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The role of the kidney in the pathogenesis of hypertension:

Time for a neo-Guytonian paradigm or a paradigm shift?

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Running title: Anomalies in the Guytonian paradigm?

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Abstract

The 'Guytonian paradigm' places the direct effect of arterial pressure, on renal excretion of salt and water, at the center of long-term control of blood pressure and thus the pathogenesis of hypertension. It originated in the sixties and remains influential within the field of hypertension research. However, the concept of one central long-term feedback loop, through which arterial pressure is maintained by its influence on renal function, has been questioned. Furthermore, some concepts in the paradigm are undermined by experimental observations. For example, volume retention and increased cardiac output induced by high salt intake do not necessarily lead to increased arterial pressure. Indeed, in multiple models of salt-sensitive hypertension the major abnormality appears to be failure of the vasodilator response to increased cardiac output, seen in salt-resistant animals, rather than an increase in cardiac output itself. There is also evidence that renal control of extracellular fluid volume is driven chiefly by volume-dependent neurohumoral control mechanisms rather than through direct or indirect effects of changes in arterial pressure, compatible with the concept that renal sodium excretion is controlled by parallel actions of different feedback systems, including hormones, reflexes, and renal arterial pressure. Moreover, we still do not fully understand the sequence of events underlying the phenomenon of 'whole body autoregulation'. Thus, the events by which volume retention may develop to hypertension characterized by increased peripheral resistance remain enigmatic. Finally, by definition, animal models of hypertension are not 'essential hypertension'; progress in our understanding of essential hypertension depends on new results on system functions in patients.

Abstract word count = 254

Introduction

Thomas Kuhn identified the processes through which new scientific paradigms arise (70). The process begins with 'normal science', where we work within an existing paradigm that defines our scientific approach. But normal science generates anomalies that can only be resolved through a 'revolution' which generates a new paradigm to replace the old one. Kuhn defined an anomaly as a "violation of the paradigm-induced expectations that govern normal science" (70). Kuhn's definition of a paradigm included anything "sufficiently unprecedented to attract an enduring group of adherents away from competing modes of scientific activity" and "sufficiently open-ended to leave all sorts of problems for the redefined group of practitioners to resolve" (70). Arthur Guyton and Thomas Coleman's theory of the role of the kidney in long-term control of arterial pressure and the pathogenesis of hypertension fits nicely with this definition.

Nevertheless, advancement in science is characterized by the replacement of established paradigms with new ones. This is why paradigms are so useful; they allow us to advance our theoretical understanding of, in our case, human biology and medicine, by making it 'less wrong'. In this article, we examine the anomalies that could be considered to challenge the 'Guytonian paradigm' of the role of the kidney in long-term control of blood pressure. Our intention is not to propose a new paradigm, but to consider where we are in the 'Kuhn cycle' that drives paradigm change (70). We particularly highlight the evidence that, except in experimental models associated with extreme volume retention, both renal excretory dysfunction and dysfunction of the systemic vasculature are associated with the development of hypertension.

There is a long history of criticisms of the Guytonian paradigm, dating back to the time soon after the first publications of Guyton, Coleman and colleagues' on the subject (36). Moreover, some of these authors have even suggested what might be called alternative paradigms (20, 65, 71, 89). In this respect, it could be argued that we have little new to offer. But rather than advocate for or against the Guytonian paradigm, we aim to identify the central questions that should be addressed to advance the field.

76   **The Guytonian paradigm**

77   Arthur Guyton described with passion the moment of epiphany, in which he and Thomas

78   Coleman arrived at the interdependent conclusions that define what we will refer to herein as the

79   Guytonian paradigm: (i) that hypertension can only develop if the relationship between arterial

80   pressure and sodium and water excretion is shifted to a higher level of arterial pressure and (ii) that

81   the renal body-fluid mechanism has infinite gain to control arterial pressure (46). The concept has

82   endured for more than 5 decades, perhaps in part because it shares many of the characteristics of a

83   good theory outlined by Kuhn (69). That is, the Guytonian paradigm is (i) accurate in the sense that

84   its consequences are largely in agreement with the results of existing experiments. It has been

85   bolstered by the results of computational modelling, which have allowed the predictions of the

86   paradigm to be compared quantitatively with experimental observations. Generally, the more

87   reliably a particular model is able to simulate experimental observations made under disparate

88   conditions, the greater confidence we can have in the theoretical basis of the model. However,

89   concordance between simulated data and the results of real experiments does not necessarily qualify

90   all elements of the model as different models may provide similar results. Models are wonderful

91   workshops of hypotheses, but not necessarily sponsors of reality. The Guytonian paradigm is also

92   (ii) internally consistent and was different from then current concepts, so novel. The great

93   breakaways were the crucial involvement of the kidney in long-term blood pressure control. This

94   conceptual breakthrough was based on unique (albeit initially pathophysiological) long-term

95   experiments demonstrating narrow relations between (a) blood volume and cardiac output, (b)

96   cardiac output and blood pressure, and (c) blood pressure and volume excretion, and the application

97   of comprehensive modelling of these and associated relationships. It also (iii) has a broad scope,

98   offering a coherent framework for understanding of both physiological control of arterial pressure

99   and the development of hypertension, (iv) is relatively simple, in that its centerpiece comprises only

100 two concepts (above) (45-47) although they imply several operational features based on modelling

101 alone, and (v) has been fruitful in the sense that is has driven multiple lines of research over

102   decades. It is disappointing; however, that the mechanisms of pressure natriuresis remain unclear

103   despite the explosive increase in insight into cellular and molecular biology (30), and that progress

104   with regard to understanding the mechanisms of essential hypertension has been limited.

105   The consequence of the paradigm is that sodium excretion is a monotonous function of

106   arterial pressure. Therefore, the long-term set point of arterial pressure must be at the point of

107   intersection of the pressure natriuresis curve and the daily intake of salt and water (23, 47). That is,

108   arterial pressure varies around an average level that allows maintenance of homeostasis of

109   extracellular fluid volume (Fig. 1). There are several important criticisms of the paradigm set out in

110   Fig. 1.

111   Firstly, the 'acute pressure natriuresis' curve shown schematically in Fig. 1A was derived

112   exclusively from studies of anesthetized animals and isolated perfused kidneys, in which the renal

113   excretory responses to manipulation of renal perfusion pressure could be observed. As previously

114   discussed (11), multiple studies document that anesthesia and surgery induce major changes in

115   multiple regulatory pathways, and that results obtained in anesthetized animals are not necessarily

116   meaningful with regard to sodium homeostasis.

117   Secondly, in the 'chronic pressure natriuresis curve' depicted schematically in Fig. 1B the

118   independent and dependent variables are not presented in the conventional way. The data upon

119   which this figure is based were derived from experiments in which both sodium excretion and mean

120   arterial pressure were measured at various levels of sodium intake. Yet the independent variable

121   (sodium intake estimated from sodium excretion) is plotted on the ordinate and the dependent

122   variable (mean arterial pressure) is plotted on the abscissa.

123   Thirdly, in most of the experimental studies in which this relationship was derived in intact

124   animals, its slope did not differ measurably from infinity (22), or was even negative (92),

125   compatible with the notion that arterial blood pressure is not sensitive to salt intake. It could be

126   argued that the absence of a finite slope of the pressure-natriuresis relationship under steady-state

127   conditions is the consequence of a long-term regulatory mechanism operating with infinite gain.

128 Real cellular and systemic mechanisms compatible with such control have not been proposed, but

129 might involve integrative control (activity being a function of the time integral of the error signal)

130 rather than the usual proportional control (activity being a function of the magnitude of the error

131 signal). However, even such a hypothetical, integrative control system would require an initial error

132 signal in order to initiate regulation. As we discuss below, there is also an important caveat that

133 must be applied to the concept of infinite gain of the renal-body fluid feedback mechanism for the

134 long-term control of arterial pressure (see Misinterpretation 2, below), Moreover, robust increases

135 in sodium excretion with sodium loading may well occur without any increase in blood pressure

136 (see anomaly 1 below).

137   Nevertheless, provided that some kind of causal relationship between renal arterial pressure

138 and sodium excretion does hold true even for small changes in arterial pressure, the Guytonian

139 paradigm provides an explanation for the development of hypertension when the excretory function

140 of the kidney is impaired. That is, water and electrolyte homeostasis can only be maintained at the

141 cost of chronically increased arterial pressure. In addition to the questionable assumption of a causal

142 relationship between arterial pressure and sodium excretion, it is vital to this concept (i) that

143 baroreceptor reflexes and other extra-renal counter-regulatory blood pressure control mechanisms

144 reset in response to sustained changes in arterial pressure, and (ii) that renal excretory function does

145 not reset (82). These two concepts are widely accepted, although the degree to which arterial

146 baroreceptors reset has remained a matter of controversy (77, 104). Indeed, the Guytonian paradigm

147 has its critics. As reviewed by Montani and Van Vliet, some of these criticisms are based on

148 misinterpretations of Guyton and Coleman's theory (83). Our intention is not to review the evidence

149 for a role of the kidney in the pathogenesis of hypertension. For this, we refer the reader to some

150 excellent recent reviews (15, 24). Rather, our intention is to focus on the potential anomalies that

151 might challenge the Guytonian paradigm. But first we will address some misinterpretations of the

152 Guyton-Coleman theory that were not addressed in detail by Montani and Van Vliet, (83) before

153 discussing what we see as true anomalies.

154 **Common misinterpretations of Guyton and Coleman's theory**

155 *Misinterpretation 1: Initial salt and water retention and increased cardiac output is a necessary*

156 *pre-requisite for development of hypertension*

157   Many of the early studies of Guyton and colleagues and their contemporaries employed

158 models of hypertension induced by maneuvers that severely reduced renal function and/or increased

159 salt and water intake. These models included one-kidney, one clip (1K1C) hypertension in rats (72,

160 73) and dogs (9, 32), salt-loading in dogs (18, 28) and rats (78) with reduced renal mass, cellophane

161 wrap hypertension in dogs (one kidney, one wrap; 1K1W) (32-34), and a combination of

162 intravenous angiotensin II infusion and salt loading in dogs (68). In the latter model, hypertension

163 could be prevented by servo-control of total body water, indicating a critical role of extracellular

164 fluid volume expansion (66). In each of these models, hypertension was initiated by salt and water

165 retention and (when measured) increased cardiac output (CO). But over a period of time ranging

166 from days to weeks (depending on the experimental model), total peripheral resistance (TPR)

167 increased and CO fell. Similar observations were made in anephric humans who were overhydrated

168 over a period of weeks (16, 17) (Fig. 2). These observations led to the classical view of so-called

169 'volume-dependent' hypertension, in which a shift in the pressure natriuresis relationship to the

170 right results in volume retention and so increased CO. Peripheral resistance then increases in

171 response to tissue hyper-perfusion, through still ill-defined mechanisms (so-called 'whole body

172 autoregulation'), so that hypertension is sustained by increased TPR rather than by increased CO

173 (Fig. 2) (17). Thus, this view of the pathogenesis of hypertension conflated two concepts; (i) that

174 hypertension could develop from salt and water retention and (ii) that autoregulatory mechanisms

175 could transform a hyper-dynamic state into a state of elevated TPR. We will return to the vexed

176 issue of whole body autoregulation later, but first consider the proposition that volume retention

177 represents a common pathway to the development of hypertension.

178   In contradiction to what some have claimed (e.g. (65)), Guyton himself acknowledged that

179 hypertension need not be associated with an initial increase in CO (17). He accepted that some

180   experimental models of hypertension are associated with well-maintained or even decreased CO

181   during their early phases. His interpretation was that "The contrasting results suggest that if

182   angiotensin or other vasoconstrictors can bring renal perfusion pressure back to normal without

183   changing the blood flow to the other tissues, then the autoregulatory response will not be initiated"

184   (17). In other words, whole body autoregulation is not a necessary element of models of

185   hypertension associated with marked peripheral vasoconstriction. A good example is hypertension

186   induced by chronic infusion of norepinephrine in dogs, which is associated with an initial

187   natriuresis and contraction of extracellular fluid volume (48, 50) (Fig. 3). Here, the pressure

188   natriuresis relationship is shifted to the right. Furthermore, arterial pressure increased more, and did

189   not reach a steady state, when renal perfusion pressure was servo-controlled to its level prior to

190   infusion of norepinephrine (48, 50). Nevertheless, because a major effect of norepinephrine is on

191   TPR, the hypertension is associated with contraction of extracellular fluid volume even in its very

192   early stages.

193   There is also good evidence that renovascular hypertension can develop even when salt and

194   water retention is prevented. In animals on a standard laboratory diet, hypertension induced by

195   constriction of a clip on a single kidney is usually associated with an initial retention of salt and

196   water and, when it has been measured, increased CO. However, others have observed reduced CO

197   during the onset of 1K1C hypertension in dogs (87) and renal wrap hypertension in rabbits (36).

198   Furthermore, 1K1C (19, 101) and 1K1W (27, 38) hypertension still develops in dogs in which

199   sodium intake is restricted to prevent increased extracellular fluid volume. Qi and colleagues also

200   showed development of hypertension in Dahl salt sensitive rats, when placed on a high salt diet,

201   even if body weight (and thus total body water) was servo-controlled (95). All of these observations

202   are compatible with a role of the kidney in the development of hypertension, but not with an

203   absolute requirement for sodium retention and increased CO.

204   If the contributions of increased CO and TPR vary in the initial stages of experimental

205   hypertension, it seems plausible that they might also vary in human essential hypertension. Indeed,

206   this appears to be the case. In so-called borderline or mild hypertension, relatively high CO has

207   been observed in some but not all reported studies (reviewed by (79, 98)). This variability is likely

208   real, reflecting the varying contributions of increased vascular tone and increased extracellular fluid

209   volume to the development of hypertension. Consequently, if we are to understand mechanisms

210   mediating the pathogenesis of human essential hypertension, we must consider dysfunction of both

211   renal excretory capacity and peripheral vascular tone. But we also must accept that the

212   hemodynamic profile in established hypertension tells us little, if anything, about the pathway(s)

213   leading to the development of hypertension. Arthur Guyton made this point himself at least 35 years

214   ago (45).

215   *Misinterpretation 2: The concept of 'infinite gain' implies that the pressure natriuresis relationship*

216   *does not reset in response to chronic changes in arterial pressure*

217   The kidneys not only respond to neurohumoral control systems, but are also the master

218   controllers of one of the most important of these mechanisms; the renin-angiotensin-aldosterone

219   system. Thus, changes in arterial pressure alter renal excretory function not just through intrinsic

220   mechanisms (i.e. pressure natriuresis), but also by altering extrinsic (i.e. hormonal and perhaps even

221   neural) control of renal excretory function. Let us assume that changes in extracellular fluid volume

222   necessarily lead to changes in arterial pressure, and that small changes in arterial pressure

223   necessarily lead to changes in sodium excretion. We will address these assumptions later

224   (Anomalies 1 and 2). Nevertheless, if they hold, the proposed infinite (or near infinite) gain of the

225   renal-body fluid feedback mechanism for the long-term control of arterial pressure would be

226   capable of returning arterial pressure to (or very near) its long-term set-point in response to any

227   perturbation *that does not influence renal excretory function* (48). But this set-point is itself

228   determined not just by intrinsic factors within the kidney, but also by the influence of neurohumoral

229   (extrinsic) factors on kidney function. Thus, the only way to alter the arterial pressure to which the

230   kidney is exposed without also altering the neurohumoral mechanisms that influence renal excretory

231   function, is to block these neurohumoral mechanisms (100). Such manoeuvers necessarily open the

232   feedback loops that govern renal control of extracellular fluid volume, and thus the long-term set-

233   point of renal control of arterial pressure. Pressure natriuresis and neurohumoral control of sodium

234   excretion can be considered as parallel, but inter-dependent mechanisms. Consequently, the

235   pressure-natriuresis relationship could only truly have infinite gain if all neurohumoral regulators of

236   renal excretory function were blocked. This caveat reduces the utility of the concepts of infinite

237   gain, and the kidney's long-term set point of arterial pressure, for our understanding of long-term

238   regulation of arterial pressure.

239   Under some conditions, renal arterial pressure and neurohumoral control might be expected to

240   influence sodium excretion in opposite directions. This has been addressed experimentally in

241   conscious animals by use of sophisticated and demanding techniques.

242   Reinhardt and colleagues provided strong evidence that extrinsic (neurohumoral) factors can

243   modulate renal excretory function in the face of chronic changes in renal perfusion pressure (97,

244   100). By remote control, they servo-controlled renal arterial pressure in conscious, freely moving

245   dogs, for a period of 4 days, to a level 20% below each dog's control systemic arterial pressure (e.g.

246   from 115 to 92 mmHg). Total body water and sodium and systemic MAP increased across the first

247   day, but thereafter remained relatively stable, even though the servo-control of renal artery pressure

248   kept said pressure at 92 mmHg (Fig. 4). They dubbed this mechanism 'pressure escape'. This

249   escape from the volume retaining effects of reduced renal artery pressure could potentially be

250   explained by altered extrinsic control of the kidney. Reinhardt and colleagues observed decreased

251   plasma aldosterone and increased atrial natriuretic peptide concentrations, consistent with a role of

252   extrinsic factors. Notably, volume retention in response to the reduction in renal arterial pressure

253   did not occur when the renin system was blocked (i.e. the 20% reduction in renal arterial pressure

254   did not per se contribute to volume retention). In subsequent studies they showed that the 'pressure

255   escape' phenomenon could be prevented by clamping the renin-angiotensin-aldosterone system at

256   baseline levels by continuous intravenous infusion of angiotensin II and aldosterone along with an

257   angiotensin converting enzyme inhibitor. During continued hormone infusion, sudden release of the

258   vascular clamp reintroduced the pressure escape situation at the expense of a 20% increase in renal

259   arterial pressure. However, the elevated renal artery pressure did not correct the hormone-mediated

260   volume surplus, and blood pressure remained elevated (100).

261   Mizelle and colleagues (82) performed an experiment similar to that of Reinhardt and

262   colleagues (97, 100), but servo-controlled renal arterial pressure to only one of the two kidneys, to a

263   level ~12 mmHg (~14%) below baseline systemic arterial pressure. Using a split-bladder technique,

264   they performed side-specific urine collections in this well controlled analogy in dogs of the 2-

265   kidney-1-clip model of renovascular hypertension. Consequently, the two kidneys were exposed to

266   identical (extrinsic) circulating hormones, but different levels of arterial pressure. Sodium excretion

267   by the kidney exposed to a lower arterial pressure decreased, but sodium excretion from the kidney

268   exposed to the slightly elevated systemic arterial pressure increased (Fig. 4). Surprisingly, they

269   found that the antinatriuretic effect of the 12 mmHg decrease in renal artery pressure in one kidney

270   was matched precisely by the 4 mmHg increase in systemic pressure and thus pressure to the

271   contralateral kidney, despite the concomitant 2.3-fold increase in plasma renin activity. These

272   changes were maintained at a relatively stable level for the 12 days of the experiment. Thus, when

273   extrinsic factors controlling the two kidneys were identical, changes in the intrinsic factors

274   controlling renal function were unable to reset the pressure natriuresis relationship. This result is

275   also remarkable because it shows that in the unperturbed kidney a minute elevation in arterial

276   pressure is able to override a substantial increase in systemic renin system activity seemingly at

277   odds with the results of the Reinhardt group (see above). However, it aligns with Guyton's

278   representation of the renal-blood volume pressure control complex as the dominating pressure

279   servo-control system (45).

280   Notably, these two unique sets of protocols were carried out under different baseline

281   conditions, particularly with regard to baseline arterial pressure (measured 20-23 h/d) which

282   averaged 115-120 mmHg in the Reinhardt study and 87 mmHg in the Mizelle study, despite similar

283   sodium turnover. Neither study seems to have been repeated by independent parties. More

284   surprisingly, neither protocol seems to have been subjected to computer simulations. Yet regardless

285   of their apparent inconsistencies, the findings of these two studies do allow us to conclude that

286   chronic changes in arterial pressure, that are sufficient to alter the activity of the renin-angiotensin

287   system, will reset the relationship between arterial pressure and renal excretory function. However,

288   there is no support for the idea that direct effects of altered renal perfusion pressure on the kidney

289   can reset this relationship.

290   **Anomalies**

291   Thomas Kuhn proposed that "Discovery commences with the awareness of anomaly, i.e. with

292   the recognition that nature has somehow violated the paradigm-induced expectations that govern

293   normal science. It then continues with a more or less extended exploration of the area of the

294   anomaly. And it closes only when the paradigm theory has been adjusted so that the anomalous has

295   become the expected." (70). According to this approach, the pathway to a neo-Guytonian paradigm,

296   or a paradigm shift, must begin with the identification of anomalies in the Guytonian paradigm.

297   *Anomaly 1: Volume retention and increased cardiac output during salt loading does not necessarily*

298   *increase arterial pressure*

299   One of the central concepts in Guyton and Coleman's theory of long-term control of blood

300   pressure is the notion that retention of salt and water (through changes in the so-called mean

301   systemic filling pressure) increases MAP by increasing CO (46, 47). However, there are a number

302   of conditions in which MAP remains remarkably stable in the face of altered extracellular fluid

303   volume and/or CO. One of these is the response to changes in salt intake in 'salt resistant' animals

304   and man. In man, plasma volume increases by about 1.5 ml per mmol increase in daily sodium

305   intake (25, 96). Kjolby et al. varied daily sodium intake in dogs across more than an order of

306   magnitude (64). While they observed considerable changes in plasma volume, arterial pressure

307   changed little in response to altered sodium intake. The maintenance of arterial pressure was

308   possibly due to compensatory changes in the degree of activation of the renin-angiotensin-

309   aldosterone system, since the plasma concentrations of components of this system varied linearly

310   with the logarithm of the intake of sodium. These observations accord with those of Krieger and

311   colleagues, who found that 7 days of high salt intake in previously salt-depleted dogs resulted in

312   retention of salt and water and increased CO, but that MAP remained relatively stable due to

313   reduced TPR (67). In contrast, when dogs were salt loaded while receiving a continuous intravenous

314   infusion of angiotensin II, the increased CO was associated with a gradually increasing TPR, so that

315   MAP increased (68). This form of experimental hypertension was completely prevented by servo-

316   control of total body water (66). Collectively, these observations indicate that there is considerable

317   scope for neurohumoral mechanisms, including the renin-angiotensin-aldosterone system, to

318   maintain MAP at a relatively stable level in the face of altered CO, by altering TPR. Thus, under

319   physiological conditions, small changes in body fluid volume do not necessarily lead to changes in

320   arterial blood pressure.

321   Evidence that the failure of such compensatory mechanisms might be important in the

322   pathogenesis of hypertension came from studies of Dahl salt-sensitive (SS) and salt-resistant (SR)

323   rats. Greene and colleagues examined the responses to increased salt intake (by intravenous

324   infusion) in Dahl SS and SR rats, with or without servo-control of body weight (and thus total body

325   water) (44). They found that servo-control of body weight prevented development of hypertension

326   in SS rats exposed to a high salt diet. However, when body weight was not servo-controlled, SS and

327   SR rats had similarly increased blood volume, but MAP increased only in SS rats. In a separate

328   protocol, in which CO was measured by thermodilution, increased dietary salt intake was found to

329   increase CO in both SS and SR rats. Importantly, hypertension only developed in SS rats, because

330   of failure of a compensatory reduction in TPR (Fig. 5). Thus, while volume retention was a

331   necessary pre-requisite for hypertension in the SS rat, salt-loaded by either intravenous infusion or

332   dietary intake, it appears not to be the critical mediator. Rather, the critical deficit may lie in failure

333   of counter-regulatory mechanisms that control vascular tone. This concept has recently been dubbed

334   the 'vasodysfunction theory' by Kurz and colleagues (71). It has also been central to arguments for

335   a pivotal role of the central nervous system in the development of hypertension (89).

336   The findings of Greene and colleagues (44)   are consistent with those of Ganguli and

337   colleagues in SS and SR rats, studied under anesthesia three days after commencing a high or low

338   sodium diet (40). That is, CO apparently increased in response to increased salt intake in both SS

339   and SR rats, but TPR fell only in SR rats. Simchon and colleagues described changes in arterial

340   pressure, CO and renal blood flow (RBF) during development and maintenance of hypertension in

341   SS rats on 8% NaCl (102). They found that the increase in MAP after 4 weeks was mediated by

342   increased CO, but at 46 weeks CO was sub-normal and TPR was elevated. They were unable to

343   detect a significant increase in CO in SR rats, although it certainly tended to be increased at the 4

344   week time-point. Importantly, in these three sets of experiments (40, 44, 102), volume expansion

345   and increased CO was apparently a requirement for development of hypertension in the SS rat.

346   However, in each case the critical difference between the SS rat and SR rat appeared to be the

347   response of the resistance vasculature to increased salt intake. This notion also accords with the

348   findings of renal transplantation studies in Dahl rats, indicating roles for both intrarenal and

349   extrarenal factors in salt sensitivity of blood pressure in this model (85). However, it is not

350   consistent with the idea that salt-sensitivity of arterial pressure arises from dysfunctional

351   neurohumoral control of renal excretory function (Fig. 1), which would appear to be a critical test of

352   the Guytonian paradigm.

353   The observations described above raise two important questions: (1) what are the critical loci

354   for the disparate vascular response in SS compared with SR rats, and (2) how relevant are

355   observations in the Dahl rat to our understanding of human essential hypertension? Regarding the

356   first of these questions, it is possible that the kidney represents a major locus for the disparate

357   vascular response in SS compared with SR rats. For example, Simchon and colleagues observed

358   selective renal vasoconstriction (but not systemic vasoconstriction) at the 4 week time point in SS

359   rats on 8% NaCl (102). These observations are strikingly similar to those from a recent study of a

360   group of carefully selected patients with mild, uncomplicated hypertension, whose renal vascular

361   conductance was much smaller than that of a control group while the non-renal vascular

362   conductances were indistinguishable (26). That is, the greater TPR in the patients, compared to

363   control subjects, could be attributed entirely to augmented renal vascular resistance. Thus, while it

364   would be dangerous to extrapolate from studies in the Dahl SS rat to human essential hypertension,

365   these findings indicate that abnormal renal vascular tone and/or renal vascular structure could play a

366   critical role in the pathogenesis of hypertension, not just through its effects on renal excretory

367   function, but also through effects on TPR.

368   There may also be inherent differences in the non-renal vasculature between individuals

369   susceptible to hypertension and those not. In anephric patients, volume expansion increased arterial

370   pressure only in individuals who had been hypertensive prior to nephrectomy (88).

371   Regarding the second question posed above, it seems likely that vascular dysfunction does

372   play an important role in salt-sensitive hypertension in humans. For example, Schmidlin and

373   colleagues demonstrated similar increases in CO in salt-sensitive and salt-resistant individuals

374   placed on a high-salt diet. Arterial pressure increased in salt-sensitive individuals because, unlike

375   the salt-resistant subjects, TPR did not fall when salt intake was increased (99). Furthermore, Kurtz

376   and colleagues recently presented a detailed argument that Mendelian forms of salt-sensitive

377   hypertension could be driven by failure of the counter-regulatory vasodilatation that normally

378   occurs when salt intake is chronically increased (71).

379   The considerations described above do not necessarily require us to reject Guyton and

380   Coleman's view of the pathogenesis of hypertension, but they certainly do require it to be deployed

381   with some subtlety, a point emphasized by Guyton and his colleagues (45). We accept the concept

382   that hypertension can occur either in the absence or presence of volume expansion. But the critical

383   subtlety, as we see it, is that we must also accept that a combination of altered renal excretory

384   function AND altered control of peripheral resistance vessels must be a hallmark of forms of

385   hypertension other than those associated with rapid and frank volume expansion. There are a

386 number of candidate mechanisms that might mediate this altered control of vascular tone, including

387 the sympathetic nervous system (4, 37), multiple signaling cascades mediated by endogenous

388 ouabain-like factors (13, 74), reductions in vascular nitric oxide bioavailability induced by

389 asymmetrical dimethyl-arginine (99), certain G-protein (G_q-G_{11} and G_{12}-G_{13}) signaling cascades

390 (106), and interactions between immune cells, cytokines and oxidative stress (80).

391   In conclusion, as pointed out by Guyton and his colleagues (45), the notion that essential

392 hypertension develops initially from salt and water retention, and that increased CO is transformed

393 to increased TPR (Fig. 2), is likely a gross over-simplification of the clinical situation. This concept

394 arose from early studies of models of hypertension characterized by marked fluid retention (e.g (16-

395 18)), which probably have little direct relevance to human essential hypertension. Moreover, there

396 is strong evidence that arterial pressure can be maintained in the face of increased extracellular fluid

397 volume and CO, and that at least some forms of hypertension are attributable to failure of this

398 compensatory vasodilatation.

399 *Anomaly 2: Day-to-day and hour-to-hour renal regulation of salt and water homeostasis is not*

400 *driven by changes in arterial pressure*

401   This issue has been reviewed in detail previously (10, 12, 25, 59, 100), so it will only be

402 discussed briefly. There is now strong evidence that the major driver of day-to-day changes in

403 sodium excretion, in response to day-to-day changes in sodium intake, is the renin-angiotensin-

404 aldosterone system, at least in animals and humans in which this system is intact. That is, acute and

405 chronic changes in salt and water intake, either orally or via intravenous infusion, are usually

406 accompanied by changes in salt and water excretion that maintain salt and water homeostasis,

407 without appreciable changes in arterial pressure. Indeed, natriuresis has even been observed during

408 acute sodium loading in the face of reduced arterial pressure (1). However, acute and chronic

409 changes in sodium intake are accompanied by marked changes in the activity of the renin-

410 angiotensin-aldosterone system, which appears to be the dominant mechanism mediating changes in

411 sodium and water excretion (12). It is also relevant to note that the phenomenon of 'pressure

412   escape' initially described by Reinhardt and colleagues (97) (*vide supra*), could be abolished by

413   'clamping' the renin-angiotensin-aldosterone system (100) (Fig. 4). This group also found no

414   significant correlation between spontaneous diurnal variations in arterial blood pressure and the

415   concomitant rates of sodium and volume excretion (100). Thus, it appears that neurohumoral

416   mechanisms can readily over-ride the influence of minor changes in renal perfusion pressure on

417   renal excretory function.

418   All of these observations are consistent with the view that the relationship between blood

419   pressure and natriuresis is exquisitely sensitive to neurohumoral status (Fig. 1). The effects of

420   altered activity of the renin-angiotensin-aldosterone system (or of renal sympathetic nerve activity,

421   atrial natriuretic peptides, or indeed any other regulatory mechanism) may well be considered to be

422   mediated via a shift in the pressure natriuresis relationship. Nevertheless, we also must concede that

423   the major factor that controls short-term changes in salt and water excretion under physiological

424   conditions is neurohumoral status, not renal artery pressure.

425   Based on the discussion above, and as suggested previously (12, 100), we can envisage

426   multiple lines of defense against the development of salt-sensitive hypertension (Fig. 6). The first

427   line of defense is the response of the kidney to altered neurohumoral influences, including the renin-

428   angiotensin-aldosterone system, which are initiated by volume-dependent mechanisms. This allows

429   sodium and water balance to be achieved, albeit at the expense of some expansion of extracellular

430   fluid volume. The second line of defense is the response of the vasculature to altered neurohumoral

431   influences, which allows compensatory reductions in TPR so that MAP is not increased, even in the

432   face of increased CO. The third line of defense is the pressure natriuresis mechanism, which is

433   engaged when arterial pressure increases, presumably as a result of malfunction of the first two

434   mechanisms. These three mechanisms must operate within some hierarchy. The nature of this

435   hierarchy remains one of the central questions in our understanding of the mechanisms that control

436   blood pressure in the long-term, and thus the pathogenesis of hypertension. Nevertheless, it seems

437   reasonable to propose that all three lines of defense must malfunction in order for chronic

438   hypertension to develop.

439   *Anomaly 3: Sodium homeostasis might rely on extrarenal mechanisms*

440   This concept has been reviewed in detail recently (105). In brief, recent evidence suggests that

441   sodium can be stored in skin and muscle in an osmotically inactive form bound to

442   glycosaminoglycans, providing sinks and sources of free sodium ions under conditions of increases

443   and decreases, respectively, of total body sodium. There is evidence that these storage depots are

444   regulated by a complex interplay between immune cells and the lymphatic system. These concepts

445   represent an anomaly for the Guytonian paradigm, which is based on the underlying assumption

446   that the various components of the extracellular fluid volume are in equilibrium. The presence of

447   osmotically inactive sodium would allow some level of uncoupling of total body sodium from total

448   body water. The apparent existence within the body of mechanisms buffering changes in total body

449   sodium will not, by their buffer capacity alone, change the principles of body fluid regulation.

450   However, they may well explain how the magnitude of changes in body fluid can deviate

451   quantitatively from those predicted from the physico-chemistry of simple electrolyte solutions. The

452   implications of these relatively new findings, for our understanding of the long-term regulation of

453   sodium homeostasis and arterial pressure, must await further research.

454   *Anomaly 4: The mechanisms underlying 'whole body autoregulation' have not been identified*

455   We have already established that hypertension need not be initiated by volume retention and

456   increased CO (see Anomaly 1). There is also evidence that some forms of experimental

457   hypertension can be associated with increased CO, with no evidence of progression towards

458   increased TPR. For example, Fine and colleagues assessed the effects of increased dietary salt

459   intake in rats in which the renin-angiotensin system was clamped by combined intravenous infusion

460   of the angiotensin converting enzyme inhibitor enalapril and angiotensin II (35). Arterial pressure,

461   measured telemetrically, increased when the animals were placed on a high salt diet for 7 days, due

462 to increased CO (measured by transit-time ultrasound flowmetry). Over the course of the 7-day

463 protocol there was no evidence of increased TPR. On the other hand, progression from increased

464 CO to increased TPR has been observed in many forms of hypertension associated with salt and

465 water retention. These include 1K1C hypertension in the rat (72, 73) and dog (32, 33), 1K1W

466 cellophane wrap hypertension in the dog (34), hypertension in dogs subjected to increased sodium

467 intake with reduced renal mass (18) or during infusion of a low dose of angiotensin II (68). It has

468 also been observed in response to volume loading in anephric patients in some (16), but not all (63)

469 studies. The only plausible theory to explain this transition relies on the phenomenon of whole body

470 autoregulation (47). That is, that the long-term set-point of local (and thus total) peripheral

471 resistance is determined by the requirements of the tissues for blood flow. In Guyton and Coleman's

472 original formulation of the renal-body fluid system for arterial pressure control it merited little

473 discussion; as if it was assumed that local autoregulatory mechanisms would naturally respond on a

474 whole-body basis (47). Yet this concept remains controversial and poorly defined.

475   There is also good evidence that whole body autoregulatory mechanisms can operate when

476 arterial pressure is chronically decreased. Until the seminal work of Horace Smirk, it was widely

477 believed that pharmacotherapy to reduce arterial pressure would be dangerous because it would lead

478 to tissue ischemia (29). Smirk was able to show that arterial pressure could be safely lowered in

479 patients with hypertension, by pharmacological ganglion blockade (103). This work paved the way

480 for larger clinical trials of antihypertensive therapy that definitively demonstrated the beneficial

481 effects of these drugs. Later studies provided more direct evidence that diuretic agents, in particular,

482 lower arterial pressure through an initial reduction in CO which is later transformed to a reduction

483 in TPR (21, 39).

484   So-called borderline or mild hypertension has been of considerable interest to the protagonists

485 of the whole body autoregulatory theory, since it is generally thought to reflect the early stages in

486 the pathogenesis of hypertension. The observation of relatively high CO in patients with borderline

487 hypertension would therefore provide support for the theory This has been observed in the majority

488   of reported studies (79). However, the observation that the difference in CO between patients with

489   borderline hypertension and controls is abrogated by assuming a sitting position or exercise

490   suggests that abnormally high CO in the recumbent position might have dubious significance (61).

491   Nevertheless, it seems reasonable to propose that volume retention and subsequent whole body

492   autoregulation might contribute to the pathogenesis of human essential hypertension in at least a

493   subset of patients. But what do we mean by 'whole body autoregulation' and what are the

494   mechanisms that mediate it?

495   For our current purposes, we can define autoregulation as any phenomenon that opposes

496   changes in blood flow in response to altered perfusion pressure. At least three mechanisms might

497   mediate whole body autoregulation in response to increased arterial pressure: (1) vasoconstriction,

498   either as a direct response to the increased perfusion pressure or as a longer-term consequence of

499   increased sensitivity of the vasculature to constrictor agents, (2) vascular rarefaction, and (3)

500   vascular hypertrophy or (eutrophic) remodeling of resistance vessels around a smaller lumen.

501   Unfortunately, we currently have very limited understanding of the relative contributions of these

502   mechanisms to whole body autoregulation.

503   *Acute mechanisms:* Autoregulation can be observed in most organs and tissues when

504   perfusion pressure is acutely altered. The underlying mechanisms are tissue-dependent, although

505   some generalizations can be made. Firstly, acute autoregulatory responses to increased perfusion

506   pressure are largely mediated by the so-called 'myogenic response', whereby stretch of vascular

507   smooth muscle increases cytosolic calcium concentration leading to smooth muscle contraction and

508   thus vasoconstriction. In contrast, metabolic factors likely dominate the response to reduced

509   perfusion pressure, whereby hypoxia itself or accumulation of local metabolites such as adenosine,

510   carbon dioxide and hydrogen ions drive the vasodilatation. In some organs, such as the kidney,

511   additional mechanisms come into play (62). From a 'whole body' point of view, acute

512   autoregulation encompasses mechanisms that maintain adequate oxygen delivery to tissue in the

513   face of changes in either driving pressure or oxygen demand. This is achieved both through a

514   combination of changes in oxygen extraction and the state of dilatation of local resistance vessels

515   (101). Whole body autoregulation has been observed acutely in experimental animals, beginning

516   with the seminal studies of Guyton and Coleman in dogs in which the central nervous system had

517   been destroyed (17) and extending to studies in conscious dogs (81) and rats (55-58) in which

518   cardiovascular reflexes had been blocked. However, for two reasons, such acute mechanisms are

519   unlikely to make much contribution to the transition from increased CO to increased TPR in

520   essential hypertension. Firstly, if the relatively high CO in borderline hypertension were to reflect

521   'over-perfusion' of tissues, the arteriovenous oxygen concentration difference in these individuals

522   might be expected to be relatively low, but this has not been observed (79). Secondly, the time

523   course is all wrong. Acute autoregulatory mechanisms operate over a time-course of seconds to

524   hours (41), whereas the transition from increased CO to increased TPR takes days or weeks in

525   experimental hypertension (16, 18, 32-34, 68, 72, 73) and perhaps years in human essential

526   hypertension (79).

527   *Chronic mechanisms:* Candidate mechanisms include changes in the sensitivity of the

528   vasculature to vasoactive agents, vascular rarefaction, and vascular remodeling.

529   Increased sensitivity to vasoconstrictors has been observed in established hypertension (8), as

530   has reduced influence of endothelial-derived vasodilator factors (54). There is also evidence for

531   altered calcium signaling in the vasculature in certain forms of hypertension, perhaps driven by

532   endogenous ouabain-like factors (13, 75, 76, 94) or by increased expression of L-type calcium

533   channels induced by increased arterial transmural pressure (93). An increased propensity of

534   resistance vessels to constrict leads to functional rarefaction (14). Functional rarefaction, in turn,

535   can lead to loss of the microvasculature (structural rarefaction) (14).

536   Structural rarefaction has been observed in multiple animal models of hypertension, including

537   the spontaneously hypertensive rat (SHR) and reduced renal mass hypertension (42, 52, 78).

538   Evidence of structural rarefaction has also been obtained in established human hypertension (3),

539   borderline essential hypertension (2), high-output borderline hypertension, and in individuals with a

540   familial predisposition towards hypertension (86). Furthermore, computational models predict that

541   rarefaction could make a significant contribution to the increased vascular resistance in established

542   hypertension (43). There is also evidence that antihypertensive pharmacotherapy can reverse

543   rarefaction (6). But is rarefaction an important factor in the hemodynamic alterations in

544   hypertension?

545   Hallback and colleagues examined the characteristics of the relationships between flow and

546   perfusion pressure in the isolated hind-limb of SHR compared with normotensive controls. Their

547   findings indicated that vascular rarefaction could not adequately explain the alterations in hind-limb

548   pressure-flow relationships in the SHR. Rather, they concluded that the vascular abnormality in the

549   SHR is best explained by structural changes in pre-capillary resistance vessels, leading to reduced

550   lumen diameter even at maximal vasodilatation (51). Such structural changes amplify the effects of

551   constrictor factors on peripheral resistance and thus arterial pressure. In intact rabbits with 2K2W

552   hypertension Wright, Angus and Korner provided evidence that this 'vascular amplifier' makes a

553   major contribution to the enhanced sensitivity of the circulation to constrictor factors, and thus

554   maintenance of hypertension (107, 108). Critically, there is evidence that oxidative stress can drive

555   development of vascular hypertrophy (54). However, remodeling of the resistance vasculature has

556   traditionally been viewed as an adaptive response to hypertension, rather than a primary pathogenic

557   event (31).

558   Unfortunately, most experimental studies of the changes in microvascular (42) and resistance

559   vessel (65) structure and function in hypertension have been performed in animals with established

560   hypertension. Structural rarefaction has been observed within three days of commencing a high salt

561   intake in rats. But these responses were similar in rats with reduced renal mass to those of sham-

562   operated rats who did not develop hypertension (53). Functional evidence of vascular remodeling,

563   consistent with the vascular amplifier concept, has been seen as early as 2 weeks after initiation of

564   angiotensin II-dependent hypertension (84). However, to our knowledge, no true time-course

565   studies have been performed. Consequently, we really do not know whether these structural

566   changes occur over a time-course consistent with a role in the phenomenon of whole-body

567   autoregulation, or whether they simply reflect a structural adaptation to increased arterial pressure.

568   Furthermore, the relative contributions of functional and structural rarefaction, changes in vascular

569   sensitivity to vasoactive agents, and remodeling of resistance vessels, remain unknown.

570   *Anomaly 5: The Guytonian paradigm does not allow us to understand the sequence of events that*

571   *lead to the pathogenesis of hypertension.*

572   One argument that is often used to support a critical role of the kidney in long-term control of

573   arterial pressure and the pathogenesis of hypertension can be encapsulated in the statement that

574   'hypertension is always accompanied by a right-ward shift in the pressure natriuresis relationship'.

575   While we accept the truth of this statement, we also concede that it represents a tautology. A 'right-

576   ward shift in the pressure natriuresis relationship' is a physical necessity; the statement reiterates

577   that sodium balance occurs in chronic hypertension. It is true under all conditions of steady state in

578   all forms of hypertension. Therefore, it does not add any insight into these states (7). Indeed, if we

579   accept that volume retention need not lead to increased arterial pressure (Anomaly 1), that hormonal

580   and neural factors, rather than renal perfusion pressure, dominate renal control of extracellular fluid

581   volume (Anomaly 2), that non-renal mechanisms contribute to control of sodium homeostasis

582   (Anomaly 3), and that we have little understanding of the mechanisms that mediate whole body

583   autoregulation (Anomaly 4), it could be argued that such a statement really only serves to divert out

584   attention from the important questions in the field. We believe these important questions relate to

585   the inter-relationships between dysfunction of control of CO by the kidney and venous system, and

586   control of TPR by resistance vessels. Our interpretation of the available literature is that essential

587   hypertension must be driven by the interplay between the dysfunction in these two components of

588   the cardiovascular system. A focus on any one of these systems in isolation from the other is

589   unlikely to lead to major advances in the field.

590

591   **A way forward for 'normal science'**

592   The anomalies associated with Guytonian theory, we have described above, hardly constitute

593   a crisis that in the near future might lead to a new paradigm in our view of the role of the kidney in

594   the pathogenesis of hypertension. However, a number of the experimental results seem to justify

595   that 'pressure natriuresis' should be considered as one natriuretic mechanism operating parallel to

596   other control mechanisms. An immediate benefit would be to eliminate the need for the complex

597   explanation that volume mediated natriuresis, occurring along with concomitant decreases in blood

598   pressure and renin system activity, is due to shifts of the former rather than to deactivation of the

599   latter. The inclusion of parallel actions of multiple hierarchical, primarily independent natriuretic

600   control systems into the concepts of Guyton could be considered an adjustment justifying the label

601   of a 'neo-Guytonian' paradigm. Otherwise, the anomalies probably indicate that there is

602   considerable scope for normal science, as defined by Thomas Kuhn (70), to proceed. But how might

603   this normal science best be directed towards a neo-Guytonian paradigm?

604   The massive research effort in hypertension, in the 20 years since Arthur Guyton's last

605   published contribution to the field (49), has yielded a wealth of understanding of the molecular

606   mechanisms that influence cardiovascular control and that drive development of hypertension in

607   animal models (60). However, we would argue that they have not got us much closer to

608   understanding the mechanisms that drive the pathogenesis of human essential hypertension. This

609   failure might be partly a result of 'the molecular revolution', which we would argue has led many

610   researchers to focus on their favorite molecule rather than on the broader integrative questions. It is

611   probably also fair to say that interest has dwindled in 'the big questions' in the field of

612   hypertension. For some these questions might seem already answered. For others they might seem

613   unanswerable.

614   We accept the Guytonian principle in so far that hypertension can only occur when renal

615   excretory function is impaired, either through intrinsic changes in the kidney or altered

616   neurohumoral control of the kidney, so that a greater level of arterial pressure is required to assist in

the excretion of the daily sodium load. However, intact experimental animals and humans that are

not susceptible to hypertension appear able to deal with some level of salt and water retention and

increased CO without increased MAP, through neurohumorally-mediated reductions in TPR (see

Anomaly 1). Simultaneously, these neurohumoral mechanisms must also influence renal excretory

function in a manner that allows homeostasis of extracellular cellular fluid volume at its new level,

without the need for increased arterial pressure. Changes in neurohumoral control of the kidney

even appear able to maintain salt and water homeostasis in the face of chronically reduced renal

perfusion pressure (see Misinterpretation 2). These observations at least partly break the

mechanistic link between altered renal excretory function and the development of hypertension, that

are at the heart of the Guyton-Coleman view of the pathogenesis of hypertension. Consequently, we

must accept that we really do not understand the sequence of events that might lead from altered

renal excretory function to the development of chronic hypertension (Anomaly 5). We even have

little understanding of the sequence of events that might transform so-called volume-dependent

hypertension into a state of increased TPR (Anomaly 4). Elucidation of these issues will probably

require a renewed and focused effort in integrative cardiovascular physiology *in human subjects*.

Prospective studies are required, with frequent follow-up, in order to characterize the sequence of

events in the pathogenesis of hypertension. Information regarding systemic and renal

hemodynamics, water and electrolyte homeostasis, small and large vessel structure and function,

neuro-humoral status, and metabolic and immunological functions will be required. Remarkable

methodological advances have been made in all of these fields in recent years, including in the use

of non-invasive methods, so such a renewed effort would be timely and feasible. Perhaps the

greatest challenge in this research effort will be to overcome the confounding effects of

pharmacological and non-pharmacological interventions that are, quite rightly, offered soon after

clinical diagnosis of hypertension.

Another important activity for advancement in the field is the development of advanced

computational models of the long-term control of arterial pressure and the pathogenesis of

643   hypertension (90, 91). Computational models were vital to the initial development of the two central

644   concepts in the Guytonian paradigm: (i) the over-riding dominance of the kidney in long-term

645   control of arterial pressure, and (ii) the principle of infinite gain of the body fluid mechanism of

646   long-term blood pressure control (45). More recently, alternative models have been developed that

647   can replicate some of the outcomes of the model generated by Guyton, Coleman and colleagues, but

648   are based on very different assumptions regarding the hierarchy of importance of blood pressure

649   control mechanisms (4, 5). For example, simulations of hypertension induced by angiotensin II and

650   high salt intake by the 'neurogenic' model of Averina and colleagues generate hemodynamic

651   profiles in that are very similar to those of the Guyton-Coleman model (4, 5). Yet this new model is

652   not based on the assumption of a direct relationship between arterial pressure and sodium excretion,

653   thereby illustrating the point that conceptually different models may provide equally attractive

654   simulation results. The complexity of the control mechanisms dictates that intimate interactions

655   between *in vivo* and *in silico* experiments are necessary to identify the most fruitful working

656   hypotheses.

657

661

662   **Disclosures**

663   None

664

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924

925   **Figure Legends**

926   **Fig. 1** The central component of the Guytonian paradigm; pressure natriuresis and the long-term

927   control of arterial pressure. A: The acute pressure natriuresis relationship. The long-term set-point

928   of arterial pressure is predicted to be at the intercept of the pressure natriuresis relationship (red)

929   and daily sodium intake (blue). The critical attribute of this system is its (theoretical) 'infinite gain'.

930   That is, changes in arterial pressure are predicted to lead to changes in sodium excretion, which in

931   turn lead to changes in extracellular fluid volume that return arterial pressure to its equilibrium

932   point. B: The chronic pressure natriuresis relationship (solid red line). Changes in sodium intake

933   (blue dashed lines for low, moderate and high salt intake) alter the pressure natriuresis relationship

934   (red dashed lines for low, moderate and high salt intake) because they alter the neurohumoral

935   influences on renal excretory function (e.g. the renin-angiotensin-aldosterone system, renal

936   sympathetic drive, and atrial natriuretic peptides). Consequently, arterial pressure can remain

937   relatively stable in the face of large changes in sodium intake, at least in so-called 'salt-resistant'

938   individuals. Figures are modified from (47).

939

940   **Fig. 2** Progressive changes in hemodynamics in an anephric female patient during volume overload.

941   Redrawn from (17).

942

943   **Fig. 3** The 'Guytonian pathway' to hypertension during infusion of norepinephrine, or some other

944   powerful vasoconstrictor stimulus that also shifts the pressure natriuresis relationship to higher

945   arterial pressure. Initially, the vasoconstrictor stimulus may increase total peripheral resistance to

946   such an extent that the increase in arterial pressure exceeds that required to compensate for the shift

947   in the pressure natriuresis relationship (1 to 2 in panel A). The resultant natriuresis causes

948   contraction of extracellular fluid volume (panel B) and so reduced cardiac output. Consequently,

949   arterial pressure falls until a new equilibrium point (3 in panel A) is reached. Redrawn from (48).

950

951   **Fig. 4** Extrinsic, but not intrinsic factors can reset the pressure natriuresis relationship. The panels

952   on the left show a schematic representation of the findings of Seeliger and colleagues (100). Renal

953   perfusion pressure was reduced bilaterally by 20% of each dog's control arterial pressure for a four

954   day period. This resulted in sodium retention and increased arterial pressure, but a new equilibrium

955   was reached (red line). Inhibition of angiotensin converting enzyme (ACEI) prevented sodium

956   retention and increased arterial pressure in response to bilateral servo-control of renal artery

957   pressure (black line). Clamping the renin-angiotensin-aldosterone system by intravenous infusion of

958   low doses of angiotensin II (AngII) and aldosterone (Aldo), along with ACEI, resulted in continued

959   increases in arterial pressure and total body sodium during bilateral servo-control of arterial

960   pressure (blue line). Panels on the right are a schematic representation of the findings of Mizelle

961   and colleagues (82). They reduced perfusion pressure to only one kidney, by ~10 mmHg, so the

962   other kidney was exposed to systemic arterial pressure. Importantly, in this experiment both kidneys

963   were exposed to the same neuro-humoral (extrinsic) influences. In this experiment, sodium

964   excretion by the servo-controlled kidney (red line) was reduced for the duration of the experiment,

965   while that to the contralateral kidney was increased (black line), presumably reflecting the level of

966   perfusion pressure each was exposed to. Figures were redrawn and modified from those in the

967   original reports (82, 100).

968

969   **Fig. 5** The critical difference between Dahl salt-sensitive rats and their salt-resistant counterparts is

970   the vascular response to increased salt intake. The figure is a schematic representation of the

971   findings of Greene and colleagues (44). A high salt diet led to volume expansion and increased

972   cardiac output (CO) in both salt-sensitive (red) and salt-resistant (blue) rats. Mean arterial pressure

973   (MAP) increased in salt-sensitive rats due to an inadequate compensatory reduction in total

974   peripheral resistance (TPR).

975

976

977   **Fig. 6** Three lines of defense against salt-sensitive hypertension. Increased salt intake leads to

978   expansion of extracellular fluid volume, but this is limited by altered neurohumoral control of renal

979   excretory function, so that homeostasis of total body sodium is re-established, albeit at a higher

980   level (first line of defense). But even when cardiac output increases, altered neurohumoral control

981   of resistance vessels can prevent an increase in arterial pressure through a compensatory reduction

982   in total peripheral resistance (second line of defense). In the face of failure of these mechanisms,

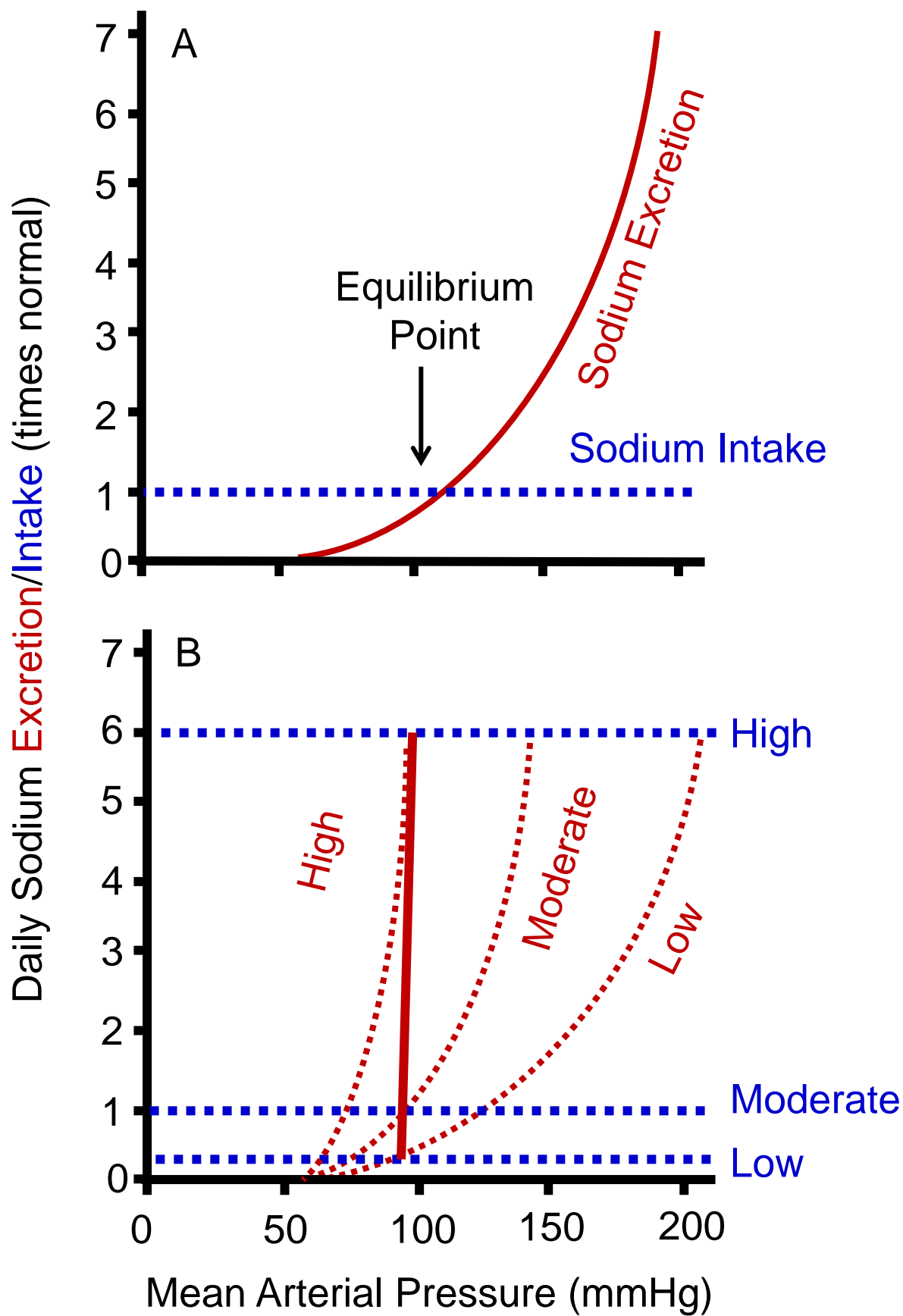983   pressure natriuresis limits subsequent increases in arterial pressure (third line of defense).

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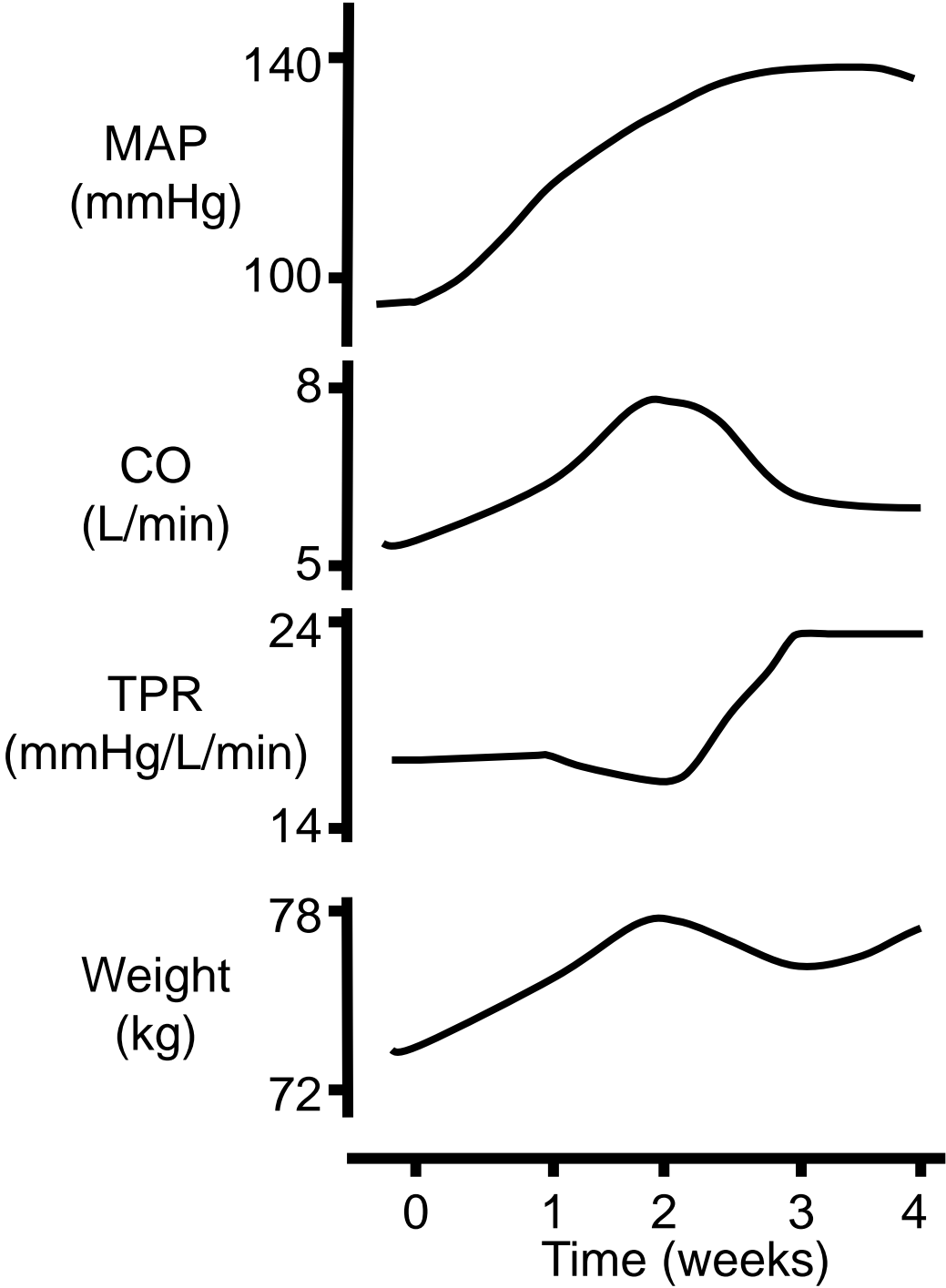
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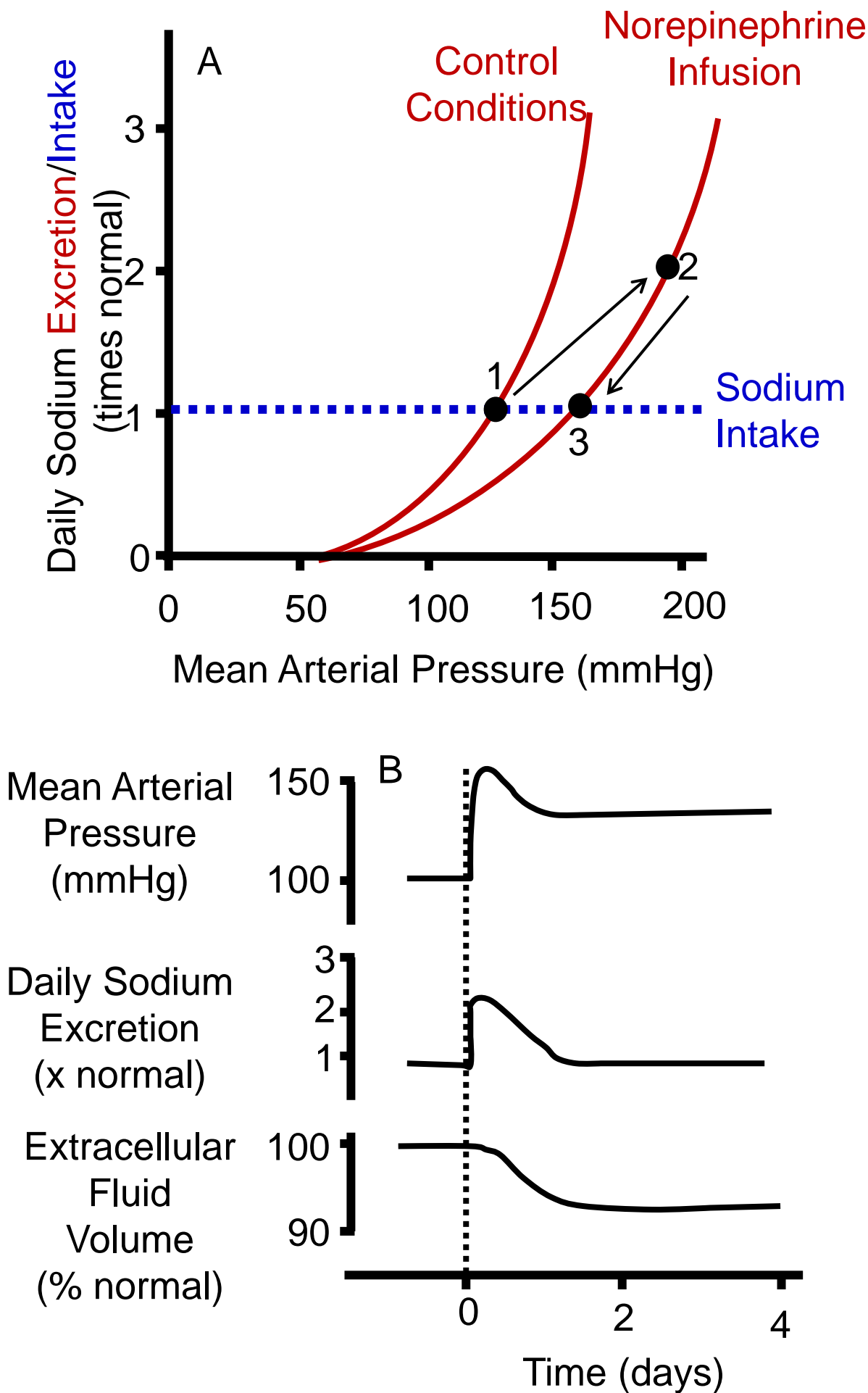
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Figure 1

Figure 2

Figure 3

Figure 4

Seeliger et al 2005 Bilateral Servo-Control

Mizelle et al 1993 Unilateral Servo-Control

ΔTotal Body Sodium (mmol/kg)

16

8

0

SC + ACEI + AngII/Aldo

Servo-Control (SC)

SC + ACEI

Mean Arterial Pressure (mmHg)

160

130

100

SC + ACEI + AngII/Aldo

SC

SC + ACEI

0   1   2   3   4

Day

Sodium Excretion (mEq/day)

80

40

0

Contralateral

Servo-Controlled

Renal Artery Pressure (mmHg)

100

75

50

Servo Control

-4   0   4   8   12   16   20

Day

Figure 5

High Salt Diet (8%)

MAP (mmHg)

150

90

CO (ml/min/kg)

600

300

TPR (mmHg per ml/kg/min)

0.45

0.15

Time from starting high salt (hours)

0   24   48   72

Figure 6

Figure 6