

Sir George Johnson FRCP (1818–96), high blood pressure and the continuing altercation about its origins

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Abstract

The widely promulgated notion that long-term elevation in mean arterial blood pressure (MAP) can be caused by raised peripheral vascular resistance remains a subject of vigorous debate. According to the 1967 mathematical model of Guyton and Coleman, such a causal relationship is impossible, kidney function being the determining factor. We explore this altercation starting with Sir George Johnson's 19th-century renal vascular histological observations in patients with Bright's disease. We note the striking physiological measurements in hypertensives by Gómez and Bolomey in the 1950s, moving on to the mathematical modelling of the circulation from the 1960s up to the ~100-parameter computer models of the present day. Confusion has been generated by the fact that peripheral resistance is raised in hypertension in close proportion to MAP whilst cardiac output often stays normal, an apparent auto-regulation, the mechanism of which is poorly understood. All models allowing for the circulation to be an open system show that isolated changes in peripheral resistance cannot lead to long-term hypertension, but models fail so frequently to account for results from experiments such as salt loading that their credibility with regard to this key finding is compromised. Laboratory animal models of adrenergic renal actions resonate with a contemporary emphasis on the sympathetic nerve supply to the kidney as contributing to the characteristically markedly elevated renal afferent resistance that appears to be the most common cause of hypertension. Remarkably, there remains no account of the way in which the fixed structural changes in vessels observed by Johnson relate to this sympathetic overactivity, which can itself be modified by drugs in the medium term. In this account, we seek to locate the crime scene and identify a smoking gun.

KEYWORDS

history of ideas, hypertension, kidney, vasculature

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FIGURE 1 Sir George Johnson. Photograph by G. Jerrard, 1881. Courtesy of the Wellcome Library

1 | INTRODUCTION: HISTORIC HISTOLOGY

1.1 | Sir George Johnson and the renal vasculature

George Johnson's mammoth 900-page *Medical Lectures and Essays* was published in the year he became Vice-President of the Royal College of Physicians, 1887 (Johnson, 1887) (Figure 1). Cholera, diphtheria, emphysema, phthisis, typhoid – the widespread afflictions of the day are given extensive coverage and the fascinating case reports always associated with the career of a physician fill pages too: medical consequences of a lightning strike; delirium caused by having a drunken wife; lead poisoning in a pale ballet dancer; Mr Brunel's inhalation of a half-sovereign; splashing succussion in hydro-pneumothorax; dangers of high-heeled boots. Johnson brings to the page vast clinical experience, but also much knowledge of post-mortem pathology and, of particular interest to us here, of the pathophysiology of the circulation and the kidney. We focus on what his life's work contributed to an understanding of what we now recognize as essential hypertension, and imagine him reflecting on our present state of knowledge and debate. We envisage him being impatient because, despite having the assistance of his own extensive work, we still have not got to the bottom of the problem.

Johnson developed early expertise in renal disease. At the age of 33 he delivered the 1852 Gulstonian lectures at the Royal College,

New Findings

- **What is the topic of this review?**

The review takes a historical approach to examining where in the body it might be possible to identify the most common cause, or causes, of long-term hypertension. It gathers evidence from histology, human and animal physiology, and computational modelling. The burden of decades of controversy is noted.

- **What advances does it highlight?**

The review highlights the distinctive pathology of the afferent renal circulation and what its consequences are for the widespread view that essential hypertension is caused by elevated peripheral vascular resistance.

associated with which was his first book, *On the Diseases of the Kidney, their Pathology, Diagnosis, and Treatment* (Johnson, 1852). In the book he admits to having 'modified the views of renal pathology which, at different times during the last six years, I have published', clearly getting into print on the subject soon after graduating MD in 1844. Much thought at the time went into distinguishing the many kinds of kidney disease, including acute and chronic. One subgroup, previously noted in 1827 by Richard Bright (Bright, 1827) as kidney disease associated with cardiac hypertrophy, grabbed Johnson's interest.

In his book of 1852, he recounted examining renal arteries down to 'minute branches' and wrote as follows: 'The most remarkable of these changes is the hypertrophy of the muscular walls... The thickening appears to be proportionately greater in the smallest arteries—e.g., the afferent vessels of the Malpighian bodies—and gradually diminishes in passing from these vessels towards the arterial trunks' (pp. 229–230). A figure here supports the statement 'I have often seen the coats of the arteries at least two or three times thicker than in the normal state' and shows a small artery of approximate diameter 0.1 mm judged from the $\times 200$ magnification of this image noted elsewhere (Johnson, 1850).

In his later paper on Bright's disease of the kidney he extended his thinking on the post-mortem appearances of the renal blood vessels (Johnson, 1868). He corrected his own earlier ideas about hypertrophied renal muscular arteries assisting 'in driving the blood onwards' through an 'impediment' in the capillaries. He realized now that 'hypertrophy of muscular tissue at the two opposite extremes of the arterial system, the propulsive power of the heart and the resisting force of the arteries—at any rate, that of the renal arteries—being simultaneously increased... are mutually interdependent, the one being provocative of the other'. He noted that the abnormal thickening of the renal arterial walls was limited to the afferent vessels

entering the glomeruli: 'the efferent vessels of the Malpighian bodies present no appearance of thickening or dilatation'. So fascinated had he become by what he called the 'stop-cock' action of small arteries that he linked his new insights on renal disease to pulmonary events in acute asphyxia. He realized that 'the anaemia of the pulmonary capillaries in cases of acute apnoea and the overgrowth of the muscular walls of the renal arteries in cases of chronic Bright's disease are the results of one and the same physiological action of the arterial stop-cocks'. His 1868 paper is arguably the earliest clear appreciation of the mechanism of what we now call 'hypoxic pulmonary vasoconstriction' as well as a step forward in chronic hypertension.

1.2 | Later assessments of renal vascular pathology in hypertension

In the era before effective treatment of hypertension, there was no shortage of interest in looking for tell-tale signs of associated pathology throughout the body, often in patients with remarkably severe disease. In 1930 McGregor of Boston reviewed histological changes in (and around) the glomerulus in essential hypertension, and added 51 cases of his own in which hypertensive patients had died from stroke, heart disease or kidney failure, and made comparisons with nine age-matched non-hypertensives (McGregor, 1930). He characterized 'hypertensive' glomeruli as a quarter to a half of those examined in hypertensive patients (and only 0.8% of those in non-hypertensive patients). He found that 'every hypertensive glomerulus has an afferent vessel which is definitely narrowed and sclerosed in some portion of its course'. He reasoned that, since some narrowed arterioles supply apparently normal glomeruli, 'apparently the arteriolar change takes place first'. In all cases, he found efferent arterioles to be normal.

A lively debate through the 1930s, 1940s and 1950s focused upon whether hypertension preceded or resulted from renal vascular damage: one being 'provocative of the other', as Johnson had put it, but which way round? The debate lives on. The arrival of an effective treatment for hypertension in the 1940s provided an excellent opportunity to take a large histological sample from hypertensive kidneys: the surgical operation of thoraco-lumbar sympathectomy at Massachusetts hospitals provided access to kidneys for biopsy of the cortex in 1350 patients, in many patients from both kidneys (Sommers et al., 1958; Whitelaw et al., 1964). Biopsies from 12 non-hypertensives were also available. Grades of afferent arteriolar abnormalities were defined. In all but 14 hypertensive patients, arteriolar 'sclerosis' was recognized, mostly of a high grade, and in 13 of the 14 without a structural change, the histology suggested 'spasm' on account of seeing 'abnormal concentric overlapping of otherwise normal appearing smooth muscle cells that composed their walls'. This kind of spasm was seen in only one of the 12 non-hypertensives. The authors inferred that the sequence of events was 'spastic arteriolar contraction' preceding increasingly marked structural changes in the blood vessel walls.

The question arises of whether in the modern era it is possible to observe the histological changes brought about by uncomplicated hypertension, given that hypertensive patients are now extensively treated pharmacologically. The problem is illustrated by a contemporary histological study of human afferent arterioles from nephrectomised kidneys in hypertensives and normotensives: 'There were no hypertensive patients without RAS blockers in our hospital, because antihypertensive treatment with RAS blockers is the standard approach in Japan' (Nagai et al., 2020). They recruited from elsewhere to make possible a comparison between patients taking renin-angiotensin system (RAS) blockers and those receiving calcium channel blockers (CCB), as well as between these two groups and normotensives. A main finding in 92 kidneys was that significant afferent arteriolar wall thickening was present in both groups of hypertensives (quantified using a ratio of internal to external diameters). The arcuate arteries, upstream of the afferent arterioles, were also affected, in this case with an almost doubling of wall thickness in the hypertensive groups in the presence of similar outer diameters. Given that the histological measures of smooth muscle hypertrophy in those on RAS blockers were robustly different from the patients on CCB antihypertensives, the study cautions conclusions about the effects of hypertension alone on these vessels. Added to idiosyncratic drug effects, there is the problem that the hypertensives, all on treatment, had blood pressures similar to the normotensives (Nagai et al., 2020).

It follows that many of the histological observations made in the modern era are reported without detailed appreciation of type of therapy and level of blood pressure control. Nevertheless, extensive research has shown that essential hypertension is associated with changes in renal small artery and arteriolar structure, usually resulting in thickening of vessel intima by replication of elastic laminae and hyalinization, and thickening of the vessel media by hypertrophy, hyperplasia and remodelling of smooth muscle cells (Olson, 2015). Glomerular and tubular changes downstream of these vessels are often attributed to ischaemia but also sometimes attributed to exposure of the delicate structures to high blood pressure via enlarged vessels. Hill et al. in their study of 2006 found a wide range of glomerular appearances in hypertensives and also in normal ageing, including normal, hypertrophic and sclerosed glomeruli, and a wide range of diameters of arterioles feeding glomeruli (Hill et al., 2006). Hypertension was associated with a shift in the distribution away from 65% normal glomeruli in normal ageing to 12% in the hypertensives, but even normal glomeruli had different dimensions and arteriolar sizes in the two groups. Their results suggest that thickened vessels deny some glomeruli adequate blood supply whilst other glomeruli become damaged by exposure to high pressures. Given the known lower number of nephrons in patients with hypertension (Keller et al., 2003), the complex histology alone does not make it tractable to judge the overall resistance of the renal vessels in hypertension. That result is best judged from functional studies. The focus of this paper will be the methodology of physiological studies and associated mathematical modelling of arterial blood pressure regulation.

2 | METHODS: PHYSIOLOGY AND MODELLING

2.1 | Human physiological studies to locate a main trouble-spot in hypertension

The seminal early study investigating renal haemodynamics in humans is that of Gómez (1951). He compared the renal and systemic haemodynamics of 16 hypertensive patients with 22 normotensives (mean arterial pressure (MAP) 91 mmHg). The most striking abnormality observed was that afferent (pre-glomerular) renal resistance was 5.4 times greater in hypertensives. In these hypertensives a renal blood flow that was 66% of normal flowed through this very high afferent resistance from a MAP of 145 mmHg into glomerular capillaries at a pressure of 46.8 mmHg, where the glomerular filtration rate (GFR) was 70% of normal. Glomerular capillary pressure in normotensives was 63.5 mmHg. Efferent and venous resistances in hypertensives were raised by 12% and 64%, respectively. Incorporating further data to cover a total of 51 hypertensives, Gómez found that the distribution of afferent resistances in hypertensives and normotensives showed no overlap whatsoever. Distributions of the efferent and venous resistances showed much overlap between groups. Gómez suggested that the higher downstream resistances appeared to reflect lower pressures and calibres of these vessels in hypertensives.

Two years earlier, Bolomey et al. had used cardiac catheters to compare 19 hypertensives with 18 normotensive but otherwise similar controls (Bolomey et al., 1949). They found similar percentages of normal with regard to hypertensive renal blood flow (64%) and GFR (66%) to those later seen by Gómez. Cardiac output showed no significant difference between the two groups, being 97% of the control value in hypertensives. Gómez himself did not measure cardiac output but inclined to the view, based on the work of Bolomey et al. and others, that cardiac output is usually unchanged in hypertension, so that MAP reflects changes in peripheral resistance.

The picture that emerges from these thorough early studies is that essential hypertension is characterized by an increase in renal afferent resistance that is by far out of proportion with the increase in peripheral resistance that is seen. If MAP is seen to double, the afferent resistance will be found to have increased five times or more.

The approach of Gómez suffered from uncertainties. These included the difficulty of estimating in humans the glomerular filtration coefficient and the difference in the Starling forces driving reabsorption from the renal tubule to the peritubular capillaries. Gómez assumed a net Starling force for reabsorption of zero. In 1970, Lowenstein et al. diverged from Gómez's assumption and took tubular and peritubular capillary hydrostatic pressures to be identical (calling them 'intrarenal pressure'), and measurable by retrograde wedging of a 0.9-mm renal vein catheter (Lowenstein et al., 1970). They thus assumed a net driving Starling force for absorption equal to the oncotic pressure of blood, around 25 mmHg. In a comparison between 21 patients with essential hypertension and 18 normotensives, the wedged-catheter measurements and assumptions of Lowenstein led to estimates of glomerular capillary pressure of 72.4 mmHg in

hypertensives and 62.6 mmHg in normotensives. This approach to measuring glomerular capillary pressure seems not to have been supported by later studies. Nevertheless, like Gómez, Lowenstein et al. concluded that the predominant increment in resistance in their hypertensive individuals was in the preglomerular vasculature.

An ambitious fresh approach to delineating renal haemodynamics was taken by Kimura et al. in a collection of studies (Kimura et al., 1991; Sanai & Kimura, 1996). The method involved stabilizing hypertensives and normotensives on regular and low salt diets for a week each and thereafter extrapolating the results to determine a notional pressure at which renal sodium clearance would cease (as if on a zero-salt diet). From this a net glomerular filtration pressure with a normal diet was predicted, and corresponding afferent and efferent renal resistances calculated. Good agreement with the Gómez method was found, again with glomerular capillary pressures in hypertensives being low to normal (56 mmHg) and afferent resistances being highly elevated (Kimura et al., 1991). Kimura et al. were interested to find that the glomerular filtration coefficient of their hypertensives appeared not to be lower than normal, at 0.154 ml/s/mmHg.

The 'Kimura' method makes an assumption that is not always, or necessarily commonly, borne out. It is assumed that, in the change to the low salt diet, the fall in MAP equals the fall in glomerular capillary pressure. To be correct, this in turn would require no change in the afferent resistance or renal blood flow (or, strictly, their product) in the week following a change in salt intake. An example of a finding that is difficult to explain without incurring a change in afferent resistance during sodium restriction is the marked reduction in salt sensitivity of arterial pressure with the diuretic mefruside (Saito & Kimura, 1996). Given that diuretics (with the possible exception of indapamide) have their long-term antihypertensive effect without changing GFR or renal blood flow, it appears that their dominant action is one of reducing afferent resistance (Digne-Malcolm et al., 2016). The reduction in salt sensitivity of arterial pressure by a diuretic is, thus, consistent with a salt sensitivity in afferent resistance, which accords with recent findings of the mechanism by which diuretics inhibit tubulo-arteriolar feedback of macula densa and other distal tubular cells (Wang et al., 2015). An example from animal studies that is unlikely to be consistent with salt restriction leaving afferent resistance unchanged is the observation of Hall et al. in dogs (Hall et al., 1980). In these experiments conducted over a 4-week period, arterial pressure changed only minimally (<7 mmHg) over a very large range of salt intake from 5% to 500% of normal dietary content (Hall et al., 1980). Similar minimal changes in arterial pressure with large changes in dietary sodium have been seen in normotensive humans (Parfrey et al., 1981a,b). If MAP were to be completely insensitive to the amount of salt in the diet, the Kimura method would predict a constant net glomerular filtration pressure of zero and consequently an unphysiological glomerular capillary pressure of ~35 mmHg (Digne-Malcolm et al., 2016). The Kimura method can only be helpful, therefore, where afferent resistance is presumed to remain constant. That there has been good agreement between the method of Gómez and that of Kimura in untreated hypertensives suggests that these patients tend to have a 'fixed' afferent resistance that is affected little by changes in dietary salt intake, in

contrast to the adjustment that is seen to occur in healthy humans (and dogs).

One of the fascinating questions has been why some hypertensives show a marked salt-sensitivity to their elevated arterial pressure and others show much less salt-sensitivity. Light may have been shed on this by a later study from Kimura and a colleague in which 15 hypertensives were divided into seven sodium sensitive and eight non-sensitive according to whether their MAP was reduced by more than 10% by sodium restriction (Sanai & Kimura, 1996). This small study using the Kimura analysis of the pressure–natriuresis relationship found that sodium sensitivity of arterial pressure was associated with a higher glomerular capillary pressure (59 vs. 47 mmHg) and a lower glomerular filtration coefficient (0.068 vs. 0.221 ml/s/mmHg), whilst no significant differences could be found between the groups with respect to MAP, GFR or renal plasma flow. However, given the possibility that the assumption underlying the Kimura method, of a fixed afferent resistance, might not hold in both groups, it remains possible that the different degrees of salt sensitivity of hypertension might arise from different degrees of salt sensitivity of afferent resistance.

2.2 | Mathematical modelling

It is unusual in the scientific journals for authors to headline their findings in emotional terms, writing about ‘the elation that we felt when we realized that the kidney-fluid mechanism for controlling arterial pressure has an infinite feedback gain’ (Guyton, 1990). It was in 1966 that Thomas Coleman and Arthur Guyton set about using their computer model of the circulation to confirm what ‘without doubt everyone already understood that increased total peripheral resistance did indeed cause chronic hypertension’. Their result from the modelling showed the opposite: absolutely no effect of total peripheral resistance on long-term arterial blood pressure (Guyton & Coleman, 1967; Guyton & Coleman, 1969). To the authors, it proved to be ‘sudden light at the end of a tunnel’, ‘almost ecstatic euphoria’ (Guyton, 1990). These remarkable comments are worth noting half a century on because many patient websites, much teaching material for students, and some academic papers continue to attribute the *cause* of hypertension to an increase in peripheral resistance rather than recognizing the relationship as an association (Beevers et al., 2015; Jackson & Bellamy, 2015; Joyner et al., 2016; Pettersen et al., 2014; Pocock et al., 2017).

What is the issue here? The peripheral resistance (R) of the circulation is defined as the ratio of a pressure drop to a flow. The pressure drop is from the systemic arteries, where the mean pressure is MAP, to the central veins, where the mean pressure is central venous pressure (CVP). The flow is the cardiac output (\dot{Q}). We know this as a form of Ohm’s law:

$$R = (\text{MAP} - \text{CVP}) / \dot{Q}. \quad (1)$$

Note that this is the definition of a ratio that can only be determined by measuring the variables on the right-hand side of the equation;

peripheral resistance cannot be identified or measured separately. It follows from Equation (1) that hypertension, being a long-term elevation of MAP, must be associated with a high cardiac output, a high peripheral resistance, or both (CVP not commonly being much changed):

$$\text{MAP} = (\dot{Q} \times R) + \text{CVP}. \quad (2)$$

Since measurements, like those of Bolomey et al. (1949), have tended to show that cardiac output differs little from normal in hypertensives, it looks as though high MAP may be not just associated with high peripheral resistance but *caused* by high peripheral resistance.

When Coleman and Guyton formed their computer model of the circulation that realistically permitted it to be filled from a daily intake of salt and water and emptied primarily by the output of salt and water by the kidney, the insight dawned that all or most of the variables in Equation (2) are dependent upon how full the circulation is. In addition, the kidneys’ ability to keep up with the daily intake of salt and water itself depends upon how full the circulation is. The argument, therefore, ends up viewing MAP (along with \dot{Q} , CVP and possibly peripheral resistance) as all dependent upon kidney behaviour. One can use the term ‘final common path’ to describe the kidney as what determines these variables, along with the rate of intake of salt and water, which the kidney has to match to keep the body in fluid balance. Other modellers have emphasized this inescapable feature of a circulation that is open to input and output (Kimura et al., 1986; Keener & Sneyd, 2009; van den Berg, 2011).

Coleman and Guyton focused on the observation that renal output of sodium increased when MAP increased, and advocated plotting a graph with MAP on one axis and daily sodium intake/output on the other, drawing a ‘pressure–natriuresis’ line or curve expressing this relationship. This led to the view that the only way to obtain a chronic increase in MAP at a constant sodium intake was to ‘shift’ the pressure–natriuresis line to higher pressures and that nothing could achieve this except some change in renal function. However, this pressure–natriuresis line is affected by other factors, and many have been identified. Indeed, in many experiments, sodium intake/output turns out to be so minimally dependent on pressure (once a threshold has been reached) as to lead to the conclusion that pressure is not an important factor at all and that the other factors dominate. Authors have felt it to be necessary to generate a large volume of literature centred on arguing whether sodium elimination by the kidney that is independent of MAP can be regarded a pressure natriuresis modified by the other factors or simply not a pressure natriuresis at all (Beard, 2013; Beard, 2017; Kurtz et al., 2016; Lohmeier & Pruetz, 2016).

Unfortunately, this heated exchange about the steepness or flatness of a line on a graph has become confused with the quite separate question of whether it is possible for long-term regulation of MAP to be independent of the kidney. The first of these questions is a matter of nomenclature as well as a question about how the output of the unregulated, isolated kidney responds to a change in perfusion pressure. The second of these questions is one of what terminology to use to describe mass balance. Here the argument concerns an open

system in which the output of salt and water is primarily via the kidney (rather than faeces, sweat, humidification of expired gas, etc.) and whether it is unavoidable that the fullness of the circulation and MAP become determined by renal function.

The 'vasodysfunction' school of thought sees 'abnormal vascular resistance response' as the cause of high blood pressure associated with high salt intake and with hypertension (Morris et al., 2016) and focuses attention away from the kidney onto the peripheral resistance. A 'neurogenic' school of thought argues that renal function 'is not the only factor that affects the long-term level of arterial pressure' (Averina et al., 2015; Osborn et al., 2009) and focuses on the autonomic nervous system as being capable of regulating blood pressure without necessarily involving the kidney. Again, the peripheral resistance becomes centre-stage in this approach.

An extreme approach illustrates the debate. In their fairly recent model of the circulation, Averina et al. numerically matched sodium elimination to intake with a simple time lag of 0.3 days, not specifying by what mechanism this might be achieved (Averina et al., 2012). Here the elimination of salt by the kidney keeps track of its input regardless of the pressure in the circulation, and the result is that arterial blood pressure can remain at any level. In effect, the circulation has become a closed system without the possibility of gradual long-term changes in its fluid capacity. The approach was described by the authors as 'a new conceptual paradigm' that examines 'non-kidney-based theories of hypertension'. The failure of the model to take into account the physiological reality of the circulation being an open system has been commented on (Clemmer et al., 2017; Judge & Dorrington, 2013).

3 | RESULTS: KIDNEY PLUS CONTROVERSY

3.1 | Huge kidney models have not led to consensus

The early model of the circulation of Guyton and Coleman has been updated progressively as new details have been elucidated about the complexity of the renal, hormonal and neural regulation of the cardiovascular system. A major step forward was made by Karaaslan et al. (2005), who included renal sympathetic nerve activity (RNSA) in a model with 41 components (involving 84 variables) contributing to the regulation of arterial blood pressure, each component being characterized and calibrated by reference to the experimental literature. The focus of this paper was to explore the role of RNSA on long-term sodium excretion. A later paper suggested that these authors too underwent a light at the end of the tunnel experience when they showed that 'no difference in renal sodium excretion could be observed between intact- and fixed-RNSA conditions', perhaps forgetting briefly that, in the long-term, the real or virtual patient has to be in sodium balance, whether or not their renal sympathetic nerve supply is intact (Karaaslan et al., 2014). The later paper allowed for two kidneys to be separately innervated or not (plus some further sophistication), and thus provided a fine left versus right comparison of the individual renal sodium fluxes resulting from an eight-fold

step increase in sodium intake over 5 days. The final result of this gargantuan effort was the finding that the kidney with an intact (responsive and reduced) RNSA contributed ~70% of the total urinary sodium excretion and the kidney with a fixed (unresponsive) RNSA contributed only ~30% of the excretion, clearly not pulling its weight. This was the most thorough physiological model to date of the relationship between long-term arterial blood pressure, sodium intake and renal function. In the hands of others, it has gone on to make an impressive contribution to the study of hypertension.

Hallow et al. developed the model of Karaaslan et al. (with further sophistication, including pathological nephron loss) to examine the capacity for single- and multi-factor perturbations to induce hypertension, to form a virtual cohort of hypertensive patients, and to examine the effect on them of single and multiple drug regimens (Hallow et al., 2014). The search for single factor perturbations most capable of generating a substantial rise in arterial pressure is revealing. The strongest candidates are afferent arteriolar (and any pre-glomerular) resistance, the liveliness of tubular sodium reabsorption, and RNSA. A huge range of total peripheral resistance (–50% to +250%) corresponded to a tiny range of arterial pressure (~1 mmHg – interestingly not quite the zero change lauded by Guyton and Coleman), and it is informative to explore why that is so. The model allows changing right atrial pressure to modulate RNSA and atrial natriuretic peptide concentration, both of which contribute to a tiny effect of peripheral resistance on long-term arterial pressure (via the kidney). The infinite gain of Guyton and Coleman is not quite so infinite as their euphoria had suggested, but nearly so (Guyton, 1990; Hallow et al., 2014).

A feature of the modelling by Hallow et al. (2014) that appeared to diverge from what is seen in many hypertensive patients was that changes in arterial blood pressure of ~16% brought about by single factor perturbations were only associated with small (~8%) changes in peripheral resistance, whereas we know that many hypertensive patients maintain a normal cardiac output. That requires similar percentage changes in arterial pressure and peripheral resistance, as shown by Equation (2). In a further development of the models we have explored above, Hallow and Gebremichael add in a degree of tissue autoregulation to return a perturbed cardiac output back to its original 'set point' via a proportional-integral controller, and further explore pharmacological interventions after accounting for salt-sensitivity in hypertension by allowing for changes in renal interstitial hydrostatic pressure (Hallow & Gebremichael, 2017a,b).

Another strand of updating the old model of Guyton and Coleman continues from Coleman and Hall, led most recently by Clemmer (Clemmer et al., 2017). HumMod is a software package claimed to be 'The most complete, mathematical model of human physiology ever created' (<http://hummod.org/origin-story/>) (Hester et al., 2011). The package 'includes over 8000 independent variables that interact in a time-dependent manner to regulate multiple physiological systems' and has been used to model the regulation of arterial blood pressure (Clemmer et al., 2017). It comes as somewhat of a surprise, therefore, that application of the model to a set of human data on 7 days of salt loading proved so weak at predicting experimental results (Kurtz et al.,

2018) that an associated editorial by Beard concludes that 'the Guyton model and its descendants are intriguing, flawed, ambitious in scope, wrong' (Beard, 2018).

This is a most extraordinary situation. Factions in the scientific community are dismissing each other's work much in the manner associated with rival religious sects or political ideologies on a topic discussed over half a century or more.

3.2 | Weaknesses and strengths of current modelling

So where have we got to following much work generating a model of renal function and arterial pressure of byzantine complexity and, in some contexts, apparently remarkable predictive powers? Following the 1966 'elation' experienced when modelling showed the opposite of what the experts at the time 'already understood', we would be hard-pressed to say that the computer modelling has injected big surprises over and above that with which our basic knowledge of renal and circulatory physiology has provided us. A long-term elevation in arterial blood pressure can be induced by increasing pre-glomerular resistance (arterioles and arteries), enhancing sodium reabsorption and stepping up renal sympathetic nerve traffic (Hallow et al., 2014; Hallow & Gebremichael, 2017a; Karaaslan et al., 2005, 2014). Smaller effects are seen from reducing the glomerular hydraulic conductance or the number of functional nephrons (Hallow et al., 2014). Whether essential hypertension will ever be regarded as having a single-factor aetiology or be a multi-factor condition, it is doubtful that the factor or factors have failed to be included in some form in the 96-parameter model that is increasing in complexity by the month (K. M. Hallow personal communication) (Hallow & Gebremichael, 2017b). It may be that it remains, or they remain, hidden.

What no mathematical model has been able to show is that an isolated rise in peripheral resistance, involving neither renal vascular resistance nor any aspect of renal function, is capable of inducing a long-term rise in arterial pressure. The purest assessment of this in an animal laboratory model is the remarkable study by Crowley et al. in anatomically localized angiotensin II receptor (AT₁R) knockout mice subjected to a 20-day angiotensin II infusion (Crowley et al., 2006). A combination of whole-body knockout and vascularized kidney transplantation surgery (taking the renal artery and vein with cuffs on the aorta and vena cava, respectively) generated four groups. Angiotensin II infusion was unable to generate a prolonged rise in MAP in either of the two groups lacking renal AT₁R, though a transitory elevation in MAP over 6 days was induced in the group with only systemic AT₁R present, in which the persistent rise in peripheral resistance was unable to generate a prolonged elevation in MAP.

It is difficult to envisage an equivalently pure study in humans in which the kidney and renal vasculature are excluded from a persistent rise in peripheral resistance. A clinical study in amputees before and after surgery has the potential to do this. No such study appears to be available. However, using control patients, in 2019 Bhatnagar et al. examined 442 unilateral lower limb and 146 bilateral lower limb

amputees over several years (Bhatnagar et al., 2019). They found no elevation of MAP in the unilateral amputees and a 1.7 mmHg increase in the bilateral amputees. The authors commented on differences in sympathetic responsiveness and predisposition to metabolic syndrome with increasing severity of amputation.

One challenge at this stage is to note the extent to which existing modelling has failed to replicate what we see in hypertension. We still have not seen modelling that can predict the level of hypertension noted in the 1950s before effective therapy was introduced, in which pressures such as 250/150 mmHg were not uncommon (Doyle & Smirk, 1955; McGregor, 1930). Although models now incorporate the possibility of an autoregulatory return of cardiac output to a normal physiological value following the onset of hypertension, we have not yet seen published values of the high peripheral resistances needed to achieve this in the presence of a high arterial pressure; thus, the mechanism of autoregulation of blood flow to tissue requirements has not so far been well modelled.

The effects of anti-hypertensive agents remain to be accurately modelled. For example, a survey of the 50-year literature of human renal haemodynamic responses to anti-hypertensive drugs found that angiotensin converting enzyme inhibitors tend to elevate GFR (and hence glomerular hydrostatic pressure), whereas the modelling predicts a fall (Digne-Malcolm et al., 2016; Hallow & Gebremichael, 2017a). The literature survey noted that thiazides have not been found to change GFR in their long-term anti-hypertensive use (the 'thiazide-like' indapamide being an exception); the modelling predicts a fall (Digne-Malcolm et al., 2016; Hallow & Gebremichael, 2017a). Several studies reviewed in the survey showed a rise in glomerular hydrostatic pressure with the calcium channel blocker amlodipine; the modelling shows zero change (Digne-Malcolm et al., 2016; Hallow & Gebremichael, 2017a).

A theoretical modelling approach helps us understand some of the constraints on possible mechanisms of hypertension. First, for example, if enhanced sodium reabsorption were the primary defect (as is known to be the case in some congenital forms of secondary hypertension such as Liddle's syndrome), then we would anticipate an elevation in peritubular capillary hydrostatic pressure arising in order to maintain sodium homeostasis and maintain an appropriate net Starling force between the renal tubule and the peritubular capillary. This in turn would be associated with a higher hydrostatic pressure along all of the renal vascular path, and a higher GFR.

Second, if afferent arteriolar constriction were the primary defect (mimicked by renal artery stenosis, another cause of secondary hypertension) we would anticipate normal or lower hydrostatic pressures downstream of the constriction, with maintained or lowered GFR, according to the extent to which arterial pressure rises to overcome the increased afferent resistance and restore normal hydrostatic pressure from the glomerular capillaries onwards through the renal vasculature.

Third, an important conclusion comes from all models of the circulation that allow it to be an open system, from that of Coleman and Guyton to those of the present day, that a primary increase in peripheral resistance (not involving the renal vasculature) is not capable

of inducing a long-term rise in arterial pressure. It is fascinating to see how all-pervasive the assumption remains that increasing peripheral resistance can determine a long-term rise in blood pressure and lowering it therapeutically is the main line of treatment (Beevers et al., 2015; Foex & Sear, 2004; Jackson & Bellamy, 2015; Klabunde, 2021). Thus, even authors recently arguing for an elevation in renal vascular resistance as the final common pathway to hypertension summarize that 'BP is *determined* by the product of cardiac output and systemic vascular resistance' (present authors' italics), when the interrelationship between these three variables is descriptive (Johnson et al., 2015). Indeed, in the context of long-term circulatory changes addressed by those authors, it is more helpful to think about cardiac output being determined by blood pressure (BP) and peripheral resistance.

The vehement criticisms of the sons and daughters of the Coleman and Guyton model of the circulation articulate around weaknesses in the existing models in predicting the effects of salt-loading experiments whilst using these inadequacies to try to undermine the solid result that renal function is an indispensable determinant of arterial blood pressure.

4 | DISCUSSION: SYMPATHETICS AND STUDENTS

4.1 | Animal studies of renal sympathetic activity

George Johnson had little in the way of animal studies to guide his assessment of whether hypertrophy of the renal vessels was 'provocative of the hypertrophy' of the heart, or vice versa, though he referred much to asphyxia experiments to elucidate his 'stop-cock' view of the small pulmonary arteries. He would have been fascinated by experiments on the functional effects of the renal nerve supply. There is evidence from short-term experiments that sympathetic nerve activity can markedly affect the renal vasculature and epithelial transport.

In a remarkable study on anaesthetized rats in 1981, Hermansson et al. measured the plasma flow to, and GFR of, individual nephrons and their acute changes during direct stimulation of the renal sympathetic nerves at 2 and 5 Hz (normal physiological frequencies being commonly ~1 Hz) (Hermansson et al., 1981). This extensive delineation of haemodynamics and filtration in this model showed that increasing sympathetic stimulation reduces blood flow and filtration rate in association with constriction of both afferent and efferent arterioles, the former being most affected at 5 Hz. A 10-Hz stimulation was found to stop flow completely and used to assess integrity of the preparation. The overall acute effect of stimulation was, as anticipated, one of reducing urine flow and thereby conserving body water.

Lower levels of sympathetic stimulation appear able to reduce urine flow without affecting renal haemodynamics or GFR in the short term, by direct stimulation of tubular epithelial reabsorption. Using anaesthetized dogs, Slick et al. (1975) were able to demonstrate a fall in urinary sodium loss brought about by low-frequency sympathetic stimulation (0.5–2 Hz) in the complete absence of any effect of the stimulation on renal blood flow or glomerular filtration. This presumed tubular epithelial action of the nerve stimulation was eliminated by

adrenergic blockade with guanethidine, a drug that inhibits release of noradrenaline from adrenergic nerve terminals. Higher frequency stimulation (20 Hz) gave a much larger reduction in urinary sodium excretion to which haemodynamic changes also contributed; they too could be eliminated by guanethidine.

These experiments left the relative α - and β -adrenergic contributions of these effects of sympathetic activity unattributed. A study by Zambraski et al. (1976) helped to resolve this issue. In anaesthetized dogs, sympathetic outflow to the kidney was enhanced by arranging for the carotid baroreceptors to be stimulated by a fall in perfusion pressure from which the kidney was protected, an elegant way of achieving a more physiological sympathetic stimulation of the kidney than putting electrodes directly on nerves. A fall in renal sodium excretion occurred without any change in renal haemodynamics or GFR. It was completely inhibited by both locally infused guanethidine and the α -adrenergic receptor blocker phenoxybenzamine. This suggests a dominant adrenergic action via α -receptors. However, it should be noted that experiments such as these do not exclude a possible effect of circulating adrenaline on any β_2 -adrenergic receptors that might be present; locally released noradrenaline from sympathetic nerves is likely to have little effect on these receptors.

Short-term experiments of this kind do not show long-term effects of renal sympathetic activity, but contribute to the large literature linking sympathetic overactivity with essential hypertension (Esler, 2011; Grassi et al., 2018). We have seen above how data of this kind have been incorporated into mathematical models of renal function.

4.2 | From George Johnson to computer modelling: what is today's student of biomedicine to make of it all?

Students of medicine or biomedicine are confronted by a bewildering variety of opinions and information about the regulation of arterial blood pressure. Many will have arrived at college from school without a clear idea of what is meant by 'pressure' and why it can be measured in so many different units. Part of the course will focus on rapid ups and downs of pressure as people stand up, exercise, sleep, get angry or even suffer penetrating trauma with blood loss. Another part may focus on gradual changes in pressure with ageing or chronic disease. The student may become aware that a particularly adversarial debate has simmered for years about the causes of high blood pressure. The student may be tempted to think that, if the experts cannot sort it out, what hope has the newcomer of reaching some understanding. Here we take the view that nobody is barred from taking an informed view of the vast literature on hypertension. It is not necessary to be intimidated. We have considered (1) what has been seen under the microscope in tissue from patients, (2) what measurements in the living body have been made to make sense of these appearances, and (3) how observations and ideas can be brought together, often with the help of a computer.

Johnson observed that the disease we now know as essential hypertension was characterized by the presence of narrowed small arteries leading into the kidney. He liked the word 'stop-cock'. He noticed

later that blood vessels throughout the body were often abnormal as well. Physiological measurements in patients in the 1950s found hypertensives to have a strikingly high resistance in the afferent renal vessels, along with an elevated resistance elsewhere in the body sufficient to keep the cardiac output normal in the face of the raised arterial pressure. Mathematical modelling has shown that prolonged elevation of arterial pressure cannot be brought about by isolated elevation of peripheral resistance or alteration of cardiac function. It can be brought about by elevated afferent renal vascular resistance, by overactive tubular sodium reabsorption, and by enhanced RNA, the latter possibly causing the former two. The finding that peripheral resistance and cardiac contractility cannot generate long-term hypertension has been a feature of simple and complex mathematical models over many years. It follows that essential hypertension must be viewed as primarily a disease of the renal vasculature or its regulation. Any associated disease elsewhere in the cardiovascular system cannot bring about the observed elevation in pressure.

A particularly simple model of the circulation that can help students see the role of the kidney in determining long-term blood pressure, and the effect of changing peripheral resistance, is one suggested by Kimura: a 'water tank model' (Kimura et al., 1986). Using this, we can think of the body's circulatory system as a garden water tank receiving rain and emptying via an open tap about half way up its side. The depth of the water in the tank represents the arterial blood pressure. The rain represents drinking and the tap represents the kidney. We imagine that the width of the tank can be varied; this width represents (the inverse of) peripheral resistance. All existing computational models that allow for independent in-flow and out-flow from the body are similar to this most basic model. The reason for this is that the model simply represents Equation (2). (The volume of water in the tank is proportional to cardiac output.)

The water-tank model shows us that varying the peripheral resistance (the width of the tank) can only have temporary effects on the depth of water in the tank. In the long term, it is the height of the tap and how open or closed it is that are the main determinants of the depth of water. The abnormality in the kidney that Johnson was seeing down his microscope 150 years ago can be represented by the tap being abnormally high in the side of the tank. The amount of rainfall into the tank can also have an effect on the depth, particularly if the tap is not fully open. The model is a reminder that the frequently observed close relationship between arterial pressure (depth of water) and peripheral resistance (width of tank) in patients over long periods of time is one of association, not one of causation; changing the width cannot lead to a persistent change in depth unless the position of the tap is also changed.

An extension of this model, using one tank for the arteries and one tank for the veins, can clarify for students how altering the properties of the heart in isolation is also unable to bring about long-term changes in arterial pressure (Dorrington & Pandit, 2009; Herring & Paterson, 2018).

If we are content to trust existing models to demonstrate the role of the kidney in the long-term regulation of blood pressure, what is it about the complex versions of these models that appears to be failing

to represent some of the salt-loading experiments to which they are subjected and the effects of anti-hypertensive drugs? Our observation is that current models are defective in two particular respects. The first is in failing to represent the mechanisms of the body's autoregulation of blood flow to tissues (and thereby the near normality of cardiac output in hypertensives). The second is the inadequate representation of tubulo-arteriolar feedback regulating afferent renal resistance, new forms of which have recently been uncovered (Ren et al., 2013; Wang et al., 2015). It is remarkable, for example, that we do not understand how most diuretics have the long-term effect of acting as afferent renal vasodilators (Digne-Malcolm et al., 2016). Students continue to be taught exclusively about the effects of diuretics on tubular epithelial transport but it looks likely that their effects on tubulo-arteriolar feedback may be of greater importance in the treatment of hypertension. It is not surprising, therefore, that the vasodilatory behaviour of most diuretics has so far not been incorporated into existing models.

Much evidence points to an elevation of sympathetic nerve activity to the kidney as influencing its function. To cite Esler: 'It now seems certain that the renal sympathetic nerves are pivotal in the pathogenesis of essential hypertension' (Esler, 2011). Their main known effects are on vascular tone (some via renin release) and epithelial sodium transport. The haemodynamic measurements in essential hypertension suggest that the vascular effects are the most significant.

There seems no escaping the conclusion that George Johnson's stop-cocks remain the main crime scene in this disease and that there is a need to refocus detective efforts at that site. An aspect of them appears to be a third factor neglected in all the modelling: Johnson and successive histologists noted structural changes in blood vessels, including hypertrophy, sclerosis and hyalinization of vessel walls. Current mathematical models deal with a complex network of interacting reflexes without being clear about what features are structural and fixed, and what features might be amenable to modulation by drugs and sympathectomy. Future attempts to mimic or model the behaviour of the circulation will have to define better these components to do justice to Johnson's remarkable observations. One senses that he might be very impatient about the progress we have made (Johnson, 1887).

COMPETING INTERESTS

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

The historical approach to a topic of current interest was conceived by K.L.D. Both authors drafted and revised the original manuscript, and approved the final version of the manuscript. Both authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Both persons designated as authors qualify for authorship, and no other person qualifies for authorship.

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