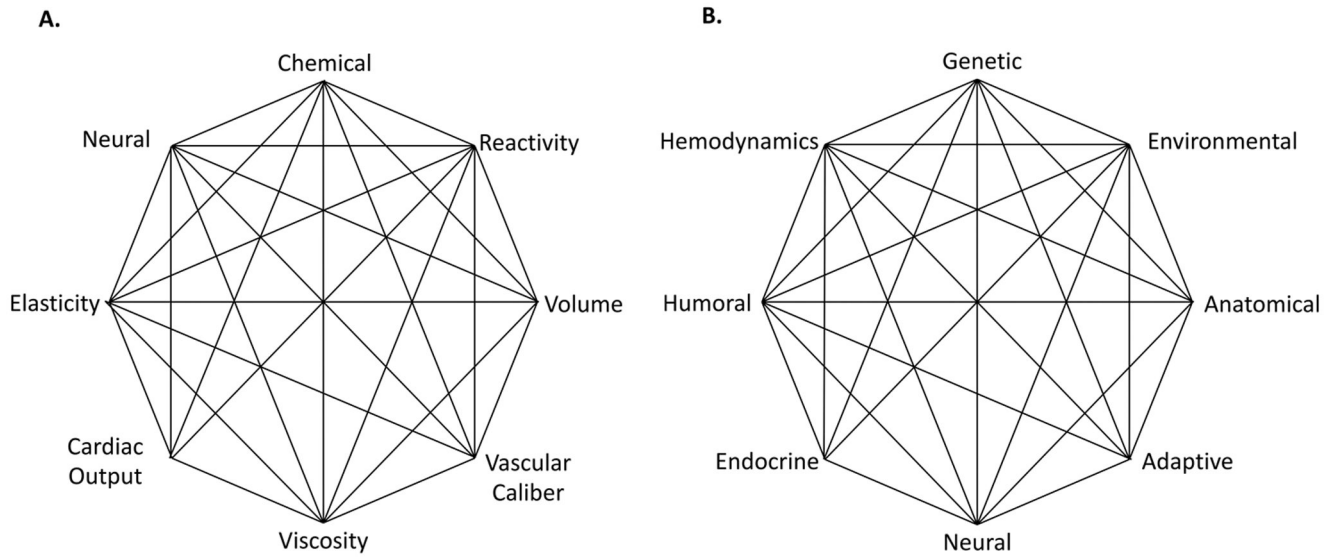
A.

B.

Figure 1:
The original (A) and revised (B) Mosaic Theories proposed by Page.

A.

Increased sodium retention/
Altered pressure natriuresis
Increased renin release
ROS induced ADMA production
Enhanced renal afferent nerve traffic
Immune activation

B.

Altered
Vasomotor Tone

Remodeling/VSM
Hypertrophy

Vascular Stiffening/
Fibrosis

Enhanced vasoconstrictor activity
due to altered GPCR activation
Reduced NO bioavailability
Loss of myoendothelial junctions
Increased stretch/endothelial
activation leading to immune
activation and pro-thrombosis

C.

Enhanced sympathetic outflow
Vasoconstriction
Increased sodium retention
Increased Renin release from JG cells
Immune activation
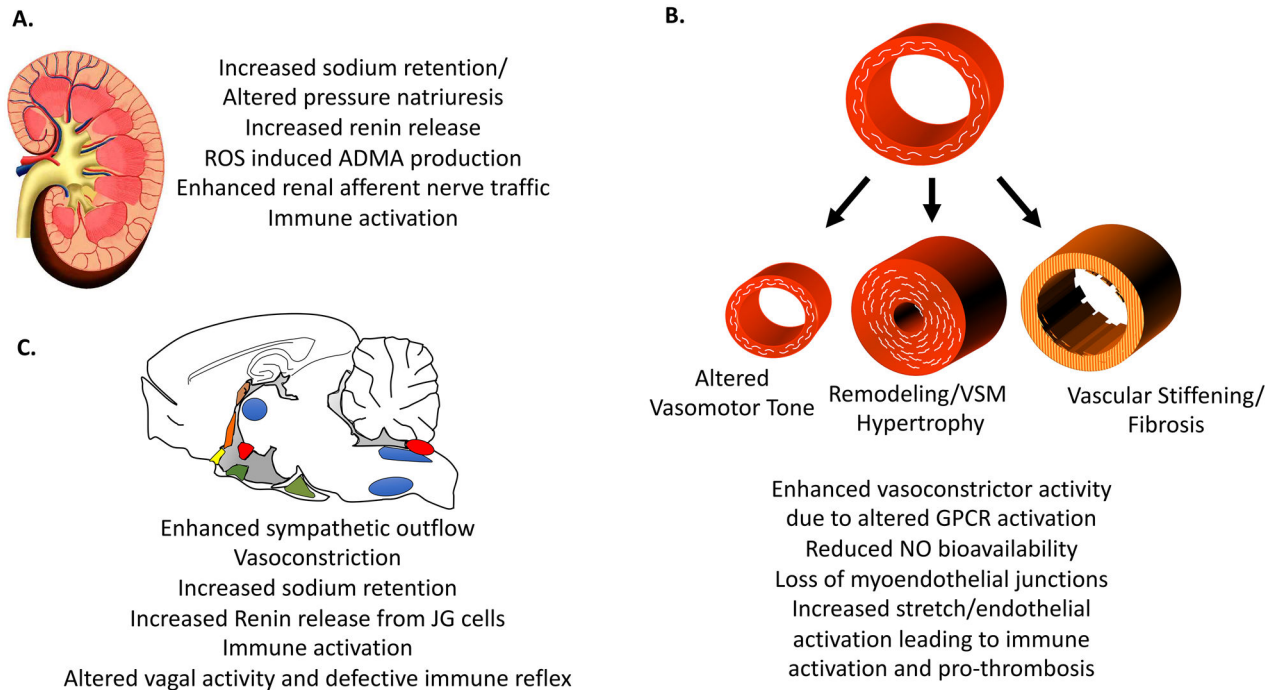Altered vagal activity and defective immune reflex

Figure 2:

Perturbations of the kidney (A), vasculature (B) and central nervous system (C) contributing to hypertension.
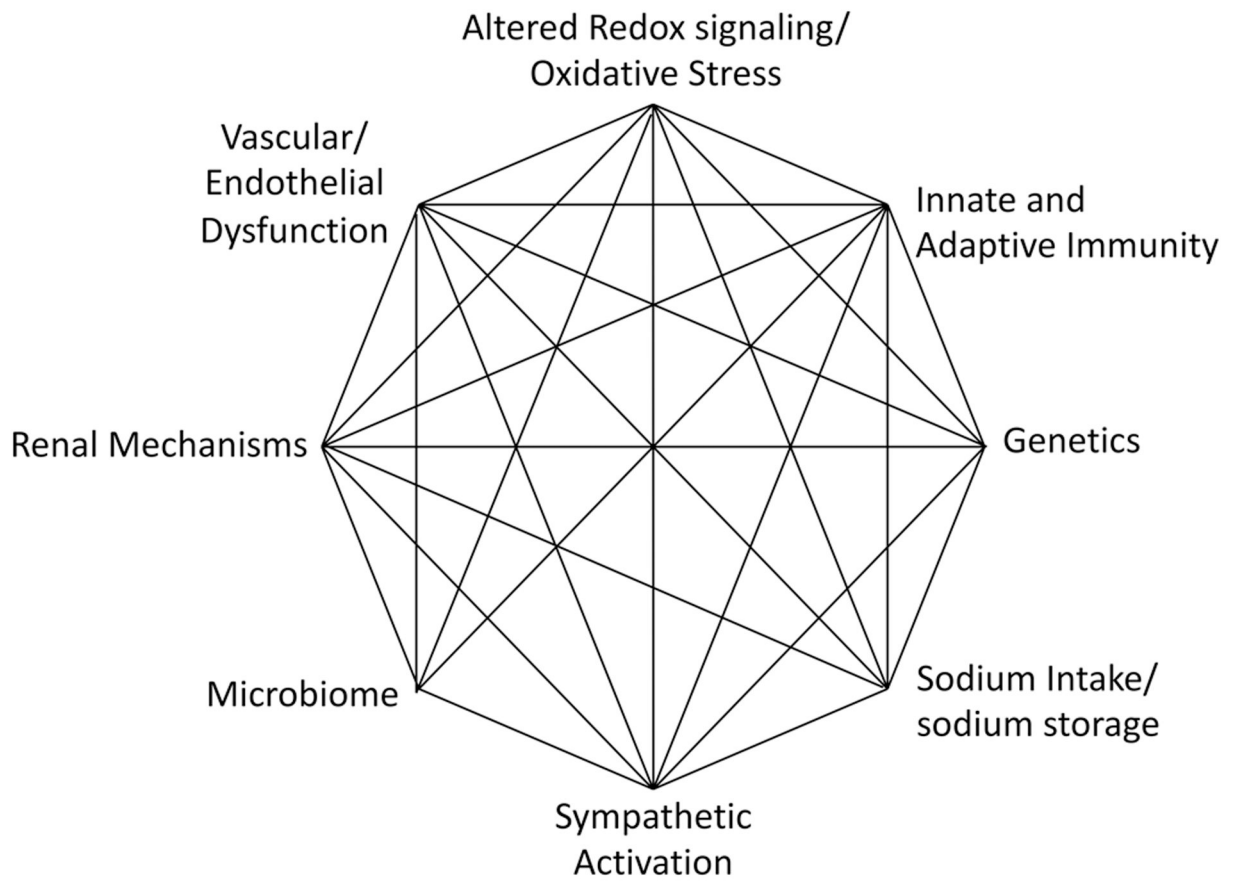
Figure 3:
A revised Mosaic Theory incorporating new understanding of cellular, environmental and genetic mechanisms.