During recent decades, the multifactorial nature of primary essential hypertension has become widely recognized; there are at least three major components that can be discerned.1,2 Thus, in both humans and animals a polygenic predisposition (the first component), random in humans but fairly uniform in each of the various rat strains, constitutes the sine qua non element behind the rise in blood pressure. The second component is environmental mechanisms, which interact with these various genetic makeups and are mainly composed of neurohormonal psychosocial influences and dietary factors such as salt intake.1-4

Then where does the third component, the "structural factor," fit in and how was its important role in hypertension discovered? As is the case in largely all tissues, structural cardiovascular adaptation is a normal and essentially local response to sustained average changes in load or tissue activity,2,3 although a range of "trophic" influences no doubt exerts modulatory actions.2,5,6 Because the muscle hypertrophy and associated luminal changes can develop quite rapidly, they are involved and interact with functional pressor elements from the very start. Actually, these structural vascular changes soon dominate the hemodynamics of hypertension, particularly at the systemic resistance level, and in some variants of primary hypertension, for example, in spontaneously hypertensive rats (SHR), they even appear to be genetically reinforced, thus becoming one of the "prime movers" as well.2,5,6

The structural factor in hypertension had a relatively uneventful gestation 3-4 decades ago. To some extent it has suffered from the fads and fashions of hypertension research, which, at least in part, explains why such a long developmental period was needed before its role in the hemodynamics of hypertension became widely understood and accepted. The present article is meant to give a personal account of how some of these insights were obtained experimen-
tally and of my views of how the structural factor relates to the other etiological determinants of primary hypertension.1-3 However, in this context I want to pay tribute to the many outstanding contributions given to this field of research by colleagues all over the world.

History

In 1836, Richard Bright7 had already noted how left ventricular hypertrophy and aortic wall thickening characterized what was called “Bright’s disease.” Further, well before blood pressure was first measured in humans,2 George Johnson8 discovered in 1868 that arteriolar, but hardly venous, walls were also markedly thickened. In 1877, C.A. Ewald9 confirmed Johnson’s findings and proposed that the thickening was truly a hypertrophic muscle response to raised pressure (tension), “übermässige Spannung im Gefass-System,” a correct interpretation that, however, took a long time to be accepted. Ewald even hinted vaguely at possible hemodynamic consequences,2,9 but these intuitive speculations remained neglected for nearly a century. The reasons were related, in part, to the great difficulty in quantifying the histological findings of microvascular changes in terms of luminal versus wall dimensions. In fact, acceptable techniques for doing this have only become available in the last 2 decades,2,3,5 and the morphometric approach still meets with several problems.

Another reason why the great hemodynamic importance of altered resistance vessel design took so long to be recognized has been a matter of research fashions and the associated strong psychological peer pressures. For example, Harry Goldblatt’s classic introduction of experimental renal hypertension in 193410,11 seemed to create a “eureka” reaction in hypertension research, which was reinforced by the discovery of the role of the renin-angiotensin mechanism by Irvine Page and Eduardo Braun-Menendez and their respective coworkers in the early 1940s. Therefore, almost all attention in experimental hypertension research for a long time was concentrated on mechanisms that increase the activity of vascular smooth muscle. It also acted as a magnet to researchers in primary hypertension research who subsequently applied concepts from endocrinology, nephrology, and autonomic neurophysiology in the search for the etiology of hypertension, where “unitary” functional hypotheses dominated the scene for decades.2 Our group had demonstrated in 1956-1958 a hemodynamically dominating “upward structural resetting” of human hypertensive resistance vessels12,13 that was soon confirmed and extended by Conway,14 but it was largely disregarded for a long time. In any case, it certainly did not inhibit the intense search for a purely functional explanation of the elevated resistance in this “disorder of regulation,” and such a trend is, in fact, evident even today.

Biophysical Aspects

What is important to recognize, but has been widely overlooked, is the physical inevitability of the hemodynamic effects ensuing from an altered microvascular design of the type present in hypertension. These effects are, in fact, easily demonstrated by comparison of, for example, the pressure-flow relations in two rubber tubes of equal length and external radius (r e) but differing in wall thickness (w) and inner radius (r i) and thus in w/r i ratios. If the two tubes are then exposed to equal and concentric compressions of r e, which simulates how particularly neurogenic vasoconstrictions normally start from the outer media surface as the sympathetic constrictor fibers here exert their direct action, with nexiontransferred engagements of all muscle layers, the inevitable hydrodynamic effects due to the initial differences in r i and in w/r i ratio become obvious: The tube with the lower r i naturally exerts a higher initial resistance to flow. Further, on equal concentric compressions a higher w/r i ratio gives rise to the “geometric amplifier” effect, to use Paul Korner’s expressive term,15 which accentuates the luminal narrowing in proportion to the w/r i ratio increase. Thus, once such a type of structural resetting is in effect in hypertensive resistance vessels, blood pressure can be normal only if smooth muscle activity or cardiac output are subnormal, as is acutely achieved, for example, by antihypertensive drugs (see below).

Furthermore, for purely physical reasons, the in vivo hemodynamic behavior of systemic resistance vessels depends not only on 1) their smooth muscle activity and 2) their geometric design, but also on 3) wall distensibility, and 4) the distending pressure. The complex interactions of these four factors, where too often only the first factor is considered, as well as their individual impacts on resistance hemodynamics, were recently experimentally examined in paired-perfusion studies of vascular beds of SHR and Wistar-Kyoto (WKY) rats.16 These results, illustrated and discussed below, should be considered seriously, because the interrelations of the previously mentioned four factors are indeed essential for the understanding of the hemodynamics of hypertension.

It has long been known, and is routinely applied in engineering, that the higher the pressure, the higher must be the w/r i ratio of a tube and, further, any increase in r i at a given pressure for the same reasons calls for a proportional increase in w. This is in accord with Laplace’s law

$\sigma = \frac{P \times r_i}{w}$

where $\sigma$ is the wall tension per unit wall thickness, P is the transmural pressure, r i is the radius, and w is the wall thickness. There are ample a priori reasons to assume that biological tubes must also conform with this fundamental law, and the normal design of arteries, veins, and heart chambers, as well as their adaptation on pressure changes, show that they certainly do so.

Furthermore, Poiseuille’s Law implies that the greatest in vivo hemodynamic consequences of changing both activity and structure in vascular smooth muscle will occur at the level of the resistance
vessels, as vascular resistance to blood flow is inversely proportional to $r_i^4$. In addition, in the heart filling and stroke volumes are functions of $r_i^3$, while changes in venous $r_i$ influence venous capacitance in proportion to $r_i^2$.

**Experimental Explorations of Structurally Based Hemodynamic Influences**

**Early Background Studies**

In the late 1940s, when I performed animal experiments on precapillary myogenic tone and “functional autoregulation of blood flow” as part of my PhD dissertation in physiology,17-19 I also had to face the medical doctor examinations in medicine and special pathology. My pathology professor knew that I was studying vascular physiology; during the exam he grilled me in his friendly but demanding way for over an hour on the topic of the morphological changes in heart and vessels in hypertension, based on those described in Boyd’s classic text. My heart sank when he finally asked: “... As you work on blood vessels, tell me how they manage to keep up the blood pressure at such high levels in hypertension without getting tired.” I frantically scanned my memory for any remnants of knowledge but in the end had to admit: “I am sorry, sir, but I don’t know.” I feared that I had failed the test, but to my enormous relief, he ended the examination with the statement “Neither do I, but isn’t it interesting!”

After that confrontation, thoughts about hypertension and cardiovascular design were never far away and influenced my experiments on vascular physiology and biophysics. My first few years in physiology at the University of Lund (1943–1945) (spent mainly with F. Buchthal from Copenhagen, who reinforced our department after escaping from the Nazi war terror in Denmark) were most rewarding and taught me some basics also in skeletal and cardiac muscle biophysics (e.g., concerning relations between contraction and distension).19 I applied this experience increasingly to my studies on the behavior of resistance vessels when exposed to rapid pressure changes. In this situation “passive” distension–recoil events are opposed by the ordinarily powerful “active” myogenic and local–metabolic adjustments of smooth muscle tone. However, because the passive events are much more rapid than the active effects, the two could be analyzed separately. In addition, the presence of a truly myogenic “basal tone” in precapillary resistance vessels could be demonstrated.17–20 Also, the entire systemic vascular bed of denervated kittens was cross-perfused from donor cats,20 showing what later became labeled “whole body autoregulation,” which, in fact, Ewald had intuitively anticipated in 1877.9

These studies initiated the first tentative outline of some hemodynamic consequences of arteriolar wall hypertrophy in hypertension, although at that time I still did not know about the structural narrowing of $r_i$. It should be stressed that the early microscopic observations of hypertensive microvessels by George Johnson and followers could not give any answers about average $r_i$ because this calls for exact control of both prevailing smooth muscle activity and transmural pressure.2,3 The work was presented at the 1953 Montreal UPS congress where the formidable Carl Wiggers, resting his chin on his walking stick in the front row, managed to damp my intense nervousness with some encouraging comments. Thus, the abstract ended:

It is concluded that normally the passive distension is effectively compensated for by reactive changes of smooth muscle tone, a circumstance of possible importance for the maintenance of increased peripheral resistance in hypertension. Compared with normal vessels, hypertrophied hypertensive vessels must be relatively more resistant to distension, while the increased bulk of contractile tissue reasonably should allow undiminished reactive tonus changes.

Other factors being unchanged, this new equilibrium level between distension and “inherent” tonus changes might be one of the factors maintaining the increased peripheral resistance, once compensatory vascular changes are induced.

**Hemodynamic Studies in Human Primary Hypertension**

Our first experiments on the comparison of resistance vessels in human primary hypertension and in normotensive control subjects started in 1954. Dr. Bertil Hood from the Department of Medicine in Göteborg kindly supplied us with suitable hypertensive subjects, while reasonably matched normotensive control subjects were obtained from the nearby ear clinic. The results were first published in 195612 and in a more complete version in 1958.13 We used the experience and techniques from our earlier animal experiments and aimed to estimate the prevailing level of tonic vascular smooth muscle activity by relating regional “resting” resistance ($R_r$) to that at complete vascular smooth muscle relaxation ($R_{min}$). Mean arterial pressure (MAP) was measured, as was regional blood flow, by forearm plethysmography, where we had a decade of experience in connection with student laboratory courses and demonstrations. Briefly, our results showed that $R_{min}$ in hypertensive patients was raised almost in proportion to the MAP elevation (Figure 1). In these studies, therefore, the ratio $R_r/R_{min}$ was closely similar in both hypertensive and normotensive subjects. When, however, we induced acute hypertension in ourselves and some other colleagues by intravenous norepinephrine infusion, $R_{min}$ remained the same while, as expected, $R_r/R_{min}$ ratio increased in proportion to the MAP rise. The inescapable conclusion, which was quite “heretical” at the time, was that, at least in the resting state, there was no evidence that resistance vessel tone was increased in established primary hypertension. Instead, the resistance vessels had evidently undergone a “structural upward resetting” with a narrowing of average $r_i$, which was almost proportional to the elevation in MAP.
pressure (MAP) and resistance to flow at maximal dilatation (Rmin) in the 1956–1958 studies by Folkow et al., as based on individual data from subjects with primary hypertension and from normotensive control subjects. Here MAP was measured in the opposite, resting arm, while forearm peak blood flow was measured by a water-filled, heated plethysmograph after prolonged ischemia and superimposed forearm muscle exercise. Also mean values (*) of these measurements in the two groups are given: 2.46 PRU/100 in hypertensive subjects and 1.81 PRU/100 for normotensive subjects (36% difference). Furthermore, these mean Rmin values are recalculated (•) as described in detail in Reference 22, where correction has been made for 1) water pressure in the plethysmograph, 2) indirect versus intra-arterial method for MAP measurement, and 3) increased pressure drop along subclavian and brachial arteries during peak forearm blood flows. Thus, these Rmin values (1.90 PRU/100 in hypertensive group and 1.35 PRU/100 in normotensive group; 40% difference) better reflect the true situation concerning forearm vascular resistances at maximal dilatation in these hypertensive and normotensive groups.

Furthermore, we showed in physical-mathematical models what must be the full hemodynamic consequences of an increase in Rmin, particularly when the latter occurred in combination with an increased wall (media) thickness, for which morphological evidence had steadily accumulated since the pioneer findings of Johnson and Ewald. There were four such consequences; the first two were physically inevitable, the third a logical consequence of these, and the fourth a reasonable alternative to the common ideas of genetically based functional changes: 1) Implicit in the structurally determined narrowing of rj is an upward resetting of the very baseline (i.e., the Rmin), from which all increases in smooth muscle function must start. 2) A "vascular hyperreactivity" ensues due to the structural increase in w/rj ratio. This increased reactivity is therefore essentially nonspecific, or at least the nonspecific component of overall vascular responsiveness (i.e., the "structural amplifier" of vascular resistance changes) as we later explored in vitro in rats and which has been studied also in vivo by Sivertsson and by Korner’s group. As a result of this “geometric” influence, the rise in vascular resistance will always be greater in hypertensive than in normotensive persons, for a given change in smooth muscle activity, thanks to structural w/rj ratio increase, to which comes upward resetting inherent in the raised Rmin. If generalized to all circuits, this change of resistance vessel design allows maintenance of a raised systemic resistance in H even at normal tonic smooth muscle activity (compare points C and A). It was, however, earlier widely assumed that chronic resistance elevation in hypertension should principally be due to a shift from A to B along the smooth muscle curve by way of increased smooth muscle “tone.” No account is here taken for differences in wall distensibility, for simplicity’s sake. Modified with permission from reference 22, 23.

**Figure 1.** Plot showing relations between mean arterial pressure (MAP) and forearm resistance at maximal vasodilatation (R_{min}).

**Figure 2.** Diagram illustrating principal hemodynamic consequences of resistance vessel design in hypertension, where in the hypertensive resistance vessels (H) a structural wall (w) thickening (mainly of media) and a structural reduction of inner radius (rj) is supposed to have taken place in relation to normotensive resistance vessels (N). In N, w/rj ratio is set to 0.2 at maximal vasodilatation, when resistance (R_{min}) is set to 1.0. In H, w/rj ratio is set to 0.3 associated with some rj reduction, which raised R_{min} to 1.3. Media contraction is assumed to be initiated from outer muscle layer, as vasoconstrictor fibers here exert their action. This pushes the wall mass inward, whereby it also normally acts as a “geometric amplifier” in reducing rj. Note the still more exaggerated resistance increases in H on smooth muscle activation, thanks to structural w/rj ratio increase, to which comes upward resetting inherent in the raised R_{min}. If generalized to all circuits, this change of resistance vessel design allows maintenance of a raised systemic resistance in H even at normal tonic smooth muscle activity (compare points C and A). It was, however, earlier widely assumed that chronic resistance elevation in hypertension should principally be due to a shift from A to B along the N curve by way of increased smooth muscle “tone.” No account is here taken for differences in wall distensibility, for simplicity’s sake. Modified with permission from reference 22, 23.
resistance and hence pressure increases, which, if long sustained, are bound to induce additional structural changes and so on, gradually elevating the "set point" of systemic resistance. 4) Finally, one of our early suggestions was that, in primary hypertension, the structural factor itself might be genetically reinforced,\(^13\) as the likelihood for this should a priori be about as good as genetic reinforcements of functional mechanisms. If so, even quite modest and "normal" pressor influences, like those occurring in the course of ordinary daily life, could be enough to "start the ball rolling."

The first time I officially presented these ideas, and the experimental data on which they were based, was in an invited series of lectures on cardiovascular physiology at the University of London in early 1955. On this occasion, I also had a chance to discuss these matters with Sir George Pickering, who, in a review in 1950,\(^25\) had concluded \("... The present impasse in hypertension is probably chiefly due to the fact that certain fundamentally important aspects of vascular behavior are appreciated by contemporary science either dimly or not at all."") Pickering immediately became enthusiastic and remained a strong supporter throughout his life, but certainly his enthusiasm was not widely shared among "hypertensiologists" for a long time, even though the results and conclusions of Conway had been closely similar.\(^14\)

Thus, the search for a functional, more or less unitary background to the elevated resistance continued largely undisturbed, and one of the few comments in the literature about our results and ideas mainly concerned the fourth point, which was dismissed as "rather far-fetched." Today attitudes have certainly changed also in this latter respect, to judge by current intense interest in genetic predispositions and reinforcement of the vascular structural changes.\(^5,6,24,26-30\) In many ways it should, however, have been obvious from the first that genetic determinants of primary hypertension could express themselves equally cogently by causing molecular-cellular changes at the structural as at the functional level.

In any case, Sivertsson\(^23\) in our group studied instead the properties of the hand vascular bed in matched hypertensive and normotensive subjects, confirming our earlier results on \(R_{\text{max}}\) changes in the forearm and also testing by vasoactive drugs that complete relaxation really was achieved. He further demonstrated that, during intra-arterial norepinephrine infusions, the structural amplifier caused proportionally steeper rises in resistance in hypertensive than in normotensive subjects (vascular hyperreactivity), even though the distending pressure was much higher for the hypertensive vessels (Figure 3). On the other hand, the sensitivity of vascular smooth muscle, based on estimates of threshold, was similar in the two groups.\(^23\)

A corollary of these effects of hypertension was observed in model experiments in cats,\(^31,32\) where we showed that regional hypotension in one hind limb results in reduction in vascular reactivity due to reduction of the average \(w/r\) ratio value when compared with that of the normal limb.\(^31\) On the other hand, the normally quite thick-walled cutaneous arteriovenous anastomoses were markedly hyperreactive compared with ordinary resistance vessels without any evidence of increased smooth muscle sensitivity.\(^32\) There is now a substantial body of data that fully support these early findings in humans and cats, where the numerous studies by our own and other groups on various rat models of hypertension are important because far more penetrating and precise measurements can be performed,\(^2,3,5,15,24,26-30\) as will now be discussed.

**Experimental Analysis in Rats**

In the late 1960s we obtained the SHR model, thanks to Al Sjoerdmsa's kind help, which allowed us
to greatly extend our exploration of the structural properties in primary hypertension. In addition, we studied renovascular hypertension (two-kidney, one clip renal hypertensive rats [RHR]) both as a model of secondary hypertension without genetic reinforcement and because pronounced hypertension can be established within a week or so. The rat models have several obvious advantages: 1) uniform genetics; 2) easy access to matched controls; 3) short lifespan; 4) six times higher metabolic rate than in humans, which speeds up all metabolic processes and evidently also those responsible for structural adaptation (it takes only 3 weeks to produce whole new rats in pregnancy); 5) easy control of the intake of food, water, and electrolytes; 6) control of the psychosocial environment; and 7) far more penetrating experimental analyses than can be performed in humans.

Our results were reviewed in 1972,23 and 1973,34 and this seemed to greatly increase the interest in structural factors in hypertension. Thus, during the last 10–15 years, many research groups have embarked on important and original lines of study, mainly Korner’s group using a spectrum of techniques,25,26; also Mulvany,27,28 with micromyographic and morphometric analyses of isolated, small resistance arteries, Johansson29 with morphometric estimations mainly along the entire cerebral vasculature, Gray30 and Bohlen31 using microcirculatory techniques, Strauer’s group32 mainly studying the heart, and Schwartz’s group33 using methods of molecular and cell biology. The above references represent reviews of their work and present new findings and new approaches to the study of structural factors in hypertension.

**Methodological aspects.** Turning to our own studies in rats, we continued to mainly use hemodynamic methods, both because we had a great deal of background experience in this field and because pressure, flow, and resistance measurements can also most sensitively reflect vascular structural design when properly used.40 After all, resistance estimations applied to flow in tubes are no more “indirect” than are the very precise and widely used estimations of resistance in electric circuits based on Ohm’s law. Further, changes in overall resistance (pressure/flow) are here amplified in inverse proportion to the fourth power of \(r\), although they then reflect merely the average structural alterations of the resistance compartment as a whole. The relative contributions of the different series resistances can, however, also be determined by recording pressure at appropriate precapillary sites.41 We have used “isogravimetric” techniques to estimate mean capillary pressure,2,41,42 thus distinguishing between the precapillary and postcapillary resistances. We could in similar ways determine both the total renal resistance and the preglomerular and postglomerular resistance ratio in SHR, WKY rats, and in clipped and unclipped RHR kidneys,43 revealing early structural resettings also of the renal “barostat” function, both upward (SHR) and downward (clipped kidney in RHR). Another great advantage is that such measurements are automatically performed at the appropriate distending pressures if arterial inflow and venous outflow pressures are kept normal.

In addition, our method of paired in vitro constant-flow perfusion of various vascular beds in hypertensive and normotensive rats provides information not only about \(R_{\text{min}}\) but also gives complete “doseresistance response curves” (see below in Figure 4), where the difference in curve slopes reflects the structural w/r ratio difference, while the maximal contraction (pressor) response largely reflects the media contractile strength.40-42 Assuming muscle strength per unit area to be essentially equal in, for instance, SHR and WKY rats, the difference in media thickness is then reflected by the difference in maximal pressor response, as corrected for the prevailing resistance values. Thus, we can obtain quite an accurate insight about the average values of \(r\), \(w\), and of \(w/r\) ratio relations in the entire bed, or in its major precapillary and postcapillary sections, while differences in smooth muscle sensitivity show up as parallel displacements of the resistance curve.45

If, however, \(R_{\text{min}}\) alone is increased (e.g., by microvascular “rarification”) without any \(w/r\) ratio increase due to media thickening, neither the curve slope nor the maximal pressure response are increased during constant-flow perfusion.42 The reason is simply that, without any media thickening (and the consequent increase of strength and reduced wall distensibility), resistance vessels can neither display true vascular hyperreactivity nor maintain a normal range of flow adjustments at hypertensive pressure levels, as further discussed below. Also, in human primary hypertension, the hemodynamic approach is of greatest advantage as noninvasive hand and forearm plethysmography allow for precise and repeated estimates of \(R_{\text{RHR}}\), vascular reactivity, and smooth muscle sensitivity whereby, for example, the rate and extent of regression of structural vascular adaptation can be followed during antihypertensive treatment.

The excellent Mulvany-Halpern micromyographic technique,26,27 which complements the hemodynamic approach, has here the limitation that the geometric amplifying influence of an increased \(w/r\) ratio is “lost,” as is the amplifying Poiseuille relation between \(R_{\text{min}}\) and average \(r\). Further, sampled microvessels may not always adequately reflect the average resistance structural changes in vivo as their site and extent may vary between circuits and perhaps also between types of hypertension.

On the other hand, the Mulvany-Halpern technique is indispensable for directly relating vascular design and \(w/r\) ratios to wall biophysics and to smooth muscle contractile strength. We have used this technique to show how the vasoconstrictor nerves in SHR resistance vessels can engage the geometric amplifier to its maximal extent.
Site of adaptation and nature of stimulus. Here the main emphasis is on the structural adaptation of the resistance vasculature, although the venous system, the heart, and the large arteries are also affected, with consequences, for example, for volume receptors and baroreceptors, but such aspects are reviewed elsewhere.2,29,30,47,48 Our studies in SHR, RHR, and WKY rats indicate that all systemic beds participate in structural resetting,2,3,29,30 as in the hindquarters,40,41 the kidneys,42,43 the myocardium,49-51 and also the brain as explored, for example, by Johansson.25 The precapillary resistance sections of the circulation41,42 (in SHR kidneys, the preglomerular vessels43) are involved, and here mainly the proximal 70-80%2 while the distal “sphincter sections,” mainly controlling capillary flow, seem to be largely “protected” by the upstream structural resetting.

Our results further suggest that the key factor for initiating the structural adaptation at pressure changes is the local transmural pressure per se. Thus, prolonged pressure reduction in SHR and WKY rat hindquarters by distal aortic obstruction soon leads to a corresponding “downward structural resetting,”53 even though these low pressure vessels in SHR remain exposed to the same trophic-genetic influences as all other SHR cardiovascular sections. Furthermore, the clipped low pressure kidney in RHR shows a downward structural resetting,44 and an especially pronounced reduction of the preglomerular/postglomerular resistance ratio proves to be of greatest importance for the complex functional-structural interactions after renal unclipping.54,55

This by no means denies the importance of neuro-hormonal trophic influences, but in my view, the local pressure change per se serves as the initiating and “directing factor” of altering regional r1 and w/r1 ratio so as to keep wall stress largely constant in accordance with Laplace’s law. It is, however, likely that the pressure-induced changes in wall stress, together with the flow-dependent changes in chemical environment, activate appropriate local growth-modulating factors that, in the final analysis, direct the complex changes of vascular design.28,29

This local remodeling of the precapillary resistance vessels provides the basis for a long-term autoregulation of blood flow and of capillary pressure (“structural autoregulation”42 as a correlate to short-term functional autoregulation). Thus, both are locally induced and both tend to keep flow and, far more importantly, capillary pressure constant during changes in MAP.3,17-19 Further, for the individual vascular bed, structural autoregulation is entirely appropriate and per se a normal long-term adaptation where the giraffe offers a good example.2,3,28,29 Also in hypertension the process ensures that functional adjustments of myogenic, metabolic, nervous, and hormonal nature need not be exaggerated and can occur around capillary pressures that are close to normal.2,3,18,19,29,42 However, drastic and rapid pressure reductions may then more easily cause relative ischemia in brain and myocardium, because the amplifier properties and the raised Rmax will then cause more profound flow reductions. Otherwise, it is when precapillary structural adaptation encompasses all systematic circuits, as in hypertension, that it has deleterious long-term consequences, mainly because it then invites to the positive feedback interactions discussed earlier.

We soon noticed, however, that additional sophisticated mechanisms were involved in the structural adaptation of blood vessels,2,3,5,28,29 and also in the heart,29,30,49,50,52,53 often showing relatively independent changes in lumen and wall configurations. One example is the effect of regular exercise in SHR and WKY rats, as studied by Lundgren and Weiss in our group.56 This led to a reduction in Rmin and to an increased maximum blood flow capacity in the “trained” skeletal muscle, presumably induced by local chemical or flow-dependent signals. However, the vascular wall thickness appeared to adapt secondarily to this regional r1 increase, as the pressure-related differences between SHR and WKY rats in vascular w/r1 ratios seemed to remain the same as before. Somehow, the wall elements “sense” the increase in tension associated with an r1 increase and respond appropriately to maintain the Laplace equilibrium.28

Further, we wanted to know how the 40–50% renal hypertrophy consequent to unilateral nephrectomy affected the renal vessels. They proved to almost precisely adapt their design to the increased tissue mass, in terms of r1, w, w/r1 ratio, and even concerning the preglomerular to postglomerular balance.44 Similarly, Rmin w, and w/r1 ratio of the coronary resistance vessels in SHR become closely adapted not only to the increased bulk of myocardium, but also to the raised MAP.49-51 Further, a sustained reduction of MAP almost normalizes coronary vascular design both in relation to the reduced left ventricular afterload and to the consequent regression of myocardial hypertrophy.56

With respect to the heart itself, we found that the structural adaptation was equally sophisticated.51 When, for example, a reduced afterload was associated with increased preload and stroke volume, as in sustained vasodilator therapy, left ventricular design responded with an increased r1, whereas the change in myocardial wall thickness proved to depend on the balance between the r1 increase and the MAP reduction. Therefore, the net reduction in left ventricular mass was slight despite the MAP reduction because ventricular geometry had become transformed from the concentric to the eccentric pattern of hypertrophy, which is well suited for an increased stroke volume at normotensive afterloads. For such reasons measurements of only cardiac weight during model treatments of rat hypertension can give very misleading information.

Rate of structural adaptation. For this purpose we induced two-kidney, one clip renal hypertension in normal rats, as it is associated with a rapid and pronounced rise in MAP.57,58 The alterations in cardiac and vessel structure, assessed by our usual
methods, were largely complete within 1–2 weeks when related to the rate of MAP rise. On unclipping the kidney, where the complex events behind the rapid pressure fall are discussed elsewhere, full regression occurred about as rapidly if hypertension was of only 4–5-week duration. However, the more prolonged the preceding hypertensive state, the slower the regression and the more incomplete it appeared to be, presumably because of increased interstitial endowment in vessels and heart.

Thus, in the ordinary, relatively gradual development of primary hypertension, structural adaptation is not likely to be rate-limiting, simply because it can be so rapidly induced and completed. Actually, during acute pressure overload of perfused rat hearts, the active uptake of amino acids increases within 20 minutes, and their incorporation into proteins is well underway within the hour, as shown by other colleagues in our department. Thus, the cellular processes that lead to muscle hypertrophy become engaged very rapidly by alterations in loading conditions, which obviously apply to vascular smooth muscle as well. In general, biological function and structure interact continuously and represent, so to speak, two sides of the same coin. If, however, in this interaction, the cellular processes behind structural adaptation themselves are genetically reinforced, and therefore "sensitized" to pressure changes, this may give the impression that the structural factor even "runs ahead" of the functional pressure load, as will now be discussed.

Extent of structural adaptation: genetic and trophic reinforcement. These problems were briefly considered in relation to our first studies of human primary hypertension. In SHR and often also in human primary hypertension, part of the genetic predisposition is expressed as a mild central hyperreactivity to environmental stimuli that influences the cardiovascular system through complex neurohumoral links, and our group has devoted much work to their elucidation. The involved neurohumoral factors can no doubt impose pressure loads, but they may of course also affect cardiovascular muscle growth via "extrinsic" trophic influences.

Genetic and trophic factors in primary hypertension may, however, also be "intrinsic," that is, localized to some of the intracellular mechanisms involved in muscle growth, thereby reinforcing these normal processes. In an early study, we therefore tried to interrupt an obviously important neurohumoral link behind SHR hypertension by immunosympathectomizing newborn SHR and normotensive control rats (NCR). This resulted in a considerable lowering of adult MAP levels compared with those of untreated SHR and NCR. However, a nearly proportional difference in MAP and in the design of the resistance vessels remained between the treated SHR and NCR, although at lower levels for both. We interpreted this as suggesting some "intrinsic" genetic-trophic reinforcement (i.e., associated with intracellular growth-modeling processes in the SHR vasculature itself), although extrinsic hormone-like actions could, of course, not be excluded. Actually, recent evidence suggests that both intrinsic and extrinsic reinforcing actions are important.

In our other early studies, the structural changes for a given elevation of MAP often appeared to be greater in SHR than in RHR (e.g., \( R_{\text{pre}} \)) again suggesting genetic reinforcements of the structural changes in SHR. This has received further support in our more recent comparison of differences between SHR and WKY rats at various ages, where in 6-week-old "borderline hypertensive" SHR the degree of resistance vessel adaptation was even "ahead of the MAP elevation" in agreement with findings by other groups. Actually, in this early phase, a state of "hyperkinetic circulation" prevails in SHR (as is often the case in early human hypertension as well), and then tonic vascular smooth muscle activity in vivo in skeletal muscles is often below normal even during "rest," and as a consequence of the superimposed neurohumoral pattern. Thus, genetic-trophic mechanisms here seem to provide reinforcements of the pressure-related structural vascular resetting from which, however, functional control mechanisms can adjust regional smooth muscle activity in both directions (e.g., often decreased in skeletal muscle, increased in kidneys).

In adult (12–14-week-old) SHR, when cardiac output is largely normalized, the structural vascular resetting was in more direct balance to the elevated MAP and could therefore alone largely account for the raised systemic resistance, at least in the hindquarters. Again, this vascular structural adaptation in SHR was, concerning \( R_{\text{pre}} \), clearly more pronounced than in RHR after 20 weeks of hypertension. The difference between SHR and WKY rats is shown in Figure 4, which in the left part also illustrates the earlier mentioned interactions between 1) level of smooth muscle activity, 2) resistance vessel design, 3) wall distensibility, and 4) distending pressure in "early established" SHR hypertension versus matched WKY rats. As these interactions are most complex, but also crucial for the full understanding of the structural factor, they will now be discussed in some detail.

Figure 4, right part, which is derived from the experimental data in the left part, shows how the SHR resistance vessels are clearly hyperreactive compared with WKY rat vessels, even when exposed to the 45% higher pressure in vivo (166 vs. 115 mm Hg), thanks to their structural upward resetting. When these resistance responses, representing a state of constant-pressure perfusion in vitro, are instead expressed as flow responses (P/R), the range of these flow responses proves to be almost the same in SHR and WKY rats, even though both the perfusion and the transmural pressures are 45% higher in SHR. Here we know from our earlier studies, using separate measurements of the precapillary and postcapillary resistances, that this structural resetting...
in SHR is essentially confined to the precapillary resistance sections.

It is also clear from Figure 4 that if WKY resistance vessels had been exposed to the high MAP level of SHR their responses, and range of flow changes, would be markedly attenuated because of their weaker media, higher wall distensibility, and lower w/r. Conversely, should SHR vessels without a change of design be forced to operate at the lower MAP level of WKY rats, even fairly modest smooth muscle activations might threaten the oxygen supply of, for example, brain and myocardium, because their vascular hyperreactivity would then be less opposed by the pressure-dependent wall distension.

Thus, in established SHR hypertension the resistance vessels are, concerning design and reduced wall distensibility, so closely adapted to the raised pressure level that a closely normal range of flow changes can be covered by an entirely normal range of smooth muscle activations. Further, the raised "resting" resistance can be maintained at a normal smooth muscle tone, though regional differences can, as mentioned, prevail between, for example, kidneys and skeletal muscles. This is, however, not the case when renal hypertension is established in genetically normotensive rats, as here the extent of cardiovascular structural adaptation usually does not fully match the pressure rise, then calling for an increased smooth muscle tone as well.

Concerning the situation in vivo, it should be stressed that when smooth muscle constriction lowers blood flow, this effect is more or less offset by

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**Figure 4.** Left panel: Relations ("resistance lines") between distending arterial pressure (Pd) and flow resistance (PRU) at various levels of smooth muscle activity in paired hindquarter vascular beds of adult (3-month-old) spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats. Resistance lines show passive-elastic changes of resistance at sudden pressure shifts, as determined at various stable vasoconstriction levels that are evenly spread along the norepinephrine (NA) dose-resistance response curves. When plotted into this diagram, the S-shaped, constant-flow resistance "curves" of vascular beds show up as the slanting straight lines (dotted lines, SHR; solid lines, WKY rats) with maximal dilatation at 1, maximum constriction at 2, and ED50 at 3. Vertical straight lines represent the in vivo mean arterial pressures (MAP) for the SHR and WKY rat groups. Note how SHR resistance vessels are much stiffer, stronger, and "hyperreactive" than the normotensive ones. Right panel: Derived from intercepts between vertical pressure lines and curved resistance lines in left panel. By plotting these intercepts, the mean constant-pressure resistance curves for SHR and WKY rats in vitro are obtained as they would appear if the vascular beds had instead been perfused at their respective in vivo MAP at equal degrees of norepinephrine smooth muscle activations, but without the normal dampening influence of tissue metabolites occurring at flow reductions. Note considerable "vascular hyperreactivity" when expressed as resistance changes in SHR versus WKY rats, despite the higher arterial distending pressure. If, instead, flow reductions are calculated (P/R), the ranges of flow change in SHR at 166 mm Hg and WKY rats at 115 mm Hg are about the same, despite the 45% higher perfusion and transmural pressures in SHR. Consequences of perfusing SHR vessels at 115 mm Hg and WKY rat vessels at 166 mm Hg are also shown.
proportionally increased tissue vasodilator influences. This type of local negative feedback is not so far considered in the discussed situation of in vitro constant-pressure perfusion in Figure 4, to avoid "too many variables simultaneously." It may then be that hypertensive vessels respond differently to such tissue dilator influences, which could then entirely change the hemodynamic outcome. However, virtually all experiences from human resistance vessels in normotensive individuals and in patients with primary hypertension indicate that they are equally sensitive to the ordinary tissue dilator agents as released and accumulated during graded exercise or transient ischemia. Furthermore, the mentioned studies by Sivertsson on human hand blood vessels show how the structural factor fully expresses its various hemodynamic effects also in vivo. Thus, despite the 40% MAP elevation, the hypertensive resistance vessels exhibited a pronounced hyperreactivity to graded intra-arterial norepinephrine infusions, while smooth muscle sensitivity to this agent was not increased. When instead expressed as flow reductions, these were, if anything, more pronounced in the hypertensive than in the normotensive group, even though both perfusion and transmural pressures were 40% higher in the former group.

Thus, the systemic resistance vessels in established primary hypertension show structural changes that are in close proportion to the rise in MAP, both in humans and rats. Further, its presence in all vascular beds fairly closely reflects the degree of systemic pressure elevation, although regional differences in vascular smooth muscle tone are often at hand, as in normotension. By contrast, the structural vascular changes in the giraffe are very nonuniform, thanks to their 5–6 m height, which calls for an MAP at heart level of 250–275 mm Hg. This also implies extensive differences in hydrostatic vascular pressures, which result in very high w/r ratio in the lower parts of limbs compared with that of the cerebral vessels where MAP is perhaps only 80–90 mm Hg. However, here too the cardiovascular structural adaptations are entirely appropriate to the widely different transmural pressures in the different body regions of this very tall species.

As a net result, and as long as the giraffe maintains its habitual body position, this should allow the functional control mechanisms to operate like in all other species and result in corresponding flow adjustments without calling for extra excitation of the contractile elements. Incidentally, had the structurally adapted heart and vessels in human primary hypertension showed the same ability as in giraffes to withstand high chronic pressure loads without later deterioration and damage, primary hypertension would probably have been considered merely as a harmless deviation from the norm.

Hormonal "permissive" influences. In relation to factors that modulate growth, we recently examined the roles of hypophyseal growth hormone (GH) and thyroxine in structural resetting in hypertension. In the early work on SHR by Okamoto's group (see References 2 and 65), it was noted that hypophysectomy greatly attenuated SHR hypertension. We therefore considered it possible that the absence of GH leads to an attenuation of the normal process of structural cardiovascular upward resetting.

We used RHR in which we had a lot of information about the rate and extent of the structural changes. We clipped intact rats, hypophysectomized rats, and hypophysectomized rats treated with GH and thyroxine, using unclipped, otherwise similar rats as controls for each group. When compared at a given rise in MAP in the three RHR groups, hypophysectomy reduced the extent of structural upward resetting to about half. In fact, even though some of the hypophysectomized RHR throughout maintained three to five times higher renin levels than the ordinary RHR, their MAP levels were nevertheless 30–40 mm Hg lower. Thus, despite more intense angiotensin-mediated vasoconstrictions, they could not match the high pressure levels reached in ordinary RHR, because the geometric amplifier effect was so markedly attenuated, a process that ordinarily soon "takes over" in the maintenance of pronounced high pressure states in RHR. However, treatment with GH and thyroxine largely restored the normal relation between elevation of MAP and extent of structural hypertrophy.

We concluded that GH (and perhaps also thyroxine) serves as an important "permissive" factor needed to reinforce the pressure-dependent induction or the actions of more specific growth-promoting factors that together determine the extent of cardiovascular structural resetting. Once this resetting in RHR has occurred, it "takes over" most (perhaps 70–80%) of the initial role of angiotensin in maintaining the high pressure, but far less so when GH is absent. However, GH alone does not produce hypertension, as shown by the maintained normotension during excess GH administration to normotensive rats. Evidently, specific "pressor influences" are also needed to initiate a chronic hypertensive state. Finally, it should be emphasized how important it is to explore the role of growth modulators in hypertension in the intact organism and not just in vitro. Their effects are likely to be often rather different on both w and r, depending on their association with metabolic and other local and remote influences.

Therapeutic Considerations

Our described findings concerning the structural factor soon made it evident to us that a major final goal of antihypertensive therapy should be to promote regression of hypertrophy and of the $R_{\min}$ increase, as this would normalize the structural resistance vessel changes and their important hemodynamic consequences. Because the pressure elevation per se serves as the direct local stimulus for the structural adaptation and, perhaps, for activation of local trophic mechanisms as well, therapy should aim to 1) reduce pressure load, 2) dampen the...
activity of the cardiovascular musculature at key sites contributing to hypertension, and 3) reduce the effects of trophic influences. This last approach offers challenges for the future as knowledge grows.

Our early model therapeutic studies included that of Weiss, who maintained MAP of SHR at normal levels from an early age up to 8 months of age, which considerably attenuated the structural changes compared with untreated SHR. Furthermore, when treatment was stopped, MAP rose only slightly and gradually and never reached the levels of untreated age-matched SHR. Even more interesting, when 75% of the untreated SHR had died, 75% of the previously treated group were still alive. However, this dramatic effect applied only when treatment was started early in life. When treatment started in relatively elderly SHR, survival was little altered despite the attempts to control blood pressure. In general, treatment starting when SHR hypertension was fairly advanced seemed to be less efficient in bringing about cardiovascular remodeling, presumably in part because of relatively irreversible changes in the interstitium.

We later found that early treatment also attenuated the extent of the structural "upward resetting" of the renal preglobular vessels, and in relatively elderly SHR treatment slowed the rate of renal deterioration, which otherwise occurs with age. Our results of treatment on the coronary vessels and on the myocardium were briefly described above. Obviously, normalization of cardiovascular function and pressure control is not merely a matter of suppressing increased vascular smooth muscle activity as is often assumed.

One problem of therapy, particularly in humans, is the limits set by the homeostatic mechanisms of the body. With the structural changes in hypertension, relatively acute reduction in MAP to normal levels requires that the level of vascular smooth muscle activity or of cardiac output be forced to subnormal levels. However, most homeostatic mechanisms tend to oppose this lowering as they, too, are reset with "side effects" as complications, which may hinder more intense treatment in humans. Ultimately, true therapeutic normalization of primary hypertension requires full regression of structural changes. However, because the genetic predisposing factors continue to "lurk in the background," although usually fairly mild, the risk remains for a renewed gradual elevation in pressure in the absence of appropriate preventive measures. These measures may, however, then be mild and even take the form of nonpharmacological changes in lifestyle once the effects of the geometric amplifier have been normalized by efficient therapy.

Final Comments

I have particularly emphasized the hemodynamic consequences of the structural changes of the resistance vessels, partly because it is the key site of disturbance in established hypertension and partly because it is here that a potentially dangerous positive feedback process begins. However, it should be remembered that structural resetting also affects the renal barosat and most cardiovascular baroreceptors and volume receptors. Once this has occurred, the barosats try to maintain the prevailing pressures and volumes in hypertension, thus fulfilling their customary role in homeostasis, although at a higher set point. In an even wider context, we must therefore consider which are the really durable negative feedback mechanisms that, after all, maintain normal blood pressure in most individuals and also usually prevent the extreme positive feedback situation that is seen in malignant hypertension. It is, in a way, more surprising that about 85–90% of people maintain normal blood pressure throughout life than the fact that hypertension develops in 10–15%. The presence of so far poorly understood, but powerful, negative feedbacks can be suspected, and knowledge about such mechanisms is gradually emerging. One strong candidate, first discovered by Muirhead and his group, seems to be the renomedullary depressor substances medullin I and II, the role of which has been reviewed elsewhere. There may well be others, like some of the unmyelinated baroafferents, and perhaps hypertension researchers should think more about the various negative feedback systems that safeguard us.

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