Physiological Aspects of Primary Hypertension

BJÖRN FOLKOW

Department of Physiology, University of Göteborg, Göteborg, Sweden

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I. GENERAL ORIENTATION AND BACKGROUND

A. Introduction

1. Nature of topic

With a cheerfulness that only a lack of foresight can explain, I began by asking the experts for their contributions to this topic. Such an avalanche of reprints poured in that their mere inclusion in a reference list would swallow the space allotted. Even worse, virtually any factor that might contribute to this multifaceted disorder of regulation apparently found not only its convincing support but also its refutation in this mountain of scientific accomplishment. Then total surrender appeared to be the sensible way out, helped by a face-saving reference to William Harvey's only pessimistic statement in *De Motu Cordis* (1628): "I found it so truly difficult that I almost believed with Fracastorius that it was to be understood by God alone."

On second thought, however, it seemed more honorable to make an attempt, particularly since it could hardly make controversies much worse. An easy start was possible at least by summing up the few points where authorities do agree, but unfortunately points of disagreement are in the overwhelming majority. To elucidate this borders on the impossible, and to venture some sort of integrated concept is certainly to stick one's head into a hornets' nest. It therefore seems proper here to concur with another remarkable old-timer, Martin Luther. On facing the stern congregation of church authorities in Worms in 1521 to answer for his heretic theses, he concluded: "Here I stand, and cannot do otherwise, so help me God."

The frustrated reader may find solace in the wealth of other surveys covering hypertension from various angles (67, 94, 95, 272, 276, 282, 449, 450,
The trouble is certainly not meager experimental evidence but rather the great difficulty in making sense of a bewildering amount of data: "The problem is not that we know too little, but that we don't know how much we know," to quote an articulate symposium chairman. The recent encyclopedic *Hypertension* (241), like the older comprehensive books by Pickering (521) or Wollheim and Moeller (684), provides a far better access to the endless literature than this review, which often must refer to other reviews for detailed documentation. The reference list, which could easily be increased 20-fold, would otherwise become unmanageable by mere size. Faced by this frustrating dilemma I trust that the many excellent investigators referred to so indirectly gracefully consider it a tribute to the reviewers for perfect coverage.

2. Justification of topic

It may be wondered why a disease is, on the whole, dealt with in *Physiological Reviews*. Actually an authority like Pickering (521, 523) for good reasons questions the very usefulness of the term, concluding that primary hypertension rather represents the right end of the Gaussian curve for mean arterial pressure (MAP) as mainly due to a quantitatively different, multifactorial balance. Certainly true disease often ensues (521, 541, 597, 598) but mainly because the heart and vessels in most species are hardly designed to withstand long-term pressure elevation. It therefore slowly results in wall deterioration and subsequently organ lesions and premature death. With the proper genetic background, even very high arterial pressures could be perfectly physiological and well tolerated. The giraffe is an outstanding example, because without harm to its massively thick-walled cardiovascular system, this creature spends a normal life-span with an MAP around 250 mmHg to supply its modest brain, placed 2-3 m above heart level to allow for its treetop feeding habits. The giraffe's reflex MAP changes when shifting from feeding to drinking, and the concomitant pressure changes for the cranial vessels can well be imagined (251).

Even at the far lower pressure level in humans, however, MAP is by no means a fixed entity. Although it is fairly steady during relaxed rest, continuous recordings in normotensive persons (38, 51, 68, 322, 386, 457, 523, 591, 592) reveal a remarkably wide daily range (up to 2:1) and a characteristic diurnal rhythm. This persists in patients with primary hypertension but with the range set to higher levels. Nevertheless their lowest pressures are commonly well below the highest daily ones in normotensive subjects (51, 889, 457, 523). Thus MAP in normotensive subjects can vary from some 60 mmHg during deep sleep—when the brain vessels certainly need their autoregulatory capacity to maintain cerebral oxygen supply and the kidneys have little left of their effective filtration pressure—up to 120-130 mmHg during emotional eruptions. Peak systolic pressures then banging on arterial walls are impressive indeed.
This variability certainly does not argue for strict lines between normotension and hypertension, particularly not on the basis of single pressure measurements, and the distinction between normotension and hypertension remains a pragmatic convention. Obviously the daily average MAP level over longer periods represents the true wear and tear for heart and vessels, but the extent of damage inflicted also depends on genetic factors influencing design and repair. Occasional peaks are probably of little consequence, except where cerebral aneurysms might precipitate catastrophe. Whichever attitude is preferred concerning the definition of disease in primary hypertension, the present theme is justified also for quite different reasons: any physiologist interested in homeostatic mechanisms can certainly have his tour de force in facing primary hypertension, because it provides fascinating examples of how complex control mechanisms may gradually be pushed beyond normal bounds until deterioration ensues.

3. Terminology and definitions

Primary hypertension is preferred here to the clinically used essential hypertension. 1) Primary hypertension provides a better correlate to secondary hypertension. 2) Chronic high-pressure states are not particularly "essential" for anything, to quote Dustan (173), though giraffes are bound to disagree with her. 3) The prefix essential as a synonym for idiopathic becomes increasingly inadequate as knowledge accumulates, and 4) this prefix is linked to the human variant of the disorder. Several purebred variants of primary hypertension in rats are now available, each showing interesting parallels to the human condition (204, 210, 224, 226). These animal models have been a breakthrough for the exploration of this important and common disorder of regulation. Therefore an article on physiological aspects of primary hypertension and its etiology cannot avoid dealing with humans and animals alike, which makes a common terminology preferable.

The outstanding characteristic of primary hypertension, which principally separates it from all variants of secondary hypertension, is the inherited predisposition, justifying the prefix primary. As outlined later, however, these primary or intrinsic elements for their full expression apparently often need the presence of certain extrinsic, or environmental, influences, which facilitate or sometimes perhaps even precipitate the chain of events elevating pressure. As also illustrated below, however, the resulting hypertension would probably be only marginal in extent and consequence if it did not quite early induce secondary morphological adjustments. These in turn seem to form an increasingly dominating common denominator for the induction and maintenance of virtually all chronic high-pressure states, whether primary or secondary.

Secondary hypertension is more straightforward because an extrinsic interference, experimental or by way of disease, has been inflicted on one
or several of the key components in cardiovascular control (34, 108, 147, 271, 365, 432, 521). Thus secondary hypertension has generally a more clear-cut, though not always easily identified, initiating mechanism, but the same reinforcing and sustaining structural cardiovascular adaptation is also involved here (40, 43, 55, 205, 221, 321, 342, 421, 422, 492, 565, 670, 674, 679, 680). The fundamental difference is, however, that secondary hypertension does not necessitate any genetically linked predisposition or environmental reinforcements. Thus elements that in reality are expressions of secondary hypertension may gradually become superimposed on primary hypertension (95).

4. Delineation of topic

The variants of secondary hypertension may be equally fascinating but are dealt with here only to the extent that they illuminate primary hypertension, where they have been invaluable, mainly by suggesting how genetic predisposing elements might affect the cardiovascular system. Moreover secondary hypertension constitutes only 5–10% of hypertensive disease in the Western World (49, 521, 625, 684), making primary hypertension the outstanding problem for treatment and prevention.

This review is restricted to physiological aspects of primary hypertension and its etiology, for obvious reasons with emphasis on cardiovascular events. This implies a discussion of the nature and interaction of the various elements of initiation as they affect the heart, vessels, and effector cells; intrinsic and extrinsic control mechanisms; and how such coordinating mechanisms affect overall hemodynamics. Here in particular differences between normality and abnormality are marginal and often merely quantitative, at least to begin with. Therefore most sections in this review start with an outline of physiological principles, which are the natural base line for judging genetic or secondary deviations.

B. Historical Landmarks

August Comte once said that to understand a science one must know its history. This is not the place for an extensive historical survey, for which Pickering's vivid account (520) is recommended. Some colorful landmarks certainly deserve mention, however, particularly as they help to explain traditions and trends in present-day research.

1. Early milestones

Conventionally the history of hypertensive disease is considered as starting in 1836 with the classic description by Bright (86) of the disorder that for long carried his name. Bright, however, had a remarkable predecessor,
Samuel Schaarschmidt, born in a German settlement along the Volga in Russia but educated in Berlin, becoming when still young professor of medicine in that city until his death in 1747, only 38 years old (29). Thus he was in the midst of his career hardly more than a century after William Harvey’s monumental discovery in 1628 and only about a decade after the Reverend Stephen Hales in 1733 for the first time known to history measured an arterial pressure in his illustrious mare.

Based on what must have been an unusual combination of keen-eyed observation, brilliant scientific intuition, and sheer common sense, Schaarschmidt evidently had an astonishingly good grasp of what we now call primary hypertension in humans. He and his pupil Nicolai ascribed it to a “spastic constriction of the vascular bed” and noted how the circulation was in a state of “vehement agitation.” His recommended therapy is no less astonishing: he urged adjustments of the mode of living to eliminate excitement and used sedatives, venesection (for once rationally used in those days), and vasodilating medication (nitrites). This is nothing less than the modern principles of antihypertensive therapy: reduce sympathetic drive, dilate resistance and capacitance vessels, and reduce cardiac output. Schaarschmidt’s accomplishments are a healthy reminder that nothing is new under the sun and that brilliance, though always rare, has been a helpful companion to humankind since the Stone Age, not only blessing modern generations.

Bright’s outstanding work, however, is in no way belittled by Schaarschmidt’s accomplishments, of which he probably had no knowledge. Furthermore Bright’s findings triggered a series of other important contributions that established the field. Thus in 1868 in England, Johnson (348) first described arteriolar media hypertrophy, a natural correlate to the left ventricular hypertrophy and arterial thickening noted by Bright. Johnson’s findings were soon confirmed by Ewald (186) in 1877 in Berlin and subsequently by numerous investigators. Ewald also had some considerations of an astonishingly modern flavor, starting with a quotation of a young Russian in Heidenhain’s laboratory, Ostroumoff, who showed the principle of blood flow autoregulation decades before the classic (but not very good) paper of Bayliss (39) in 1902.

Ewald hinted that initial pressure rises might induce widespread autoregulatory constriction of the arterioles (today’s whole-body autoregulation) and subsequently generalized medial hypertrophy, although this, he observed, would hardly hinder vessels from constricting and dilating. Thus 100 years ago he touched on some concepts now of highest actuality, but he avoided the problem of whether these structural arteriolar changes could also be important for initiating the raised pressure. He is hardly to blame for this, because Poiseuille’s pioneer studies of basic hemodynamics were only a few decades old and vascular biophysics largely unknown.

Around this time the first successful estimations of arterial pressure in humans were also performed, in England by Mahomed in 1879 and in
Germany the year after by von Basch with a better technique, later perfected by Rocci in Italy in 1896 and Korotkoff in Russia in 1905. The ability to record pressure helped people like Mahomed, and later Albott in England, von Basch in Germany, and Huchard in France, realize that hypertension frequently occurred without renal disease. Thus high arterial pressure appeared to be a disturbance in its own right, a view partly anticipated by Gull and Sutton in 1872 in their pathological examinations of Bright’s disease. Gradually the concept of a primary hypertension emerged, and the German clinician Frank contributed in 1911 the clinically used prefix essential (“essentielle Hypertonie”), alluding to the idiopathic nature of the disturbance.

In the same period the experimental approach to hypertension had its first major landmark when the Finnish-Swedish physiologist Tigerstedt and his pupil Bergman (626) discovered renin together in 1898 and explored its pressor effects in animals. The impulse for this now-classic study came from Brown-Sequard’s concept that tissues modulate the organism’s function by producing specific signal substances. However, Tigerstedt and Bergman were far ahead of their time and might not themselves have realized all implications, and decades elapsed before further, really successful animal experimentation on hypertension got started.

2. Era of clinical studies

The most important development early in this century emerged from clinical studies. Thus in 1904 Ambard and Beaujard (8) suggested that salt intake might influence high blood pressure. Particularly important were the contributions by the great German clinician Franz Volhard, among them his classic systematization of hypertensive disorders in 1914 in collaboration with the pathologist Fahr (678). Volhard, who for decades dominated the clinical science, believed that the variant he called “red hypertension” (i.e., uncomplicated primary hypertension) depended at least partly on altered elastic properties of arteries and arterioles and, further, that not only age but also heredity was important (522).

Thus even though it took Volhard time to accept the concept of primary hypertension, the importance of inheritance gradually became clearer with direct investigations starting during the 1920’s. Really penetrating analyses appeared somewhat later, particularly by Pickering, Platt, Thomas, Miall, and Oldham and others (520, 521, 523). For years a major point of debate was whether the predisposition for high blood pressure was mono- or polygenetically transferred; the latter view finally won almost unanimous acceptance. Miall’s studies were particularly important here.

The increased pressure was long assumed to reflect an equivalent resistance elevation with little regard for cardiac performance, mainly because reliable cardiac output measurements in humans had not yet been developed. Furthermore it was widely held that structural changes of the vessels rep-
resented a late and largely irreversible sclerosis or even wall rigidity. With these views it appeared logical to consider hypotensive treatment not only useless but even potentially harmful.

This pessimistic attitude about the structural changes in heart and vessels hardly stimulated exploration of whether they might after all be dynamic and early events. Moreover the difficulties in measuring exact dimensions of the crucial microvessels, for wall thickness versus radius, appeared staggering. Therefore it was for decades (and still often is) assumed that primary hypertension was not only initiated but also essentially maintained by a continuously present increase of smooth muscle activity, with structural changes rather reflecting deterioration beyond repair. Consequently the dominating problem for speculation and research in primary hypertension was exactly how the assumed tonic increase of arteriolar smooth muscle tone was initiated and maintained. Remarkably there was no convincing experimental evidence to support this concept, but it almost became an axiom; both tradition and fashion are strong forces even in the scientific world.

3. Breakthrough in experimental approach

An almost explosive new development emerged from Goldblatt's classic work that greatly enhanced interest in the kidneys, initiated by Bright 100 years earlier and experimentally highlighted by Tigerstedt and Bergman at the turn of the century. The ingenious induction of secondary hypertension in dogs by renal artery clamping, first reported by Goldblatt et al. (255) in 1934, had an enormous impact and caused an avalanche of experiments, particularly on animal models (34). The great psychological influence of these studies was further strengthened by the independent discoveries in 1939 of the renin-angiotensin system by Braun-Menéndez et al. (82, 189) in Buenos Aires and by Page and Helmer (500) in Cleveland. The enthusiasm for a humoral origin of the raised resistance in hypertension was also reinforced by the demonstration that secondary hypertension could be induced by interferences with other hormonal systems (108, 268, 271). The only apparent, but in reality serious, drawback of these successful initiations of experimental secondary hypertension was a focusing on unitary hypotheses, mainly on a humoral basis, tending to oversimplify primary hypertension with disregard for other mechanisms. This unfortunately led research into many dead ends and caused much frustration.

In the 1930's there was a breakthrough for quantitative hemodynamic studies in humans. For example, attempts were made to localize the increased resistance along the circuits and to define its nature, mainly initiated by Pickering (517) and Prinzmetal and Wilson (530). Also at this time Byrom (105) started his fundamental and thorough explorations of the degenerative and lesional effects of hypertension on blood vessels. Based on his ingenious
experiments in humans, Pickering concluded that the resistance increase was not due to any raised blood viscosity and that it mainly resided in the smallest precapillary vessels. Further, since the elevated regional resistance in established hypertension remained after blockade of constrictor fiber activity, compared with equally treated controls, it could evidently not be ascribed to any continuous and generalized accentuation of sympathetic discharge.

Pickering, also noting that resistance even after intense vasodilatation remained proportionally increased compared with controls, was on the verge of revealing the hemodynamic importance of an altered vessel design and actually discussed the possibility seriously. However, these interesting findings were challenged on trivial technical grounds and unfortunately were not pursued with improved methodology, which may well have settled the issue. Subsequently Pickering (518) was therefore inclined to ascribe the resistance increase to some stable humoral agent. Prinzmetal and Wilson (530) arrived at similar results and conclusions; like several other investigators, except for some of Eichna's and Wilkin's findings, they noted that resistance remained increased even during intense vasodilatation.

However, blood flow values during dilatation and their wide scatter in these studies suggested that the resistance vessels were only sometimes completely relaxed, in both normotensive and hypertensive subjects. Results of this nature were also at this time commonly taken as evidence for a stable humoral pressor agent, hindering complete muscle relaxation in hypertensive resistance vessels. Apparently this interpretation reflected the impact of Goldblatt's classic results and the consequent preoccupation with unitary concepts. The fact that the findings could as readily be explained by an altered resistance-vessel design, for which there had been histological evidence since 1868, was evidently overlooked, and a new attitude to this problem emerged first during the 1950's.

In experiments on rabbits, however, Pickering, together with Wilson in 1938 (676) and later in 1945 (519), made some observations indicating that unitary hypotheses could hardly explain even the seemingly clear-cut case of secondary renal hypertension. Thus although early elimination of the ischemic kidneys promptly normalized pressure, this frequently did not occur if hypertension had lasted more than 2–3 wk. Grollman (267, 268) made similar observations and suggested a deficiency of some depressor factor normally produced by the kidney. However, an extrarenal factor might also be involved, and in 1945 Pickering strongly suspected the vessels themselves, a view he also expressed in a survey in 1950 (cf. 205), stating "for the present impasse in hypertension is probably chiefly due to the fact that certain fundamentally important aspects of vascular behaviour are appreciated by contemporary science either dimly or not at all."

Pickering (519, 520) found that the occurrence of vascular lesions appeared directly related to the height of pressure, as measured in awake rabbits. In rats with pressure measured during anesthesia, however, Wilson
and Byrom (675) found no such close relationship, therefore suggesting that lesions were the combined effect of vasoconstriction and pressure. The divergent interpretations confused this important issue for years and led to suggestions that, e.g., the renin-angiotension system might also exert "vasotoxic" effects. This controversy was settled first by the elegant demonstration of Giese (245) that wall lesions essentially occur where vascular widenings are induced by the yielding of regional smooth muscle to high pressure and not where vasoconstriction is maintained. Furthermore any pressor agent can elicit lesions in yielding parts of vascular walls, contradicting the suggestion of "specific" vasotoxic effects (245, 246).

With the prevailing emphasis on hormonal pressor influences, it surprised many, though hardly Grollman, when Braun-Menéndez and von Euler (81) in 1947 reported that bilateral kidney extirpation in rats could also cause a pressure rise ("renoprival" hypertension). In most elegant experiments Grollman and co-workers (267-269) eliminated the renal excretory function but maintained the incretory one by implanting the urethers into the caval vein. Since no pressure rise occurred, except during water-salt loading, Grollman again emphasized that renoprival hypertension may reflect the absence of some renal depressor agent or, alternatively, that renal tissue neutralizes extrarenal pressor agents. Findings by Goldblatt and by the Braun-Menéndez group also suggested that the normal kidney may somehow protect against hypertension, in addition to its release of pressor agents when threatened by ischemia.

These concepts had traits in common with findings by Wollheim (681, 683) in Germany during the 1930’s that normal urine contains depressor material ("depressan") that seems to be lacking in urine from hypertensive patients. Wollheim suggested that vascular tone is also controlled by depressor hormones and that their relative lack may contribute to primary hypertension. Such a concept of reduced production of blood-borne depressor agents is of course theoretically as interesting as the idea of an overproduction of pressor agents, but somehow it never aroused the same interest and was not as vigorously pursued. Therefore much remains to settle about the involvement of mechanisms like those suggested by Wollheim and Grollman, though interesting work has been pursued particularly by Muirhead (462) and his group (sect. IIIE26).

Neurogenic mechanisms also had able proponents at this time, and Schaarschmidt already had his keen eyes on such a possibility without any real knowledge of vasomotor innervation. Russian scientists favored a neurogenic origin of human primary hypertension, stimulated by Pavlov’s classic work on central nervous mechanisms, with clinical contributions by, e.g., Lang and Miasnikov. This line of thinking considered an involvement of the highest nervous centers, via psychoemotional influences believed to maintain a somewhat sustained increase of sympathetic activity. Some aspects of Russian experimental work contained important information (583), but this was often neglected in the Western World, partly because of unfortunate
language barriers and partly because the neurogenic concept was often over-stressed in a unitary direction.

Apart from this emphasis on corticohypothalamic levels, there were able proponents, like Heymans, of an initial alteration also in reflex homeostasis, with early neurogenic influences conveyed at lower bulbar levels and caused by some primary baroreceptor change and/or by altered bulbar integration (316, 317). This idea, however, was more or less abandoned when it became clear that secondary baroreceptor resetting occurs rapidly and regularly in hypertension (438) and hence contributes to its maintenance. A major headache for supporters of a purely neurogenic background to primary hypertension, however, was to explain why, e.g., resistance remained raised also after constrictor-fiber blockade; this is an unavoidable dilemma facing any unitary concept, when trying to explain everything by a single major disturbance.

All concepts mentioned so far rested on the almost axiomatic assumption that the elevated resistance was due to some continuous excitatory influence on the vascular effectors; quarrels among experts mainly concerned its nature. Quite a different approach emerged during the 1950's (200, 209), initiated by quantitative measurements in animals of the relationships between resistance, smooth muscle tone, and wall distensibility in resistance vessels and how design differences between arteries and veins greatly affect their function (205). After Georg Johnson's amply confirmed observations of media hypertrophy in arterioles (348), it was further shown how such changes in resistance-vessel design have important hemodynamic consequences, as outlined later (sect. II.D). In fact these structural changes appeared to influence vascular dynamics so much that virtually no increase of smooth muscle activity was needed for maintaining the elevated resistance to flow in established primary hypertension (205, 209). Had research on primary hypertension perhaps been hunting a nonexistent ghost, spellbound by the exciting findings of Goldblatt and others in early renal hypertension?

Likewise, noting an increased water-salt content in arterial walls of patients who had died from hypertension, Tobian and his group (532, 630, 633) suggested that waterlogging, if substantially increasing arteriolar wall thickness, must affect resistance-vessel behavior as well. This clear insight into the hemodynamic importance of altered vascular architecture is not belittled by the fact that later studies provide no evidence of hemodynamically significant arterial waterlogging in uncomplicated primary hypertension (357, 543). Waterlogging of the magnitude needed to mechanically affect resistance-vessel behavior may first follow acute pressor crises in advanced hypertension or may occur if normotensive vessels are exposed too rapidly to violent pressure increases, causing massive leakage and other signs of acute overload, as shown by Giese (245, 246).

These ideas and findings concerning the hemodynamic importance of altered vessel design in primary hypertension, with medial hypertrophy occurring in response to, e.g., intermittent neurohormonal increases of MAP
(201, 202, 209), aroused only scattered interest. It implied a multifactorial concept, but hypertension research at the time was dominated by an intense search for the one-and-only humoral pressor agent, or neurogenic mechanism, thought to maintain the increased resistance.

Meanwhile reliable methods for recording cardiac output (CO) in humans became available and were utilized also for comparing normotensive and hypertensive subjects (91, 214, 520, 666, 672). To the surprise of many, in early hypertension CO was often so enhanced that resistance was essentially normal, except compared with that of normotensives brought to corresponding CO levels by, e.g., light exercise (214). Besides clarifying overall hemodynamics in hypertension, such findings also contributed to a more balanced evaluation of neurogenic mechanisms, where the penetrating analyses of Brod and co-workers (87, 91, 92, 672) in Prague deserve particular mention.

They revealed in early human hypertension a cardiovascular pattern so closely mimicking the hypothalamic defense reaction in animals (180, 201, 206, 318, 695) that a definite contribution by neurogenic influences seemed beyond dispute, at least in common variants of primary hypertension. Like other signs of enhanced sympathetic activity, however, it was dismissed by skeptics as transient psychogenic effects rather than reflecting a true trigger element, and such arguments still occur. On the whole there was a disregard in hypertensive research for long-range consequences of excitatory influences that are not always present. The fact was overlooked that biological systems register phasic events if encountering them often enough, responding with biochemical and functional adaptations and certainly also with structural ones (205). This is best illustrated by the response of the locomotor system to repeated exercise.

Vivid disputes thus raged between enthusiasts for various excitatory influences considered to chronically excite vascular effectors, but little attention was paid to the possibility that these cells might themselves be altered. After all in 1902 Bayliss (39) had proposed that vascular smooth muscle could, like the heart, exhibit intrinsic automaticity, which was subsequently confirmed for a variety of smooth muscles (593), including that in resistance vessels (203, 260, 350). Smooth muscle cells were exceedingly difficult to study directly, however, and hence in this context they remained the “sour grapes” in the muscle family, until effector supersensitivity began to be discussed.

Finally, around the 1950's and 1960's it slowly dawned on experienced investigators that virtually any unitary concept of primary hypertension ended in a blind alley. Research attitudes toward primary hypertension were suffering from what recently was amusingly labeled “Mill's disease” by the Glasgow group (434). On the other hand all the mechanisms so far discussed could hardly be abandoned because this would leave nothing at all. Therefore a wider interest in a multifactorial approach slowly took shape, mainly thanks to pioneers like Pickering and Page. Particularly Pickering's ap-
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proach (521, 523) and Page's presentation of his "mosaic theory" (496) went in this direction.

A new era of great expansion of the scope of experimental investigation began with the development of rat strains with polygenetically inherited primary hypertension, first by Smirk and Hall (516, 589, 590) in 1958 with the New Zealand genetically hypertensive rats (GHR). They were followed a few years later by Okamoto and Aoki (483, 484) with the Kyoto spontaneously hypertensive rats (SHR) and by Dahl and his group (141-143, 531) with the Brookhaven hypertension-sensitive rats (HSR) and an interesting counterpart, the hypertension-resistant rat (HRR). Other recent variants are the Milan strain of spontaneously hypertensive rat (MHS) by Bianchi et al. (30, 56, 58, 59), the Sabra strain in Israel by Ben Ishay et al. (41), and the stroke-prone SHR variant by Okamoto's group (160, 689). These strains soon revealed different entrances to a final common path in primary hypertension.

Furthermore the 1950's and 1960's had a breakthrough in efficient pharmacologic therapy, initiated by the introduction of ganglionic blockers by the pioneering work of Zaimis and Paton (e.g., 694). Here the present, steadily widening spectrum of pharmacologic tools has also been of great value for analyzing pathogenetic mechanisms (273, 408, 551, 694).

Together such contributions set the stage for the current, almost explosive development of highly specialized experimental approaches, but now there is much more awareness that a combination of causative elements—primary, environmental, and secondary—must be traced to explain primary hypertension. The problems discussed now start largely where Freis (214) and Page and McCubbin (501) ended in their respective reviews.

4. Summary of acknowledged facts

Although few fields of research are as perpetually pestered by controversies as that of primary hypertension, there are fortunately some basic points, emerging from the earlier work outlined above (sect. IBl-3), on which virtually all authorities are apt to agree. It is helpful at this stage to summarize them as follows.

a) Hereditary predisposition. Primary hypertension is characterized by a predisposition that is polygenetically transferred, both in humans and in the various hypertensive rat strains.

b) Environmental influences. Primary hypertension can be influenced by at least two important environmental factors—the habits of salt intake and certain excitatory psychoemotional influences—which may aggravate and sometimes perhaps even precipitate the pressure elevation if the proper hereditary predisposition is at hand.

c) Structural adaptation. Primary hypertension is early characterized by an adaptive increase of contractile tissue in predominantly the left heart,
systemic arteries, and precapillary resistance vessels, which somehow must affect their functions, and is later followed by substantial interstitial endowment and, finally, as signs of decompensation, by degenerative and lesional changes.

d) **Hemodynamic balance.** Although early primary hypertension often exhibits an elevated CO, the established phase is characterized by largely normal CO, blood volume, and viscosity, implying that a raised systemic flow resistance is dominant.

e) **Nature of raised resistance.** The raised systemic resistance to flow must be ascribed to either a continuously increased activity of vascular effector cells and/or to a structural wall alteration that allows unrestricted but at a higher equilibrium.

f) **Effector cells.** Although cardiovascular effectors in primary hypertension have principles of myogenic activity and superimposed extrinsic local and remote controls like those in normotension, myogenic activity and/or muscle sensitivity and reactivity to extrinsic stimuli may well be accentuated.

g) **Neurogenic excitatory influences.** Whereas autonomic nervous mechanisms in both normotension and hypertension form the most swift, powerful, and differentiated link of extrinsic cardiovascular control and may thereby help to initiate primary hypertension, the chronic resistance elevation in the established phase is not a simple matter of accentuated vasoconstrictor-fiber discharge.

h) **Hormonal excitatory influences.** Although renal and adrenal components of the hormonal system are important in cardiovascular homeostasis and may well help trigger primary hypertension, the sustained resistance elevation in the established phase is not a direct consequence of blood-borne constrictor influences.

i) **Barostat resetting.** The major pressure controlling mechanisms, i.e., the short-term barostat function of the cardiovascular proprioceptors with associated reflex adjustments, as well as the long-term barostat function of the kidneys, in established primary hypertension have largely “accepted” the pressure elevation and maintain it.

j) **Renal involvement.** Last, but certainly not least, by virtue of their important excretory and incretory functions the kidneys must be considered as major potential sites for triggering mechanisms in primary hypertension, besides contributing dominant secondary influences.

In addition to these 10 points of agreement, others of course may be added, though they would hardly be as generally applicable to all variants of primary hypertension. Anyhow they may serve as a suitable platform from which to survey new findings, issues of disagreement, and mere gaps in knowledge. I hope this will illustrate how apparently conflicting findings and views may often be explained by the inherently variable nature of primary hypertension, with differences not only between variants and individuals but also between stages. In fact we may know more than we think we
know about primary hypertension, at least about its broad lines, though knowledge is certainly sparse when it comes to tracing, e.g., hereditary predisposing influences down to the molecular level.

II. MAJOR ETIOLOGICAL COMPONENTS

A. Principles of Interaction Between Primary, Environmental, and Secondary Influences

Of course the precise identification of the hereditary primary elements, as well as their location within the system, constitutes one of the major aims in hypertension research. There is, however, much evidence indicating that these hereditary predisposing elements do not work in a vacuum but are interdependent with environmental and other influences in raising blood pressure. The more it is realized that unitary explanations do not suffice and therefore a multifactorial background must be considered, the more urgent it becomes to formulate some type of principal interaction scheme for participating mechanisms. Such a scheme would not only aid the search for individual predisposing elements but also provide a more realistic evaluation of how they may exert their triggering influences.

Exploration of the hemodynamic effects, caused by early structural adaptation of heart and vessels in hypertension (200, 202, 209), made it increasingly clear that these changes contribute decisively to the multifactorial events that gradually end up in primary hypertension. This led to the formulation of a tentative scheme for interaction between at least three major types of influences (205). This scheme, which may help the subsequent discussion on the nature, location, and mode of action of individual etiological elements, can be outlined as follows.

I) A polygenetically inherited predisposition constitutes the primary sine qua non, which in humans, however, is likely to be individually variable because people, in contrast to hypertensive rat strains, are far from inbred and therefore have different constellations of predisposing genes that may also vary in power.

II) Certain environmental elements, predominantly salt-intake habits and psychoemotional influences, may strongly influence, perhaps even precipitate, primary hypertension depending on the balance of predisposing elements.

III) Certain secondary adjustments, particularly the rapid structural adaptation of left heart, systemic arteries, and arterioles, might also be genetically reinforced. This forms for the resistance vessels a positive-feedback interaction with the excitatory influences of I and II, which gradually shifts pressure upward, and also resets the barostats accordingly.

Here the mechanisms inherent in I and II serve as trigger elements. They are likely to be only marginal, however, and would probably not matter.
too much alone, but they can gradually initiate III whenever they are persistent enough. Because of its reinforcing influences, III therefore becomes indispensable both for the initiation and maintenance of chronic hypertensive states. Its gradual buildup in the positive-feedback action at the resistance level makes it so dominant that even the initial triggers may be difficult to trace.

The consequent resetting of various control elements involved in volume regulation, hormonal regulation, etc. gives the impression that they are set inappropriately high in relation to pressure, which is easily mistaken for a causative involvement. Here enthusiasts for, say, neurogenic or hormonal control systems may tend to overstate their case, illustrating the enormous difficulties confronting investigators studying primary hypertension.

The three principal elements mentioned are now outlined, but for I only in general terms because discussion of the exact nature and location of primary triggers is left for section III. Section IV attempts to formulate an acceptable summary concerning origin, maintenance, and hemodynamic characteristics of primary hypertension.

B. Hereditary Primary Predisposition

1. General aspects

Although the polygenetic predisposition to primary hypertension is now widely acknowledged in both humans (434, 507, 521, 523, 617) and hypertensive rat strains (484, 516, 531), it has some important consequences for humans that are not so immediately evident.

A genetic deviation ultimately implies that some macromolecular constituent (enzyme, carrier, membrane component, etc.) differs in design from the norm, though this is relevant only if functional characteristics are also thereby altered. When such molecular variants may, as in hypertension, via pressure elevation cause damage and death, expressions like genetic “defects” or “faults” are often used. However, a genetic alteration of an enzyme may just as well improve efficiency, though its presence in, say, vascular smooth muscle perhaps facilitates hypertrophic adaptation or myogenic activity, hence elevating both resistance and MAP. Likewise a polygenetic predisposition may depend on individually normal molecular variants, though their very constellation happens to affect cardiovascular balance so that MAP increases.

Thus when tracing a predisposition for primary hypertension to the molecular level, such intricate circumstances may prevail that expressions like “genetic defects” are indeed inappropriate. The predisposition that renders giraffes grossly hypertensive certainly does not justify such expressions, and these creatures tolerate high pressure because of other—for them profitable—genetic constellations, which humans unfortunately lack. If they had
been present also in humans, primary hypertension would have been a harmless variant of the norm.

Whichever definition is preferred, there is a long way to go before the human predisposition to primary hypertension can be traced to precise molecular links, though recent developments from some pioneer observations (412, 668) may provide an opening (sect. IIIA.). However, even complete insight into biochemical details in disorders of this type can never substitute for physiological knowledge, simply because the two represent such different facets of biologic realities. It is therefore equally important to identify the afflicted cardiovascular components. Can, for example, primary disturbances be traced to some aspect of smooth muscle function or design, to nervous or hormonal controls, to some of the renal functions, etc.? In fact, such insight may be more useful than knowledge of precise molecular deviations, at least for therapy and prevention.

The functional expressions of primary genetic alterations may seem easy to trace, at least before secondary changes are superimposed. However, initial phases of primary hypertension are so insidious in humans that they are difficult to trace and define. Furthermore quite early gradual biochemical, functional, and structural adaptations occur everywhere, making primary and secondary components so intertwined in time that their separation is exceedingly difficult. Faced with alterations in all, investigators easily overemphasize those in their own specialty, which hardly reduces controversy. If early secondary changes establish positive-feedback interactions with primary ones, however, they clearly match each other in etiological importance. To sort out such problems the hypertensive rat strains offer great advantages: 1) because each has a specific and, between individuals, uniform genetic predisposition; 2) because events can be followed throughout life along a compressed time scale; and 3) because environment can be standardized. However, even then primary and secondary elements are difficult to separate, as controversies among investigators amply illustrate.

2. Principal implications of polygenetic predisposition

The very presence of a polygenetic predisposition makes it likely that several, rather than a single one, of the many cardiovascular components are afflicted and furthermore that the constellations of such genes vary among people. Experiments with SHR, GHR, MHS, and HSR illustrate this fact (58, 141, 142, 210, 216, 291, 416, 483, 484, 516, 531, 589, 689), because these strains clearly differ in the nature of the major initiating disturbances.

There is no reason why human primary hypertension should in these principles differ from rat hypertension, except on one important point: deliberate inbreeding has given each rat strain a uniform combination of predisposing elements, whereas human reproductive behavior certainly disregards genetic uniformity. Therefore human primary hypertension must
constitute randomized variations on a theme, as though rat hypertensive strains had crossbred freely. Therefore the search for a uniform cause of human primary hypertension appears futile. It must instead represent a spectrum of variants, with dominance shifting among, say, neurogenic, hormonal, and renal primary elements (sect. III D–F). This by no means denies that some predisposing constellations may be particularly common in humans or that some dominate in certain parts of the world because of racial differences, close social contacts, etc. Such circumstances, together with environmental differences and unequal representation of different stages, probably explains why randomized population samples may differ somewhat in characteristics of human primary hypertension (118, 247, 307, 360, 418, 485, 507, 575, 576, 617, 625).

For example, separated colonies of SHR soon differ slightly even though all come from the same inbred Kyoto rat strain. Furthermore differences are indeed striking between, e.g., Wistar substrains of SHR and MHS in initiating mechanisms, severity of hypertension, impact of environment, etc. (56, 58, 210, 211, 291, 483, 689). Whereas central neurohormonal mechanisms constitute the probably dominating trigger influence in SHR (204, 689), MHS have a milder, mainly renal-based hypertension with early salt retention and consequent volume increase (56, 58, 59, 210). The SHR are particularly sensitive to psychoemotional stimuli and MHS fairly little, whereas early sodium loading would be more critical in MHS than in SHR hypertension. These rat models offer the advantage of often striking differences in genetic trigger elements and their relationship to environmental influences. In humans such principles are obscured by the randomized variability of predisposing patterns, a complex environment acting on a far more sophisticated mind, and a much longer life-span.

These considerations provide a better background for discussing the major questions in human primary hypertension. Which are the most common and dominating predisposing genetic elements, and which cardiovascular mechanisms do they primarily affect? How important are environmental influences for the precipitation of primary hypertension, and how do they interact with genetic elements and early secondary adjustments? Can genetic deviations also affect some reinforcing secondary changes (205, 209), thereby facilitating their impact on hemodynamics? If so there are no strict borders between such primary and secondary elements, and the initiation of primary hypertension should instead be sought in their interaction, as modulated by environment (205).

C. Environmental Influences

1. General aspects

Many studies have dealt with the problem of whether there are clear relationships between habitual salt intake and blood pressure (109, 485, 502,
576, 663) and whether a rapidly changing sociocultural environment via increasing psychoemotional stimulation may slowly raise the pressure equilibrium until it is also discernible in population samples (144, 275, 307, 309, 662). Of course there may be still other types of environmental influences of direct or indirect relevance for primary hypertension, though so far not as obvious or well defined.

Thus clear relationships are found between high blood pressure and overweight (47, 49, 115, 149, 535, 625), but it is not known whether this mainly reflects environmental influences (food-intake habits), if this is another facet of the genetic predisposition, or both. There are, for example, interesting relationships also in characteristic deviations in glucose metabolism (47) that suggest complex genetic associations that can be traced even to cell membrane levels (528). Intensified studies, from epidemiology to membrane analyses, are certainly justified because they may reveal additional important relations among genetic factors, environmental influences, intermediary metabolism, and cardiovascular function. This might uncover new preventive measures for predisposed individuals in nutrition, salt, psychosocial factors, exercise, etc., more suited to lifelong perspectives than pharmacologic agents only. In any case weight loss fairly regularly leads to blood pressure reduction in early primary hypertension, but it is not known in which roundabout ways it acts. An action via a concomitant reduction in salt intake has been suggested (139, 140) but is refuted by the fact that weight loss with maintained salt intake seems equally effective (535).

Compared with blood pressure in industrialized societies, blood pressure is often lower and more constant with age in cultures with habitually low intake of salt (156, 485, 502, 576) and with traditional, somewhat tribal ways of life with close family links and stability in values and occupations (307, 309). When such populations encounter the mixed blessings of Western civilization, pressure levels soon seem to approach those in the West. If this can be established beyond doubt, two important conclusions will emerge: the genetic predisposition to primary hypertension in humans is usually more or less latent, and environmental influences must be considered more often to act as precipitators rather than facilitating modulators of the gradual pressure rise. The question then is whether it is raised salt intake, increasing psychoemotional stimulation, or both—or perhaps something else again?

Unfortunately such confrontation with a new environment usually leads both to increased salt intake and to fundamental changes of mental climate, because traditional habits and value codes are commonly torn to pieces in the process. This often implies a nearly perpetual emotional strain or at least a wealth of new impressions from the more hectic and multifaceted Western life-style. It is therefore difficult from such surveys to judge the relative contribution of either environmental influence. However, it seems safe to conclude that both can influence the frequency and severity of human primary hypertension, provided that the appropriate balance of predisposing elements exists. This has been directly demonstrated in the different strains of rat primary hypertension (sect. 11C2e, 3c). Moreover these two environ-
mental elements may well reinforce each other. Thus excitatory psycho-
emotional expressions involve both neurogenic and hormonal components
facilitating renal sodium retention (sect. IIIE2b), and water-salt retention
may accentuate nervous as well as smooth muscle responsiveness (sect.
III E4, F).

2. Salt intake

a) Normal salt balance. The organism's content and concentration of
sodium chloride, the "electrolyte skeleton" of extracellular and plasma fluids
and a major component in electrochemical membrane events, is precisely
secured by a powerful central control. Intake, distribution, and loss are
closely regulated by complex neurohormonal links (12, 13, 36, 62, 71, 154, 197,
240), where the excretory adjustments depend on neurogenic influences an-
tidiuretic hormone (ADH), aldosterone, the putative natriuretic hormone
(sect. III E4), and local renal controls (sect. IIIF).

The craving for salt and the nearly abolished urinary losses of NaCl
during salt deprivation are vivid expressions of the sensitive and at the same
time powerful central control. For centuries salt hunger has made people
in areas with poor salt access pay almost any price for it. Salt hunger in
animals, particularly herbivores, causes behavior ensuring a sufficient so-
dium chloride content, even with minimal access to salt in their habitual
environment (154, 155). On a fishing expedition in the Norwegian mountains,
I once woke up to the bleating of hundreds of sheep, arriving from nowhere
in a district where one could walk for hours without seeing any. They crowded
around the hut to lick an accidental spillover of salt solution for fish pres-
ervation. How they got the message is beyond comprehension, but the in-
cident illustrates a remarkable ability to find salt.

This craving for salt is but one expression of a most efficient homeostatic
mechanism, buffering against both abuse and potential deficiency, with its
risks for cardiovascular collapse on sweating, accidental bleeding, vomiting,
or diarrhea. Most mammals seem well equipped for salt-poor environments,
which is particularly important for herbivores because plants are poor in
sodium, whereas carnivores enjoy what is present in herbivores. Likewise
our ancestors—with a semitropical origin, major foods probably derived from
plants, and sweat losses to cope with—must have been well adapted to salt
depredation and also equipped with strong drives to ensure salt intake. Such
basic genetic equipment in all likelihood has not changed much during mil-
lions of years (154).

b) Salt intake in modern society. High salt intake is hardly any ultra-
modern addition to potential human miseries, because coastal populations
have been exposed to it for centuries. Heavy salting was one of the few early
methods of preservation for meat and fish, which must often have caused
impressive volume expansions when balanced by equivalent amounts of beer.
There are no records of hypertension from these early times, but stroke apparently was common, at least among those enjoying affluent consumption. Modern society, however, has made salt so easily accessible that intake throughout entire populations may sometimes border on what some proponents of the "salt danger" would call abuse (154, 215, 455, 460). It is further suggested that this high intake may reset central receptors from early childhood so that a relative "salt addiction" ensues (155, 156, 215).

Several population surveys propose a close correlation between salt intake and blood pressure levels (139, 140, 215, 455, 460, 502) but correct interpretation of the really complex data is exceedingly difficult. Thus in his very careful analysis of available data Simpson (584) concludes that the combined evidence does not suggest any correlation between salt intake and blood pressure, though, e.g., Freis (215) and Morgan et al. (460) are of different opinions. In fact seldom in research have opinions clashed so much and the debate been so intense, sometimes even with evangelic overtones. Both sides in the battle muster outstanding authorities, with advocates for salt restriction like Dahl (140), Page (502), Freis (215), Tobian (629), Denton (155), Morgan et al. (460) and Weinsier (663), with the skeptics represented by experts like Pickering (523), Simpson (584), Swales (607), Paul (507), or the Framingham group (149).

Actually the problem boils down to two questions, and both sides might in fact prove correct, with the skeptics right about the first and the proponents, to some extent, right about the second. 1) Is high salt intake a potential hypertension risk for the population at large, independently of genetics? 2) Do populations contain genetic subgroups in which high salt intake precipitates, or at least greatly facilitates, primary hypertension? If so, are these groups large enough to justify generalized restriction? The skeptics would probably be inclined to say no to the second part of this question, particularly in view of the answer to the first question. Parallels to rats may be helpful here since they illustrate two things. 1) Only a minority of rats have a substantial genetic predisposition for primary hypertension (before forced breeding started). 2) In this minority the initiation of hypertension is fairly independent of salt in GHR and SHR (21, 210, 264, 416), whereas in HSR it is the crucial element (141, 142, 376) and in stroke-prone SHR (160) it can reinforce the pressure rise, though hypertension here mainly depends on other genetic elements (689).

Unfortunately the corresponding relative proportions in humans are unknown, but the handling of the situation of course would be entirely different if, say, 20–30% prove to be salt sensitive rather than only 2–3%. Much work is needed to clarify this important issue; whatever the answer, however, extreme attitudes and measures hardly offer tenable solutions. For example, it would be an abuse against a salt-resistant majority to advocate the trifle of salt intake that can be biologically tolerated, not to mention that it would be psychologically and socially untenable. Furthermore it is debatable whether such very low intakes are even physiologically optimal, when all...
potential health risks are considered. True enough, at the upper end of the intake spectrum, hypertension may lurk for some people, but at the lower end cardiovascular collapse might threaten anyone with otherwise trivial losses from sweating, vomiting, etc. The most evil of the two is a matter of prejudice, but the best choice may be in the middle, between Scylla and Charybdis. Enthusiasts for the low incidence of hypertension in salt-poor environments seldom discuss relative death rates in gastrointestinal infections or other accidental salt-fluid losses.

Therefore at present it seems reasonable to have some faith in "The Wisdom of the Body," to cite Cannon, and individually follow the advice of the central receptors, except perhaps if family histories indicate massive predisposition for hypertension, in which case medical advice may also be helpful. There are reasons to exercise balanced caution in matters influencing entire populations, as in industrial processing of foodstuffs, particularly for children. Meanwhile intensified research by population surveys and new tests to identify high-risk families might gradually find those whose salt intake is a risk and leave the rest in peace with their eating and cooking habits with, at most, mild constraints (cf. sect. IIIE4, F).

c) Inherent salt sensitivity. The preceding considerations thus make it likely that at least some subgroups among human hypertensives have a genetic predisposition in which high salt intake can facilitate or sometimes even precipitate a pressure rise. The key problems are how common such variants are, how to identify them early, which signs to choose, and, finally, how increased salt intake induces the pressure elevation.

Of course, excesses of anything—including plain water—can have detrimental effects, but in genetically normotensive humans very little happens to blood pressure even if ordinary salt intake is increased to 20–25 g/day (375, 420, 603), although blacks might be slightly more sensitive than whites (420). This is way above ordinary habitual intakes, except perhaps in northern Japan (140, 215), and the results suggest that the volume expansions with consequent CO elevations are efficiently offset mainly by pronounced reflex sympathohormonal inhibition, reducing resistance proportionally (420, 603) and favoring renal salt excretion (sect. IIIF). With a genetic predisposition for primary hypertension, however, at least a fraction of these individuals are more sensitive, since roughly a doubling of habitual salt intake leads to a significant average rise in pressure for the group (187, 420, 433). Also the consequent slight CO increase seems, on average, to be less well offset at the resistance level (603). Even an increased regional resistance, where neurogenic elements may be responsible (sect. III D, E4), can be seen (433). It would be of great interest to know whether this is so for virtually all individuals genetically predisposed to hypertension or whether wide differences also occur, as when comparing HSR with SHR or GHR. This calls for further explorations of the range of differences in both normotensives and hypertensives, not only of the average differences between groups.
Thus again parallels to rats may help illustrate these principles. The hypertension-prone HSR can no doubt be provoked to severe hypertension by salt loading (139, 141). It should be stressed, however, that this calls for enormous salt amounts compared with ordinary food intake, relatively far higher than encountered in humans, though differences in species, metabolic rate, and in time axis must also be taken into account. In HSR a major part of the predisposition is kidney-bound, as shown by cross-transplantation experiments (142), though the mineralocorticoid control also seems to be involved (531), and no doubt the renal handling of salt here is the Achilles heel. The same seems to be true in MHS, judged from renal cross-transplantation studies (58), though no extra salt is needed for induction of their mild volume hypertension. According to the thorough analysis by Dietz et al. (160), the stroke-prone variant of SHR, developed by Okamoto (484) and Yamori (689), represents another type of salt sensitivity added to a genetic predisposition otherwise similar to SHR. As mentioned, SHR and GHR are not particularly salt sensitive in early phases. When exposed to salt excess, HRR and HSR respond largely like normotensive and hypertensive humans: both increase CO, but with a compensatory resistance reduction in HRR and resistance increase in HSR (233), perhaps at least in part on a hormonal-neurogenic basis (609), as further discussed in section III\textit{F}.

In strictly salt-dependent, HSR-like variants of human primary hypertension, early phases should have, besides at least a trend toward sodium volume expansion, a compensatory reduction of renin release that also characterizes HSR and MHS. Such variants are possibly more common among blacks than whites (118, 247, 418, 575), again pointing to a whole spectrum of genetic variants in human hypertension, with ample reasons for great caution about generalizations from mean values of samples with a wide spread. It is of course far more difficult to study the early development of primary hypertension in humans, where screening must be based on some reasonably simple tests, but some insight may be provided by, e.g., renin levels and volume balance in groups with early hypertension under controlled sodium intake. As further discussed in section III\textit{B}, however, blood and extracellular volumes are then commonly in the lower normal range, and low-renin hypertension makes up only about one-fourth of the entire hypertensive population. Furthermore most of this group seems to represent advanced stages of primary hypertension in which the initiating mechanisms may have little to do with salt-volume induction (sect. III\textit{B2}).

For such reasons close human parallels to the HSR or MHS variants may account for only a modest fraction of human primary hypertension. However, with a far more mixed genetic makeup in human than in rat primary hypertension, genetic elements of primary renal salt sensitivity may be mixed with others that dominate the scene in early phases. Furthermore salt loading might exert pressor effects that are not necessarily due to renal abnormalities (sect. III\textit{E4}, F\textit{)} Therefore the frequency, relative potency, and
nature of salt sensitivity in humans may be more a gradual deviation than an either/or matter, thus being far more difficult to define and determine. Nevertheless individuals with a dominance for salt sensitivity are likely to constitute a minority only, though further explorations are certainly needed, with analyses of sensitivity differences within groups, etc.

The effects of substantial salt restriction on established hypertension may also illuminate the situation, though such results alone hardly tell how often salt is a critical inducing element. According to most earlier studies (521), roughly one-third show substantial MAP reduction on salt restriction, though this restriction must usually be so severe as to make life miserable. There is little cause for considering them all to be chronic salt abusers. Rather, studies of the salt turnover in untreated primary hypertension suggest that habitual intake, perhaps via an adapted salt appetite, becomes reduced once kidney function begins to deteriorate (48). However, other findings suggest that hypertensives might use more salt than normotensives (564) and also that even modest salt restrictions may be beneficial (460, 505). Such apparently contradictory results may again reflect how human primary hypertension contains a spectrum of genetic variants, where the salt-sensitive ones for social and geographic reasons may be more common in some regions, and also that different stages may respond differently to salt. Furthermore investigators particularly interested in, say, the influence of salt intake, or that of psychosocial factors, may especially note their respective impacts, since both are relevant if a suitable predisposition is present.

It is hardly a contradiction regarding the frequency of salt-provoked primary hypertension that diuretics are often a blessing in treatment, lowering MAP in well over half the cases (273, 408, 551). The fact that, e.g., sympathetic blockage in almost everyone lowers MAP even more certainly does not mean that increased neurogenic activity is always an important etiological element in human primary hypertension.

d) Concluding remarks. The available data seem to suggest that sodium chloride should be considered an important permissive, sometimes clearly facilitating, element in human primary hypertension, rather than as a common initiator. Initiation by salt intake should mainly occur in the apparently fairly rare variants of human genetic predisposition related to that of HSR. Those more related to the SHR or GHR predispositions should depend little on increased salt intake. However, pure genetic variants, like those in the inbred rat strains, are probably uncommon in humans compared with a variety of combinations. Therefore inherent salt sensitivity in humans may vary over a wide range, rather than being an either/or phenomenon. Thus this element may also be polygenetically linked, like primary hypertension in general. Exactly how increased salt intake exerts its actions in hypertension is poorly understood, but it probably involves several partly very intricate and indirect mechanisms (sect. III F2, F). It is almost certainly far more complex than the mere effects of volume expansion on general hemodynamics (sect. III B3).
3. Psychoemotional influences

a) General aspects. The great variability in sympathetic discharge in daily life, revealed by continuous MAP recordings in normotensive and hypertensive subjects, reflects a diurnal rhythm in excitability of limbic-hypothalamic-bulbar autonomic centers, with a high responsiveness also to environmental stimuli. Thus during sleep the MAP level is often so low as to indicate a virtual cessation of sympathetic discharge. Toward morning pressure again rises, with a peak during early parts of the day, again usually subsiding slowly (51, 457, 523, 592). This basic pattern is superimposed by, e.g., psychoemotional exacerbations with proper environmental stimuli, which can more than double MAP compared with that during deep sleep (523). Tonic sympathetic discharge generally reflects closely the degree of alertness and mental engagement, then often overswaying the reflex homeostasis, which in humans is most readily traced by the consequent changes in resting heart rate.

Continuous MAP and heart rate recordings are thus of great interest not only because they reveal the rhythm in autonomic discharge, but also because they reflect the magnitude, duration, and frequency of superimposed psychoemotional exacerbations, as well as the extent to which they elevate average MAP during an individual’s ordinary life. Clearly it must be this average daily pressure load, rather than the resting pressure, that is of pathogenetic importance, a fact often disregarded.

The human sociocultural environment, after the technical revolution characterized by an increasingly hectic psychological climate and a dwindling use of the somatomotor system, can no doubt influence the mental equilibrium. Genetics and constitution, earlier experiences, etc. also play an important role here, so that some individuals more than others experience their environment as irritating, frustrating, or unduly exciting and neurohormonally respond accordingly. However, the complex and individual human mind makes it exceedingly difficult to prove whether such interactions between personality characteristics and environmental elements really can alone precipitate primary hypertension via psychoemotional cardiovascular reactions (120, 144, 275, 296, 307, 309, 662). Although still difficult, the situation is more readily handled in animals because of their simpler neocortical function and a controllable environment. Interesting animal results have emerged in recent years that have great relevance for the human situation.

b) Normal responses to environmental stimuli. Confronted by stressful environmental stimuli, the ancient “emotional brain” engages the most appropriate among the several limbic-hypothalamic patterns for emotional expression (180, 201, 202, 318, 319, 320, 381, 695, 697, 698). Organized millions of years ago to cope with the harsh realities of primitive life, these patterns are virtually identical in humans and animals. They affect the entire or-
ganism via specific combinations of somatomotor, autonomic, and hormonal adjustments, securing maximal efficiency in danger (201, 318, 695, 697, 698).

I) UNIQUE HUMAN SITUATION. These ancient patterns of response are often inappropriate, however, for facing the sophisticated challenges, symbolic threats, and frequent arousals typical of human life in modern society. Unfortunately the emotional brain has no modernized modes of expression to offer, and the individual instead uses whatever neocortical coping mechanisms he or she may have developed.

Civilized humans are unique among species on yet another point, namely, how these ancient patterns for protection of self and species are displayed, and again this depends on a highly developed neocortex. If coping fails, social considerations force suppression of at least the more spectacular somatomotor expressions of induced emotional patterns: sudden attack or flight is seldom considered proper.

Milder variants of the defense reaction (201, 318, 695, 697, 698) are particularly common during increased attention and the symbolic confrontations of civilized life, even when experienced as pleasant and stimulating, which is most important to keep in mind. Too often central excitations of the cardiovascular system have been mistakenly supposed to occur only during negative emotions, like anger, fear, and resentment, where the term defense reaction has been taken too literally. However, these reactions are as readily induced in humans engaged in amusing but thrilling games (635) as when bullied during “forced mental arithmetic” (87, 91, 188). In fact evidence, particularly from interesting studies in awake, freely moving animals by, e.g., Hilton (318, 319) and Zanchetti et al. (697, 698), indicates marginal engagements of this pattern whenever the organism is alerted and mentally engaged to the slightest degree by the environment. This is also clear from direct continuous recordings of sympathetic activity, heart rate, and blood pressure in awake humans by Wallin et al. (643–645) and in freely moving, awake rats by Thorén and co-workers (211, 538). The stronger the arousal and emotional engagement, the more vivid the efferent expressions, though the urge for flight or attack usually remains suppressed in humans in unpleasant situations. Unfortunately the associated autonomic and hormonal adjustments meant to support such exertions cannot be suppressed and thus occur in vain.

Such enforced differentiation of normal emotional patterns, though a relief for the antagonist, may in the long run be a mixed blessing, perhaps even a health risk if often repeated. For example, emotional tension is no longer as readily defused but may be transformed into sustained irritation, resentment, or frustration, thereby also prolonging the associated neurohormonal adjustments of circulation, renal, and gastrointestinal functions and of metabolism (204, 211, 309). Furthermore the suppressed exertion also excludes exercise vasodilatation, which otherwise offsets the neurogenic pressor effects, and the neurohormonal release from nutritional depots is not as readily burnt off. In such situations substitute physical activities of
a less aggressive nature may serve as healthy antidotes, as probably many have experienced.

II) ORGANIZATION OF DEFENSE REACTION. Since the cardiovascular system can be so markedly and frequently engaged by environmentally induced defense reactions, the ensuing adjustments are outlined here in some detail. They include cardiac stimulation via enhanced sympathetic discharge and reduced vagal tone associated with neurogenic constriction of capacitance and most resistance vessels, except in skeletal muscle, myocardium, and brain, where instead neurogenic and/or hormonal-metabolic vasodilation occurs (180, 201, 202, 318, 319, 695, 697, 698). As a result CO increases, favoring muscles and brain during a somewhat elevated MAP, thus transforming within seconds resting circulation into a heart-muscle-brain perfusion, of greatest advantage if attack or flight ensues. The events are exactly the same in humans as in animals, as elegantly shown by Brod et al. (87, 91) in their extensive studies during “forced mental arithmetic.”

The buffering cardiac reflexes from baroreceptors and cardiac receptors are largely extinguished by the limbic-hypothalamic discharge via bulbar neuronal “occlusion” (206, 318, 319, 619) but not so the reflex vascular influences. Therefore tachycardia always occurs even in very mild defense reactions, making it a reliable sign of mental arousal in man. Direct recordings in awake, alert rats have shown surprisingly parallel changes in heart rate and in sympathetic discharge to, e.g., the splanchnic-renal regions (211). Such differentiated interactions between central excitatory and reflex inhibitory patterns make them in fact hemodynamically synergistic, by further enhancing muscle flow at attenuated cardiac afterload increase, thus providing more favorable adjustments than the central pattern alone (206).

Note, however, that the balance between vasodilatation, vasoconstriction, and CO increase in the defense reaction can vary much between individuals, with the situation, and even with the phase of the response. Thus the MAP increase is sometimes modest, sometimes marked, and the neurogenic CO increase can also vary considerably, both in animals (206, 697, 698) and in humans, judged from recordings during forced mental arithmetic (15, 87, 91). On the other hand, pulmonary arterial pressure is little affected even by intense defense reactions, probably because the vasoconstrictor fibers in the lungs preferentially influence pre- and postcapillary capacitance sections, with little effect on true resistance vessels (204, 206).

Hormonal responses in the defense reaction are no less impressive (204, 206, 695), causing enhanced release of epinephrine, of adrenocorticotropin (ACTH) and hence of glucocorticoids and the mineralocorticoid 18-hydroxycorticosterone (18-OHDOC), of ADH, and of renin-angiotensin-aldosterone via the renal sympathetic supply. Besides restricting renal blood flow, these latter fibers increase renin release and also facilitate tubular sodium uptake directly (70, 159, 258, 695). These hormonal links cause release from nutritional stores in skeletal muscle, liver, and fat tissues, enhance blood coagulability, reduce renal losses of water and salt, and may even
enhance their net uptake from the gastrointestinal tract (97), where otherwise most activities are suppressed via sympathetic neurogenic inhibition of the intramural cholinergic neurons. On the whole the entire cellular environment is altered by this all-out mobilization against external threat; when frequently engaged, such central patterns might seriously affect cardiovascular homeostasis also through hormonal links.

Those components of this psychogenic response pattern that increase the sodium chloride contents provide an important link with the other major environmental factor, the salt intake, with opportunities for mutual reinforcement. Here the neurogenic renin release is of special interest, also because its measurement provides one of the few tools available for large-scale examinations of humans and because, if properly used, it may reflect both neurohormonal and renal events (137, 183, 363, 396). However, defense reactions also lead to accentuated activity in unmyelinated cardiac volume receptor afferents, partly by neurohormonal inotropic stimulation and partly by enhanced cardiac filling consequent to the nervous capacitance response (206, 619). The ensuing reflex cardiac inhibition is, however, centrally suppressed, but the reflex vascular effects are not (206, 619), in analogy to the baroreceptor reflexes. These cardiac afferents particularly inhibit sympathetic activity to the kidneys (4, 164, 538, 619) and may therefore reflexly damp also the renin-angiotensin-aldosterone release in proportion to the current balance between central excitatory drive and reflex inhibitory discharge. Observations on renin release in neurogenic variants of human borderline hypertension (sect. III B3) may be interpreted along such lines, since prevailing signs of enhanced sympathetic activity, such as elevated heart rate, are not accompanied by increased renin levels if central blood volume is enhanced (183, 373).

c) Environmental stress and hypertension in animal experiments. Model experiments on animals exposed to direct stimulation of the defense area (204, 695) or to environmental stimuli that elicit psychoemotional pressor responses (212, 308, 310–312, 697, 698) help to illustrate what may occur in humans. When frequently repeated over sufficient periods, such stimuli can lead to modest hypertension in genetically normotensive animals (204, 212, 308, 310–312). The pressor influence should be emphasized, because some environmental stimuli elicit response patterns in which MAP is unaffected or even reduced (204, 206, 695), and of course such stimuli are unlikely to provoke hypertension.

Of particular interest are the experiments on mice populations by Henry and co-workers (308–311), where changes in behavior and cardiovascular and hormonal functions were studied over a life-span while well-defined environmental disturbances were introduced in these microsocieties. Although animal studies have often meant abnormal and severe stress, Henry's group utilized more ordinary stimuli, as in crowded, competitive societies with frequent confrontations, thereby better mimicking humans in modern life. Hypertension associated with cardiac hypertrophy gradually developed in
particularly exposed animals, followed by cardiac and renal lesions. The influence of heredity was also demonstrated, since some strains were particularly apt to develop hypertension. These interesting studies represent a unique and outstanding contribution to hypertension research and deserve far more attention than they have had.

However, the importance of the mental environment becomes particularly obvious in animals genetically predisposed to hypertension in terms of a central nervous system (CNS) “hyperreactivity” to environmental stimuli, like SHR (204, 211, 290, 483), but not in HSR (216) or MHS (291). Hypertension in SHR is greatly aggravated by mental stress (483), whereas deprivation of ordinary social contacts and confrontations attenuates the MAP rise (289). Light deprivation has similar consequences (389). Such experiments amply illustrate the close interaction between genetics and environment in the SHR variant of primary hypertension, where psychosocial factors are obviously important.

In a way this is a parallel to the interaction between salt loading and predisposition in HSR, which is genetically sensitive to increases in salt loading but little influenced by emotional stress (216). As in genetically normotensive animals, however, this may instead be a matter of degree and nature of psychoemotional stimuli, because severe conflict situations produce considerable MAP elevations also in HSR but less in their salt-resistant cousins HRR (216). Considering the particular genetic predisposition in HSR, this might be at least partly due to the increased ACTH release accompanying defense reactions. Furthermore a specific aldosterone-stimulating factor has recently been demonstrated (571) and might also be engaged from higher centers. In addition to the neurogenic cardiovascular and renal influences, these hypophyseal hormones would release more of the already elevated 18-OHDOC secretion in HSR (531) and also aldosterone, thus perhaps further accentuating the tendency to salt retention and helping to precipitate hypertension.

d) Involvement in human primary hypertension. Milder variants of the defense reaction in response to common environmental stimuli may occur so often and affect the cardiovascular system in so many ways, as outlined above, that its role also in human primary hypertension deserves serious exploration. In this CNS-induced pattern, endocrinologists may prefer the hormonal changes, nephrologists the altered renal handling of salt, and experts on autonomic control the neurogenic MAP increases. All have a point, but the pressor bouts are of special interest, if elicited frequently enough to enhance the average load on heart and vessels in daily life. This alone would probably be of little consequence, but the exposed cardiovascular sections also show structural adaptation with hemodynamic consequences, as outlined in section II D.

Skeptics often argue, however, that the frequent occurrence of primary hypertension in the industrial world can hardly be related to psychogenic pressor reactions, because primitive societies would then be even worse off
with more drastic and dangerous confrontations. This disregards the fact that such reactions in humans are as readily induced by the symbolic challenges and sophisticated thrills that modern life so abundantly offers. Moreover even in primitive cultures overt dangers are usually infrequent and then are eliminated by appropriate physical exertions, whereas the environment in other respects hardly implies risks for mental overstimulation because of tradition-bound habits and close tribal links.

In contrast, modern society often provides such a stream of alerting psychosocial and psychophysical stimuli, where noise is a common nuisance (16), that the ancient defense reaction may be mildly turned on in predisposed individuals most of their awake time. Anyone familiar with the dramatic cardiovascular reactions in forced mental arithmetic tests (87, 91, 323) or during more pleasant thrills (635) is hardly surprised that even trivial daily challenges and irritations may induce substantial neurogenic increases in MAP and heart rate. When such hemodynamic episodes are checked against the elegant electrophysiological recordings of regional sympathetic discharge in humans by Wallin and co-workers (643-645), the correlation is, as expected, close. The essentials of these central autonomic patterns can be easily traced by the psychogenic MAP and heart rate increases alone, however, since they regularly run together. This technique was recently utilized by Falkner, Onesti, et al. (188) in youngsters from families predisposed to primary hypertension; like SHR (290), most displayed exaggerated defense reactions in this case to forced mental arithmetic compared with controls. This important observation is discussed further in section \( \text{III} \text{B}3b, \ D. \)

The balance between CO increase and resistance change in this psychogenic pressor pattern may vary widely, but when the CO increase is prominent it is the pressor effect that really matters. However, this response pattern is often misinterpreted to mean that the CO increase per se should somehow invite hypertension. This misunderstood concept is then dismissed, based on parallels to the well-known fact that even greater CO increases, as in ordinary exercise, thyrotoxicosis, etc., do not lead to hypertension. Of course the reason is that such CO increases are so well balanced by reductions in metabolic resistance that daily average MAP remains normal. In contrast, defense reactions are pressor responses with associated CO increases that, on frequent repetition, may substantially elevate the average daily load on heart and vessels. Such elevations, even if they are marginal but continue over longer periods, may start the ball rolling, as discussed in section \( \text{III} \text{D}8. \)

Should sudden exertions ensue in defense reactions instead, the consequent metabolic vasodilatation tends to curtail the pressor bouts and may also help shorten the neurohormonal discharge by defusing the mental charge. Therefore habitual exercise might actually damp long-term consequences of frequently repeated engagements of the defense reaction during circumstances where social considerations demand suppression of the component of physical engagement. In fact exercise programs in early neurogenic variants of primary hypertension have been reported as beneficial (80, 117, 406). These questions are discussed further in section \( \text{III} \text{B}3b, \ D. \)
D. Structural Cardiovascular Adaptation

1. General aspects

Even before reliable pressure recordings in humans were available, it was known (sect. 1B) that heart, systemic arteries, and arterioles exhibit wall hypertrophy in hypertension. Remarkably, for nearly a century few attempts were made to explore whether these, the most palpable of all changes in hypertension, were important for the pressure rise and maintenance, particularly when contrasted to the immense efforts spent on vasoactive agents. Not even the recent encyclopedic *Hypertension* (241), with nearly 100 chapters and about a dozen on the renin-angiotensin system alone, devotes a single chapter specifically to structural cardiovascular changes.

This is surprising because a few moments of consideration should make it clear to anyone that an altered function must ensue when an increased muscle bulk enwraps a lumen. Comparisons of thick-walled arteries with thin-walled veins, of the systemic circuit with the pulmonary one, and of the left ventricle with the right one amply illustrate this simple fact in the normal circulation. Nevertheless relationships between cardiovascular design and function have been badly neglected in both hypertension and ordinary cardiovascular research. Therefore I cover them here perhaps more thoroughly than other elements, particularly because they influence hemodynamics so markedly and because hypertension is after all a hemodynamic disturbance, which is sometimes forgotten among other subspecialities.

2. Normotensive state

a) Principal relationships between design and function. The cardiovascular system is primarily structured to suit tissue nutritional demands, as reflected in cardiac pumping capacity, maximal flow conductance (or minimal resistance, $R_{\text{min}}$), and capillary exchange surface and network density. Cardiac work establishes the driving pressure head for flow, $P_A - P_V$, but pressure also exerts a distending force on vascular walls. Therefore their thickness ($w$) must be dimensioned both to regional transmural pressure ($P$) and tube dimension (or internal radius, $r_i$), if tension per unit wall layer ('T') remains constant according to the modified Laplace's law: $T = (P \cdot r_i)/w$. As long as $P$ remains constant, $w/r_i$ can be kept unchanged independent of bore, but if $P$ is raised, $w/r_i$ must also increase, and vice versa, for balance to prevail. Clearly all components in this relationship must be known to fully understand how blood vessels function (104). Furthermore vascular walls are also distensible, the distensibility varying with both design and degree of media activity (200, 203, 205, 207, 297). Since distension increases $r_i$ but decreases $w$, it greatly influences both $w/r_i$ and $T$, with important functional consequences (205, 207, 297).

In the small pre- and postcapillary vessels where the hemodynamic im-
The importance of the structural $w/r_i$ relationship is particularly great, it is also exceedingly difficult to measure, however, which helps to explain why its functional consequences had been largely neglected in hypertension research until recently. The difficulty lies in the fact that both $r_i$ and $w$ change considerably, but in opposite directions, with even modest shifts in smooth muscle activity and also with pressure changes because of wall distensibility. Design comparisons between vessels are of course meaningless if both are not equal and constant. It therefore is not surprising that exact $w/r_i$ estimations along the microvascular arborizations in humans became available only recently, thanks to ingenious techniques for standardization of variables (221, 231, 465, 579–581, 605).

For the systemic precapillary section such measurements show an increasing $w/r_i$ toward the small resistance vessels, despite a decreasing transmural pressure, with the highest $w/r_i$ at arteriolar-metarteriolar levels. Thus in normotensive vascular beds at complete media relaxation and appropriate wall stretch, $w/r_i$ is $\sim 0.1$ in small conduit arteries but increases toward 0.2–0.25 in the smallest precapillary resistance vessels even though pressure is lower here (231, 537, 605). This suggests a physiological specialization beyond purely physical demands, which the wall composition also reveals. Thus, while Windkessel vascular walls have many elastic fibrils to transform the rhythmic input into a more even outflow, the relatively thicker walls in the precapillary resistance section are dominated by the muscle coat (104, 537). This high $w/r_i$ is of great advantage for controlling flow, hence also resistance and MAP, for the following reasons.

The vasoconstrictor-fiber control, superimposed on a basically myogenic precapillary tone to allow remote adjustments (200, 201, 203, 350, 447), is exerted via the adventitial muscle layer only, where all neuroeffector junctions are localized (103, 410), probably activating inner layers by myogenic spread of excitation (410). At intense constrictions of the outer layer, however, the inner ones may even become unloaded, at least if pressure is not simultaneously increased (647, 648). Obviously the wall mass is pushed inward on contraction, thereby amplifying the luminal narrowing in proportion to the initial $w/r_i$ ratio. In addition both flow and resistance changes are amplified to the fourth power of the $r_i$ shift, according to Poiseuille’s law.

Some arbitrary examples from skeletal muscle illustrate these hemodynamically advantageous relationships. An average $w/r_i$ around $1/4$ in the small precapillary resistance vessels at maximal dilatation means a wall thickness of only 5 µm at an inner diameter of, say, 40 µm, but it has remarkable consequences. Thus, whereas muscle blood flow in humans averages 50 ml·100 g$^{-1}$·min$^{-1}$ at maximal dilatation, resting flow is 3–4 ml because of neurogenic-myogenic vascular tone. This 15-fold difference in flow would call for less than 30% shortening of the outer media sheath, and a 35% shortening would reduce flow about 50-fold, as occurs during intense reflex constriction. In the thicker-walled cutaneous arteriovenous (AV) shunts it would take even less contraction to stop flow; this is neurogenically accom-
plished in these specialized vessels during thermoregulation at very low rates of sympathetic discharge (201, 447).

The situation is very different in venous capacitance vessels: with a \( w/ri \) as low as 1/30-1/40, the impact of \( w \) on \( ri \) is negligible. Therefore a 35% muscle shortening produces only a fivefold resistance increase, or about 10% of the precapillary one. It is therefore of minor relevance for total resistance but of far more consequence as the denominator in the precapillary-to-postcapillary resistance ratio, because this ratio determines capillary pressure and hence intra- and extravascular fluid exchange (206, 447). However, for capacitance response it means a mobilization of almost half the voluminous contents, which for cardiac filling and overall circulation is very important. Average capacitance responses actually seldom surpass a 40% emptying, including passive-elastic recoil and luminal semicollapse (447), which implies fairly modest neurogenic shortenings of venous smooth muscle in vivo.

These comparisons illustrate the great hemodynamic importance of vascular \( w/ri \) relationships for normal cardiovascular control. Thus a high \( w/ri \) ratio is used by the precapillary resistance vessels as an "amplifying lever," allowing drastic adjustments of flow and resistance by only modest changes in muscle length. In fact normal reflex control of precapillary muscle cells must occur with a precision of \( \pm 1\% \) change in average length, if resting MAP variability should not exceed \( \pm 5\% \).

b) Structural adjustments in normotension. Biologic structure in general is far from static, and in normotension also cardiovascular design adjusts continuously to current demands. Examples are legion, perhaps the most obvious those during wound healing or the rapid collateral development on arterial occlusion (259, 409).

The bore of resistance vessels adapts rapidly to sustained alterations in nutritional demands or blood oxygenation. Thus when training leads to skeletal muscle hypertrophy, both maximal flow capacity and capillary exchange surface per unit tissue increase proportionally. Further, when altered activity patterns in rats transform phasic muscles into tonic ones, the corresponding vascular bed is redesigned for the new demands within 1 or 2 wk (332, 468).

Vascular walls, on the other hand, adjust their structure primarily to current wall tension with thickening if lumen and/or local pressure increases, and vice versa. An extreme example is provided by giraffes, where arterial pressures at cranial and at foot levels may differ by some 400 mmHg (when erect) due to the immense difference in hydrostatic pressure. The arteries are designed accordingly, with fairly ordinary \( w/ri \) in cranial vessels but with immense \( w/ri \) increases in those of the lower limbs (253). Another example also illustrates the speed of adaptation. The high pressure in the pulmonary circulation during fetal life is associated with a thick arterial media, but when pressure promptly falls on birth, rapid regression to postnatal wall dimensions ensues. The design of limb veins offers another ex-
ample. In small children venous \( w/r \) ratios are similar in arms and legs, but when the erect position becomes habitual \( w/r \) in dependent veins increases in proportion to the rise in transmural pressure (388, 608). Note that this structural adaptation occurs even though the increased pressure load is intermittently applied, being absent during the considerable part of each day spent in the reclining position. Finally, distal to arterial obstructions the arterial-arteriolar walls become thinner in relation to \( r \) (409, 585), whereas a rapid and impressive wall thickening occurs in veins used surgically as arterial bypasses.

Thus cardiovascular design allows swift and precise adaptation to new demands, and even if the detailed events are insufficiently understood, the results are only too obvious. In fact biochemical, functional, and structural changes are but different facets of biological adaptation, differing mainly in speed. A muscle can, of course, cope with increased load far more rapidly by intensified contraction than by adding more actomyosin, but this latter process can also be rapid and is usually more appropriate in the long run. This also applies to wall thickening in hypertensive states; far from being a late complication, as once widely assumed, it is so rapid that its often slow appearance in primary hypertension rather reflects the insidious engagement of triggering functional elements, as outlined next.

3. Structural adaptation in primary hypertension

a) Studies in humans. Because of the considerations just discussed, some decades ago I became interested in the functional consequences of precapillary media thickening in hypertension, known since George Johnson's days but surprisingly neglected in its hemodynamic relevance. My interest was further triggered by studies of distensibility, inherent tone, autoregulation, and nervous control in normotensive resistance vessels, because these results and techniques could be applied to hypertension (205).

Experiments were therefore designed to compare forearm resistance in hypertensive and normotensive subjects during both rest \( (R) \) and maximal vasodilatation \( (R_{min}) \) (200, 209). Any accentuation of tonic vascular smooth muscle activity in hypertension would then show up as an increased \( R/R_{min} \) ratio, like activity levels in vessel strips that are commonly judged by the ratio between contracted and fully relaxed lengths (or tensions). However, this hemodynamic approach has many advantages that, e.g., vessel strips cannot provide, and it is described in some detail because its advantages are often overlooked.

First, \( r \) changes are amplified to the fourth power according to Poiseuille's law, greatly improving measurement sensitivity and amplifying changes in average muscle length even more because of the high \( w/r \) ratio. Thus a 5% average \( r \) reduction—nearly impossible to get precisely in morphometric estimations because only segments of the vasculature are sam-
pled—implies a 20–25% increase in R, which is easy to measure and of great hemodynamic relevance. Second, R measurements reflect precisely those microvessels responsible for flow resistance, whereas excised strips represent at best their proximal parts only and at worst merely conduit arteries or veins that both in structure and smooth muscle are specialized for other purposes. Third, hemodynamic R estimations automatically average the \( r_i \) changes in many resistance vessels, as well as their differences in length, number, and tapering characteristics, which is precisely what one needs to know, with respect to function. Fourth, measurements are performed at proper distending pressures, which is very important because resistance vessels are quite distensible (205, 207, 297). Fifth, the necessary measurements [pressure (P) and flow (Q)] can be made very precisely, and the rest is simple mathematics: \( (P_A-P_V)/Q = R \) with average \( r_i \) easily derived from the Poiseuille formula. In reality important biologic parameters can seldom be measured in vivo with such precision.

Resistance-vessel dilatation, up to complete relaxation, was accomplished by increasing degrees of combined exercise, ischemia, and high temperature. This gave hyperbolic dose-response vasodilator curves, where the plateau indicated complete vascular relaxation, which was also checked in animals with intra-arterial vasodilator drugs. This plateau was achieved as readily in hypertensives as in normotensives, which argues against increased vasoexcitatory influences in human primary hypertension, since such competition would flatten the curve toward the right.

Even at complete relaxation of smooth muscle, forearm resistance was increased almost in proportion to the raised resting MAP in hypertensive subjects, implying a structural \( r_i \) reduction averaging 7–8%, despite a distending pressure 30–40% higher. Since resting forearm flows were also similar or, if anything, slightly higher in the hypertensives, there was no evidence of any significantly elevated vascular smooth muscle activity in primary hypertension, at least not in the resting steady state. Along with the amplifying effects of a structurally elevated \( w/w_i \), resting smooth muscle activity might even be slightly lower in hypertensive subjects. In contrast, when acute hypertension was induced by norepinephrine (NE) infusion in normotensive subjects, they had precisely the expected increase of \( R_e/R_{min} \), since \( R_e \) was increased in proportion to MAP but \( R_{min} \) remained largely unchanged (209).

Furthermore on theoretical models it was shown how the structural \( r_i \) reduction, when associated with the thickened \( w \), fundamentally alters resistance-vessel behavior in two ways (205, 209, 585). First, the elevated \( R_{min} \) implies a raised structural base line, so that any smooth muscle activity level provides a proportionally higher resistance. Second, the structurally raised \( w/r_i \) in hypertensive resistance vessels serves as a forceful amplifying lever in transforming muscle contraction to luminal reduction. This adds a corresponding, nonspecific vascular hyperreactivity, because given variations in smooth muscle length thereby lead to exaggerated luminal changes.
The structural $w/r_1$ increase thus provides a simple geometric explanation of the much-debated "hyperreactivity" in hypertension (217, 341), earlier ascribed to a variety of other mechanisms where moreover an unfortunate lack of strict definitions often confused debates. This has been clarified by the precise analyses of vessel behavior presented by, e.g., Johansson (341) and Friedman (217) in recent surveys. A structurally based vascular hyperreactivity is thus by nature nonspecific and independent of either smooth muscle supersensitivity (leftward, parallel shift of dose-response curves) or of possible muscle hyperreactivity [theoretically, steeper dose-response curves but with unchanged maximum and mean effective dose (ED$_{50}$)]. At normal effector adjustments the structurally altered resistance vessels simply produce exaggerated resistance and pressure alterations with, if anything, a widened range that is reset to higher levels. Smooth muscle sensitivity of course may be altered simultaneously, but the two can fairly easily be analyzed separately, particularly in animal perfusion experiments (205, 339) and to some extent even in humans (585).

It was also discussed (209) whether the genetic predisposition in primary hypertension may influence the cardiovascular effectors themselves, perhaps responding with adaptive wall thickening even to ordinary MAP variability if, e.g., key enzymatic links adapting cell structure to load are altered to facilitate this process (discussed further below).

Finally, these early studies on humans (200, 209) stressed that functional excitatory influences and a structurally based hyperreactivity would reinforce each other in systemic pressor effects, thus introducing a positive-feedback interaction that could be decisive in hypertension as a driving influence. This implies that functional triggering elements need only be of marginal strength to initiate an insidious pressor development, perhaps explaining why the triggers have proven so difficult to trace in primary hypertension. In a mathematical-biophysical approach Suga (602) recently confirmed and stressed the importance of such a positive-feedback interaction.

These findings in humans were confirmed and extended in a thorough study by Conway (131), also showing that systemic resistance was always higher in hypertensive than in normotensive subjects for equal levels of work load and exercise hyperemia (11, 134). Sivertsson (585) arrived at similar conclusions in comparisons of hand blood flow. This study also explored vascular responses to graded smooth muscle activation by stepwise increases of an NE infusion. This revealed a largely normal smooth muscle sensitivity to NE in primary hypertension, since threshold responses to NE were almost unchanged, whereas the resistance rises in response to suprathreshold NE concentrations were much steeper than in controls. Thus a vascular hyperreactivity was found, despite considerably elevated distending pressures. Other approaches in hypertensive humans have revealed a wall stiffening (297) and structural luminal reduction of the resistance vessels, with $R_{min}$ increased in proportion to the MAP elevation (10, 553).

Thus these analyses of elevated resistance in established human primary
hypertension appeared to leave little room for any accentuation of vascular smooth muscle activity at rest. The structural resetting seemed marked enough to largely account for the elevated resistance even at unchanged smooth muscle tone, at least in the circuits studied, whereas an accentuated smooth muscle activity was easily revealed as an increased $R_r/R_{min}$ in acute experimental hypertension.

This demonstrated hemodynamic importance of an altered resistance-vessel structure in human primary hypertension was soon supported by the first quantitative morphometric analyses of human resistance vessels in normotension and hypertension. Short and his group (579–581) showed that the lumina of mesenteric arterioles were quite narrow in hypertensive subjects, though total media mass was hardly increased. However, a considerable $r$ reduction means an increased $w/r$ ratio, which is what really matters here. Furuyama (231) and Suwa and Takahashi (605), in extensive morphometric comparisons of precapillary microvessels in most major circuits, found a consistent media increase in relation to $r$ in hypertensive patients and proportioned to their MAP elevation. Close to the capillaries, however, this $w/r$ increase tapered off, as also noted by Short, and was interpreted as due to gradual “downstream” pressure normalization because of increased “upstream” resistance. Friedman et al. (217, 221), measuring small arteries in hypertensive rats, arrived at similar conclusions, though different terminology. Thus Furuyama used “media hypertrophy” but Short and Friedman, comparing total media mass irrespective of coexisting luminal reductions, avoided this term. However, since it is the increased $w/r$, ratio and absolute $r$ dimensions that matter hemodynamically, and not $w$ or total wall mass alone, this boils down to mere semantics. More recently, Halpern, Mulvany, and Warshaw (293, 465) in elegant analyses on isolated microvessels from SHR and controls have studied not only the biophysical and physiological characteristics but also precise vascular dimensions, with full confirmation of the results found in humans.

b) Studies in animals. 1) MAJOR QUESTIONS TO EXPLORE. The findings in humans concerning the hemodynamic importance of an altered resistance-vessel structure in primary hypertension raised some important questions, in which the use of genetically hypertensive rats as models has been invaluable. 1) Is the structural adaptation hemodynamically important for all systemic circuits, and which consecutive sections are preferentially involved? 2) Which are the major inducing stimuli, are they continuous or intermittent, and could the structural adaptation per se perhaps be facilitated by genetic elements? 3) How rapidly can it be established on sudden stimulation, is it readily reversible, and what does then the duration of hypertension mean? 4) Since the left heart, systemic arteries, and, to some extent, also the low-pressure capacitance sections show structural adaptation, how does this affect cardiac performance, the high-pressure and low-pressure (volume-) reflex mechanisms, and the renal long-term barostat function?

The second and third questions are important even for the very initiation
of primary hypertension. For example, if some key enzyme in cellular growth processes is genetically reinforced, even ordinary pressor episodes may suffice for marginal structural adaptation of the resistance vessels, thereby inviting positive-feedback interaction between functional and structural elements (205, 209). Thus in such an alternative the structural element constitutes the primary mover in a complex and insidious development of an increased pressure equilibrium. However, even in the perhaps more common alternative, in which structural adaptation is entirely secondary to functional pressor influences of genetic and/or environmental nature, it nevertheless will exert a decisive initiating influence if it develops rapidly. This occurs because then the prerequisites for early functional and structural feedback interactions are established, though now initiated by the functional component. Moreover this may well add genetically reinforced “trophic” influences (hormonal, transmitter) that facilitate structural adaptation (see below).

In such an interaction process the weak excitatory influences, if fairly persistent, will soon have slightly amplified pressor effects because of the marginal structure $w/r$, increase that rapidly develops. The amplified pressure elevation will in turn cause additional structural adaptation, and so on. Thus ultimately marked MAP and resistance elevations may ensue from functional excitatory influences that in their own pressure effects are only marginally above the normal range, perhaps even intermittent (205).

These possibilities for mutual reinforcement between functional and structural elements may, as mentioned, also explain why the long search for dominating functional pressure elements in primary hypertension has been largely fruitless. The mode of initiation seems to differ greatly from, e.g., experimental Goldblatt hypertension models, where the early dominance of functional pressor influence has so strongly influenced ideas concerning how chronic high-pressure states may ensue. However, also in Goldblatt hypertension structural adaptation is soon established, increasingly contributing to the elevation of resistance and MAP, though apparently never as dominating as it is in primary hypertension (421, 422).

II) METHODOLOGICAL PRINCIPLES: RESISTANCE TO FLOW. Experiments should concentrate on the resistance vessels themselves, because they are so specialized in design, smooth muscle function, and hemodynamics that there is no satisfactory substitute. Furthermore resistance measurements offer great advantages in both relevance and precision, as already outlined. True enough, extrapolations from various macrovascular strips are popular but may often be more bold than realistic. Whenever possible, however, comparative studies of resistance vessels proper should utilize the experimental advantages of studies on isolated muscle strips, i.e., allowing explorations of the entire response range, from complete relaxation to maximal effector response.

Several variants of constant-flow perfusion techniques have been utilized for quantitative analyses of hypertensive and normotensive resistance ves-
sels, from complete relaxation to maximal constrictor responses. Such principles allow precise deductions of complete dose-resistance response curves in paired experiments (205, 207, 339, 422, 539, 604, 664). They provide information about $R_{\text{min}}$, average effector sensitivity, resistance-vessel reactivity, maximal contractile strength, and even wall distensibility at known levels of effector activity (207). From similarities and differences between normotensive and hypertensive circuits, their average resistance-vessel design, reactivity, and effector sensitivity can be deduced with great precision. By adding topical microvascular pressure measurements and the isogravimetric principle for capillary-exchange studies, separate measurements of proximal and distal precapillary resistances and postcapillary resistance and capacity functions have also been performed (205, 604). Furthermore a kidney variant has been used for separate estimations of pre- and postglomerular resistances (208, 257), since their ratio is a major determinant of glomerular filtration and hence of the renal long-term barostat function (126).

To study the functional consequences of cardiac structural adaptation, diastolic pressure-volume characteristics and their influence on left ventricular Frank-Starling curves at various preloads, afterloads, and inotropic states have been measured both in vitro and in vivo on hearts from SHR and normotensive control rats (NCR) of the Wistar or Wistar-Kyoto strains (424, 473, 512, 513, 514, 515). Finally, to study the importance of structural changes for resetting cardiovascular stretch receptors, the altered relationships between pressure changes, wall stretch, and afferent fiber discharge have been explored in the large arteries (1, 2, 17, 477) and left heart (474, 619).

III) DISTRIBUTION AND EXTENT OF STRUCTURAL ADAPTATION. Hemodynamic comparisons between adult SHR and NCR concerning the entire systemic vascular bed (421) or the regional ones in hindquarters (5, 195, 205, 210, 287, 392, 421, 664, 688), myocardium (205), or kidneys (44, 257) reveal an elevated resistance at complete relaxation ($R_{\text{min}}$) in SHR, regularly associated with increased vascular reactivity and maximal contractile strength, whereas smooth muscle sensitivity to, e.g., NE was usually largely unchanged (sect. IIIC). Such altered hemodynamic characteristics for a hypertensive resistance section can only ensue from a thickened muscle sheath ($w$) acting on a structurally narrowed internal radius ($r_i$), both of which can be very precisely quantified. In adult SHR, with about 50% higher MAP than NCR, analysis of the respective resistance curves suggests that the average SHR vessel, if representing the entire resistance section, has about 6–7% structural $r_i$ narrowing and a 35% media thickening.

However, separate analyses of the precapillary and postcapillary sections reveal that the alterations in resistance vessel design in SHR are almost entirely concentrated in the precapillary resistance section (205). The precapillary side has an average structural $r_i$ reduction of 8–10% with a 40% media thickening. In other words the 50% MAP elevation in adult SHR is precisely balanced by an equal structural elevation of average $w/r_i$ ratio.
(1.4/0.9) in the precapillary resistance section. Thus despite the higher transmural pressure, a correspondingly elevated resistance and a steeper pressure drop profile can be maintained without necessitating accentuated smooth muscle activity, while keeping downstream capillary and venular pressures almost unchanged (205).

Simultaneous measurements of wall distensibility at different levels of media activation in hypertensive and normotensive resistance vessels have quantitatively defined their behavior and range of responses when both are exposed to either normotensive or hypertensive pressures (207). The marked differences in distensibility, reactivity, contractile strength, and design fully reveal how fundamentally different normotensive and hypertensive vascular beds in reality are except in smooth muscle sensitivity, as previously illustrated (207). In early borderline SHR hypertension the structural changes in, e.g., precapillary resistance vessels and left heart are correspondingly less pronounced (44, 138, 205, 391, 464, 472, 665). In fact the changes in MAP level and structural cardiovascular design seem to be so parallel that from such studies alone it is difficult to say which comes first, and there are indeed suggestions that the structural change might come first, at least in SHR.

The preferential precapillary adaptation deserves to be called “structural autoregulation” (205) because it is a morphologic analogue to the well-known functional precapillary autoregulation (260, 350); both are local responses to MAP elevations, but one is chronic and structural, whereas the other is acute and functional. Both keep regional flow constant and, more important, protect the capillary-venular exchange sections from undue pressure elevations, forming a first and second line of defense against a distal propagation of upstream pressure elevations. A third line of defense, though bordering on degeneration and decompensation, is later gradually added when excess formation of collagen and other interstitial material further thickens precapillary walls (338, 486, 636, 679, 680).

These hemodynamic estimations of the altered precapillary vessel design in SHR were recently corroborated in the elegant studies by Halpern, Mulvany, et al. (293, 464-466), using instead isolated sections of proximal mesenteric arterioles for precise morphometric and physiological comparisons in SHR and normotensive controls. At complete relaxation the media bulk was increased some 50% and \( r_1 \) was reduced 10–15% in SHR, i.e., a 75–80% \( w/r_1 \) increase at equal distending pressures for hypertensive and normotensive vessels. The changes were less pronounced in young SHR largely in proportion to their milder MAP elevation, and likewise the contractile strength was enhanced largely in proportion to the media thickening. In cerebral vessels similar changes were noted by Nordborg and Johansson (472).

The relatively more pronounced structural \( w/r_1 \) increase in more proximal precapillary resistance sections should be compared with \( w/r_1 \) relationships in the most distal precapillary arborizations. To judge from local pressure levels (75, 76, 315), as much as 70–80% of the precapillary resistance
is placed upstream of these distal arborizations, which probably influence capillary flow distribution (sphincter vessels) more than they contribute to overall resistance control (205, 447). They have largely equal $w/r_i$ relationships in SHR and normotensive controls, according to in vivo estimations in cremaster vascular arborizations with modestly higher local pressures in SHR (75, 76, 315). Even considering the masking effects on $w/r_i$ of unequal distending pressures (205, 207), these findings suggest an attenuation of the precapillary structural autoregulation in SHR toward the capillary level.

This agrees well with, e.g., Furuyama’s and Short’s earlier morphometric measurements in hypertensive humans, where an increase in $w/r_i$ of only some 10–15% is noted in the most distal precapillary arborization (231, 580, 581), compared with 70–80% in more proximal resistance sections when related to normotensive vessels at equal distending pressure (231, 580, 581), or some 50% difference at their ordinary pressures (205, 207, 293). This was taken to indicate that the most distal precapillary sections are normally protected from substantial pressure elevation by a pronounced proximal structural autoregulation, encompassing 70–80% of the precapillary resistance compartment. This pronounced structural adaptation in the proximal 70–80% of the precapillary resistance section, which rapidly tapers off in the distal 20–30%, coincides almost precisely with the averaged extent of precapillary structural autoregulation deduced from hemodynamic analyses. In other words, topical morphometric data and averaging hemodynamic estimations agree, and together they show that the extent of precapillary structural autoregulation tends to precisely balance the MAP elevation (205, 207) in SHR primary hypertension.

A structurally based vascular hyperreactivity by no means excludes the possibility that smooth muscle responsiveness could vary independently and in different ways and directions (sect. III C). Structural and functional influences are often difficult to separate in the true resistance vessels, however, which explains much of the current controversies on vascular reactivity. Here vascular strips seem to offer a way out by eliminating the geometric structural element, but unfortunately effectors of larger vessels in important respects do not necessarily represent the microvascular ones (sect. III C). When used for such purposes, however, the behavior of artery strips does not suggest any dominating functional changes of vascular smooth muscle in human primary hypertension (330, 621).

By controlled hemodynamic analyses, however, structural autoregulation can be distinguished not only from changes like vascular wall waterlogging (532, 630) or microvessel rarification (303, 333) but also from functional alterations like changed effector sensitivity (205, 339). First, the unique combination of $R_{min}$ elevation, unspecific hyperreactivity, and raised maximal contractile strength characterizing the SHR precapillary resistance vessels cannot be produced by waterlogging alone, for which there is moreover no experimental evidence in uncomplicated primary hypertension (357, 548). Second, for theoretical reasons extensive vessel rarification is an un-
likely principal adaptation in hypertension, because it presupposes that microvessels, in contrast to larger vessels, should be unable to adapt proportionally to pressure elevation but rather respond by all-or-none regression. It must then also be assumed that the vanished vessels somehow reappear on sustained pressure reduction, because in rats this can largely abolish structural autoregulation in a few weeks (421, 422). Regional vessel rarification in SHR instead suggests a deviation present already at birth and not necessarily related to the later development of hypertension. Furthermore, when arteriolar rarification is mimicked by microplugging, thereby increasing $R_{\text{min}}$, the resulting resistance curves are in all other respects different from the SHR curves (205). Third, concomitant effector sensitivity changes and structural autoregulation can fairly easily be separated from each other and be individually defined by resistance-curve analyses (205, 339).

IV) MAIN STIMULI FOR STRUCTURAL ADAPTATION. It was indicated above that increased load over a sufficient period constitutes the basic and usually dominating stimulus for hypertrophy/hyperplasia in muscles in general, and this holds for SHR resistance vessels as well. Therefore when a restricted region is exposed to sustained hypotension, structural autoregulation occurs in the other direction, i.e., $R_{\text{min}}$, vascular reactivity, and contractile strength are proportionally reduced while smooth muscle sensitivity remains about the same (205, 664). Note that these regionally hypotensive resistance vessels remain exposed to the same neurogenic and blood-borne influences as other SHR vascular regions. Conversely, when regional hypertension is induced proximal to aortic obstruction, the exposed arterial walls rapidly increase their media thickness, but without appreciable waterlogging (52, 55, 492), and local pressure increases in veins have similar effects (342). In fact all kinds of sustained pressure elevation, including the variants of secondary hypertension, are associated with the mentioned structural changes whenever pressure is raised (40, 42, 43, 50, 128, 221, 321, 421, 422, 670), though not necessarily to the same extent as in primary hypertension.

For resistance vessels, certainly, the local increase in load constitutes the key stimulus for structural adaptation by elevating the wall tension against which vascular smooth muscle operates. Other influences may well contribute, either intrinsically by way of genetic facilitation of intracellular growth processes (138, 205, 209, 262) or extrinsically by way of, e.g., neurogenic (transmitter) and/or hormonal influences (53, 54, 102, 205, 210, 489, 492). The latter two may also be genetically reinforced and be conveyed, e.g., via neurohormonal influences on cardiovascular effectors. In fact structural changes seem more pronounced in SHR hypertension than when genetically normotensive rats are provoked to, e.g., renal hypertension (RHR) of similar extent and duration (421, 422, 482) and therefore account for less of the resistance increase in RHR than in SHR. Another interesting indication that SHR cardiovascular tissues may have for genetic reasons an accentuated tendency to adapt structurally is the finding by McMurtry et al. (445) that SHR pulmonary vessels showed more pronounced structural changes than
those of controls when the animals were chronically exposed to the pressor influence of high-altitude hypoxia. Furthermore soon after birth the SHR heart (138, 205) and resistance vessels (205, 391) have marginally thicker walls and develop substantial structural changes, even when largely deprived of neurogenic influences by early destruction of monoaminergic neurons (69, 210, 664).

Muscle hyperplasia seems to contribute at least in the splanchnic microvessels (466), perhaps a reflection of the particular genetic predisposition in SHR, though the cardiac enlargement seems to be mainly due to hypertension (69). It may, however, also be due to the early onset of the hypertensive state, because muscle cells in young organisms seem to respond more easily to increased load with cell multiplication also. Its presence might partly explain the poorer regression of cardiovascular structural changes in SHR than in RHR in response to pressure reduction (664), since return of cell enlargement would seem more easily accomplished than reversal of cell multiplication.

Biochemical-histochemical techniques and tracing early amino acid incorporation involved in structural adaptation are most helpful here, with excellent contributions by, e.g., Udenfriend, Lovenberg, Wolinsky, Yamori, and their groups (486, 636, 679, 680, 690, 691). Thus the first signs of such incorporation can appear 10–20 min after an afterload increase in isolated hearts, and these techniques therefore may also help distinguish between intrinsic and extrinsic trophic modulations of structural adaptation. Thus catecholamines and angiotensin facilitate amino acid incorporation into cardiac myofibrils and myocardial connective tissue, as studied in SHR hearts (572–574). The SHR arteries also show increased uptake (686) as a natural reflection of their wall thickening. Furthermore vascular growth initiated by pressure elevation is facilitated by vasoconstrictor-fiber activity as well, in young animals increasing media cell mitoses presumably via the released NE, according to Bevan’s group (53, 54). Since accentuated central neurohormonal influences appear important in both SHR and GHR hypertension, as well as in common variants of human primary hypertension (sect. II C, III B–D), they may also exert an extrinsic trophic modulation of structural adaptation. In MHS neurogenic activity is, if anything, damped (291) with low renin-angiotensin levels (56, 210), implying little contribution of such extrinsic trophic influences, which perhaps is one reason why MHS hypertension is fairly mild.

As for the basic pressor stimulus for cardiovascular structural adaptation, it matters little how this pressure elevation is induced but far more what its average extent and duration are, where intermittent increases can also be efficient. Those produced by daily psychogenic alterations of tonic sympathetic activity (sect. II C3) are often dismissed as harmless, however, because of their inherent transience, but what really matters in structural cardiovascular adaptation evidently is the average pressure load over longer periods. This is strikingly illustrated by the precise work adjustments of
human veins to the intermittent increases in regional transmural pressure consequent upon the erect position. Another example is the gradual medial hypertrophy and sustained pressure elevation in the pulmonary circuit of genetically normotensive animals in response to the transient pressor bouts caused by frequent hypoxia exposures (642). Elimination of this intermittent trigger usually leads to gradual regression of both the structural and functional changes, as studied by Widimsky's group.

Frequently repeated pressor bouts over longer periods are clearly far from irrelevant, which implies that the mental climate must be considered, at least in people prone to such reactions under mental strain. Henry's mice colonies (307, 308, 311) and Herd's monkey studies (312) strikingly illustrate what predisposed people may face in daily life.

V) SPEED OF DEVELOPMENT AND REGRESSION. If effector hypertrophy/hyperplasia is a rapid event it must contribute to the very initiation of hypertension, but its true rate would then be masked by the usually gradual pressure rise in primary hypertension. Therefore two-kidney, one-clip hypertension in NCR was utilized because MAP can thus increase more than 50% in a week (RHR). The first signs of cardiac and vascular structural adaptation appeared within a few days, and the process was almost complete in less than 2 wk, with its time course corrected for the relatively gradual load increase (421, 422). As surveyed by Meerson (446), the much more abrupt pressure rise in experimental aortic coarctation in rats leads to marked cardiac hypertrophy in almost 1 wk (674). In rabbits nearly complete structural vascular adaptation is accomplished in 2 wk (52, 55). The first biochemical signs are evident within hours, but finally it is of course the added muscle bulk that really alters the hemodynamics. Other cardiovascular tissues are also involved, for example, intensified endothelial cell multiplication in arteries during renal hypertension (565) or the thickened adventitia in SHR arterioles (464, 466).

Structural precapillary adaptation follows the gradual MAP rise in young SHR so closely that it is even difficult to say which comes first (204, 205, 210), implying that a positive-feedback interaction between structural and functional trigger influences must occur from the very start. Cardiovascular structural adaptation must develop more slowly in humans than in rats, though hardly more so than in proportion to the lower metabolic rate. Thus what in rats can be accomplished in a week or two may in humans require some months. However, human primary hypertension commonly develops far more slowly, suggesting an insidious and perhaps intermittent engagement of triggering influences as the rate-limiting element. Therefore a positive-feedback interaction with the structural component should also be possible in humans from the very start. In fact, 18- to 19-yr-old military conscripts with marginal MAP elevations show a largely proportional $R_{\text{min}}$ elevation in the hand vascular bed (553). Regression of cardiovascular structural changes is studied best in RHR because rapid pressure reduction can often be accomplished by renal artery
declipping, which not only eliminates renal pressor influences but also adds considerable release of medullary depressor agents (461, 462). If hypertension has lasted only 1-2 mo, complete structural regression in heart and vessels occurs in 2-3 wk (421, 422). However, the longer the hypertension lasts, the slower and less complete the regression (421, 422, 664), presumably because the third line of defense against pressure elevation is then established via marked collagen endowment. As shown by Udenfriend’s group (338, 486, 636), collagen is formed by the muscles themselves, presumably in response to severe and prolonged tension exposure, and is interstitially merged into filaments that may help to unload muscle from the increased transmural pressure. Unfortunately collagen has a poor and slow regression compared with the rapid reversal of muscle hypertrophy, according to Wolinsky (679, 680) and Berry and Greenwald (50).

It seems more difficult to induce structural regression in SHR than in RHR (664, 665), perhaps partly because muscle hyperplasia also occurs in SHR and partly because the third line of defense might become involved fairly early. However, intense hypotensive treatment in young SHR, when excitatory triggering influences seem to be particularly strong, is effective with respect also to the structural changes (338, 486, 572, 573, 657, 664, 691) and may greatly improve their situation later as shown by Freis (cf. 484), even if treatment is abandoned when adult age is reached (664). In humans also hypotensive treatment leads to regression of structural resistance-vessel changes (586).

An important guideline for treatment of human primary hypertension may come from these findings in rats. To achieve substantial structural regression, thereby accomplishing real reversal and not only attenuation of hypertension, treatment should start well before the third line of defense is organized. This would mean early pharmacological treatment of human primary hypertension or, far better when possible, other preventive measures in predisposed individuals. This, however, calls for improved knowledge about both genetic and environmental factors, as well as better methods for early identification of risk families (sect. IIIA, IV).

c) Functional consequences of structural adaptation. 1) CONTROL OF RESISTANCE AND CAPACITANCE VESSELS. Although I have already outlined several functional consequences of structural autoregulation, the major points nevertheless are summarized here. Precapillary structural autoregulation introduces an unspecific vascular hyperreactivity to constrictor and dilator agents alike (205, 207, 210) and to neurogenic influences (687). Thus it also reinforces the interesting “axon-reflex” vasoconstrictor-fiber adjustments in dependent resistance vessels, as shown in humans by Henriksen et al. (305). Furthermore, though the thickened, stronger, and stiffer precapillary resistance vessels are more readily brought to critical closing (24, 207, 239), they can also cope with more extensive arterial pressure elevations before yielding (205, 207). This explains why, e.g., capillary leakage and damage to the blood-brain barrier occur at much higher MAP rises in established hy-
pertension than in normotension (346, 347) and also why the lower limit for autoregulation of cerebral blood flow is raised (355, 600).

At the regional level, therefore, structural autoregulation represents a quite appropriate adaptation of vessel design to chronic changes in pressure and allows maintenance of increased precapillary resistance without any accentuation of smooth muscle activity. Precapillary resistance equilibrium is simply reset upward by the altered design, and the more distal low-pressure sections responsible for capillary exchange and venous capacitance function are thereby somewhat protected. Pressures may also here be slightly elevated even in early primary hypertension, however, initially reflecting, e.g., not only neurogenic or volume alteration but quite early marginal venous structural alterations as well (262, 263, 295, 582, 610, 638, 639, 640). Such minor pressure elevations in the capillary-exchange section explain the modest increases in plasma protein transfer and the slight volume reduction seen both in humans (506, 637, 638) and in SHR (540), even though capillary permeability remains largely unchanged (539).

The disadvantage and the potential danger of structural autoregulation stem essentially from its generalization throughout all systemic-resistance sections along with the MAP elevation. The generally enhanced reactivity invites the functional-structural reinforcement of pressor responses. This reinforcement tends to escalate the MAP rise as long as there are even marginally accentuated pressor influences, whether these derive from CO or resistance elevations. Gradual deterioration of the exposed cardiac-arterial-arteriolar high-pressure sections may follow, increasingly transmitting the pressure elevation also backward beyond the left heart toward pulmonary and right heart sections and forward to systemic capillary and venous sections. The consequent disturbances of low pressure exchange and capacitance functions imply further structural adaptation, adding to the reduced systemic venous compliance (262, 263, 295, 582, 639) and slightly elevated capillary pressures (75, 76, 315, 539, 540) noted fairly early in SHR and evidently present also in humans (637, 638).

II) CARDIAC PERFORMANCE. It has been much debated whether left ventricular hypertrophy in response to the raised afterload in hypertension should be considered an appropriate and physiological adaptation or if it represents an abnormal and disadvantageous change (615). Just as any muscle gains from increased contractile bulk when facing increased load (physical training of skeletal muscle is a striking example), it would a priori seem evident that hypertrophied left ventricle would also profit from an increased $w/r$, during expulsion, provided that the thicker wall really reflects a proportional addition of contractile elements with an adequate metabolic support. Giraffes, facing a normal MAP around 250 mmHg, have enormously hypertrophied left ventricles, judged by average mammalian standards, but they are certainly competent and enduring runners and enjoy a substantial life-span with apparently little trouble from their cardiac hypertrophy.

Nevertheless intricate problems arise when hearts adapt structurally
to elevated afterload, not only biologically but also technically for investigators [reviewed by Meerson (446), Cohn et al. (122, 123), Tarazi et al. (615), Strauer (601), and Spann et al. (594).] A major problem here is that an initially perhaps quite appropriate increase of contractile mass in the course of hypertension is often complicated by other elements, like exaggerated collagen endowment, impaired blood supply, and myocardial cell degeneration. Results of studies therefore depend much on which stage of hypertension is explored—i.e., by the prevailing extent of such complications. The end result is great difficulty in keeping track of all intrinsic and extrinsic controls of the heart during studies in vivo. It is therefore not surprising that results and interpretations have varied considerably in this field (26, 194, 424, 473, 514, 515, 595).

Even when uncomplicated, however, left ventricular hypertrophy introduces some complexities, first in the backward direction, mainly because the altered geometry of the left ventricle affects diastolic filling. For example, it is well known that in the normal heart, the left ventricle, which has much thicker walls, needs a higher filling pressure than the right ventricle to provide the same average degree of end-diastolic prestretch and hence the same stroke volume. Likewise an increased wall thickness due to hypertrophy must similarly affect the left ventricle in hypertension, thereby affecting stroke-volume regulation and potentially the entire circulation in the forward direction. Questions then arise about how extensive these backward and forward influences are and how they are balanced in established primary hypertension (205, 210). However, this problem is most difficult to clarify with studies during in vivo conditions only, because of the many influences on cardiac function. Therefore studies on, e.g., isolated SHR and NCR hearts have been very helpful because it is easier to produce independent alterations in preload, afterload, and inotropism (424, 473).

In a thickened left ventricular wall it is for geometrical reasons inevitable that average myocardial prestretch for a given preload is relatively reduced, and this is so even when the lumen is the same as that in a thin-walled ventricle. There is also the possibility that an increasing thickening of the left wall might mean that inner layers are actually somewhat slackened, without any real myofilament prestretch in the lower range of filling pressures and luminal widening. If so, these inner layers at this stage would contribute little to effective force generation, again for geometric reasons. This would also mean that total mobilization of contractile power throughout all wall layers of a ventricle with increased wall-to-lumen ratio occurs first when inner layers are fully recruited by higher degrees of luminal distension. A parallel may be drawn here to poorly stretched arterioles during contraction, when inner wall layers often become folded and therefore add little to active contraction (647, 648).

Such circumstances probably explain in part why the Frank-Starling curve for SHR left ventricles in the lower range of filling pressures is displaced slightly to the right of that for NCR left ventricles. This results in
lower stroke volumes in SHR than in NCR when preloads and afterloads are kept identical. This might be mistaken for partial myocardial failure, but rather it reflects how cardiac heterometric autoregulation is geometrically influenced by thickened walls, reducing the average degree of actomyosin filament overlap for equal low levels of afterload (424, 473). Furthermore "homeometric autoregulation" (556), i.e., the intrinsic contractility increase on acute afterload elevation, which presumably reflects improved intracellular myofibril recruitment, is also influenced by increased myocardial bulk and must therefore be considered as well. Thus hypertrophied left ventricles need a proportionally higher afterload than normotensive ones to display equal degrees of homeometric autoregulation, since otherwise the myocardium, per unit transverse section, is not challenged to the same extent.

Thus the enhanced work potential of SHR left ventricles is revealed first when they are exposed to the same degree of average diastolic prestretch as normotensive ventricles and to their ordinary hypertensive afterload. When this occurs in vitro they also produce the same stroke volume as NCR hearts when exposed to their ordinary afterload (473). The total potential of contractile strength inherent in uncomplicated myocardial hypertrophy is fully revealed first when both SHR and NCR left ventricles are exposed to preloads and afterloads, which for each produce their respective maximal degrees of heterometric and homeometric autoregulation, when extrinsic inotropic stimulation is kept equal for both. When thus compared in vivo it is clear that SHR left ventricles can expel the same maximal level of stroke volume as normotensive hearts, although the SHR hearts are exposed to an afterload about 50% higher than the afterload for normotensive hearts (424).

Furthermore estimations of the higher ratio of end-diastolic wall to lumen of SHR versus NCR left ventricles show that contractile strength and pumping efficiency are also, per unit wall layer, if anything higher in SHR than in NCR hearts. Thus, at least in this early phase of established primary hypertension, myocardial hypertrophy seems to represent a truly physiological adaptation, largely like hypertrophy of a physically trained skeletal muscle is surely a physiologically advantageous event. Recent findings on SHR [e.g., Pfeffer et al. (514, 515) and Hallback-Nordlander and co-workers (424, 473)] clearly support this idea.

However, the situation may well be different if genetically normotensive hearts are suddenly exposed to marked experimental elevations in afterload. The presence of trophic neurohormonal influences in SHR hearts (572-574), the possibilities of inherent facilitation of muscle hypertrophy in primary hypertension (see above), and the more gradual rise in afterload may in SHR result in a more adequate and balanced type of structural adaptation in SHR than when a genetically unprepared myocardium is similarly but more suddenly challenged. Furthermore these data from early established primary hypertension by no means contradict the conclusion that gradually degenerative elements tend to be added here also, ultimately deteriorating left ventricular function, just as arterial-arteriolar vessels in the long run suffer from abnormally raised loads (88, 128, 446, 615).
Even though the left heart, by hypertrophy, evidently can adequately cope with the elevated afterload, the question arises how the backward influences of left ventricular wall thickening are handled in vivo. Compensation may be achieved either by end-diastolic pressure elevation and/or by increased inotropism via accentuated sympathetic activity. The former adaptation seems to dominate in rats, at least in resting steady state, because left heart end-diastolic pressure is nearly twice as high in SHR as in NCR (474). Such an elevation in filling pressure may occur by increased blood volume or by structural and/or functional (neurogenic) reductions of compliance mainly of the systemic low-pressure side, thereby diverting more of the contents toward the left ventricle. All three principles may actually contribute in different proportions in various types and stages of primary hypertension, as briefly mentioned earlier.

Total blood volume is commonly normal or slightly subnormal in most hypertensive humans (sect. III.B) and also in SHR and GHR. However, both humans and these rat strains tend to display some volume centralization (361, 428, 547, 612), to which neurohormonal influences often seem to contribute, though this soon is supported by a modest structural adaptation of the systemic capacitance side (sect. II.D3c). Thus a combined reduction of structural and functional compliance seems to prevail in most cases. Whether this is in the long run enough to cope with a reducing diastolic compliance once cardiac hypertrophy is complicated by, e.g., increasing interstitial endowment is debatable. Such situations may demand further intensification of sympathetic discharge to integrate the pump with its low-pressure filling side to keep up stroke volume. This may well be an increasingly vulnerable point in cardiovascular homeostasis as hypertension proceeds, perhaps explaining the tendency of stroke volume to decrease with time and also the increased sensitivity to peripheral pooling or blood loss (6, 228, 251, 337, 614, 677).

A really appropriate compensation would be possible if sympathetic activity in cardiac and low-pressure sections could be mildly enhanced along with a corresponding reduction in constrictor-fiber discharge in the resistance section. Unfortunately, however, bulbar sympathetic centers are hardly capable of such contrasting differentiations (206, 381). Therefore any reflex sympathetic activation needed to maintain output would also further elevate resistance and hence MAP. Thus a neurogenic "vicious circle" might in late hypertension sometimes be added to the early positive-feedback interaction between functional and structural elements on the resistance side (6, 205). The situation approaches a point where appropriate adjustments per se may ultimately so deteriorate the system that events pass beyond the borders of the present topic.

III) BARORECEPTOR AND VOLUME-RECEPTOR FUNCTION. Bright (86) in 1836 had inferred that arterial walls are thicker and stiffer in hypertension, and it is now known that this affects hemodynamics in two fundamental ways. First, Windkessel function is correspondingly reduced, resulting in amplified pulse pressure and hence in further raised end-systolic afterload.
It also implies a more rapid and altered pulse-wave propagation, which in turn affects phasic flow patterns and pressure-diameter profiles in conduit arteries (545). Second, it contributes decisively to the well-known resetting of arterial baroreceptors, reviewed by Keszdi and Kordenat (367, 368), Korner (380, 381), Pickering and Sleight (524), and Kirchheim (374) and discussed in a recent symposium organized and edited by Sleight (587).

McCubbin, Green, and Page (438) first showed that the resetting process is basically localized peripherally, reflecting alterations either in receptor sensitivity or wall distensibility. The wider scope of reflex negative-feedback resetting is discussed in section III D, but the influence of structural wall adaptation on cardiovascular mechanoreceptors is principally outlined here.

It was first shown in experimental renal hypertension that the resetting of baroreceptor activity (1, 2, 18) and of baroreflexes (380) occurred in close parallel to the rapid wall thickening and reduction in distensibility, indicating that most resetting must depend on a structural wall stiffening. Also primary hypertension of both humans and animals has the prerequisites for structural receptor resetting. Thus aortic-arterial walls of SHR become thicker and stiffer, in pace with the MAP rise exhibiting media hypertrophy and hyperplasia and also increased elastic and collagen endowment (336, 693). Furthermore carotid and aortic baroreceptor discharge shows resetting in close proportion to the MAP elevation, whereas early hypotensive treatment in SHR proportionally reduces both the resetting and wall thickening (477, 554, 555).

Nearly all baroreceptor analyses, however, are performed on the medullated baroafferents, which are outnumbered some 3:1 by unmyelinated C-fiber afferents. These C-fiber afferents also exert a powerful negative-feedback influence, though at far lower rates of discharge (3, 356, 620). Recent analyses of both baroafferent types in rabbits and rats show that in normotension most receptors with myelinated afferents begin to discharge well below ambient MAP but that most unmyelinated ones first discharge beyond this level (3, 356). When renal hypertension was established, however, the C-fiber receptors were reset far less, so that most were active at the raised MAP equilibrium, whereas the myelinated ones were fully reset (356, 620). The same general principle also seems to hold for unmyelinated C-fiber afferents in SHR primary hypertension (620).

Thus, although normally serving more as auxiliary brakes, arterial C-fiber receptors seem to exert an accentuated damping influence during hypertension. Perhaps some C-fiber arborizations penetrate the media, thereby also sensing wall tension and state of contraction, as first proposed by Landgren (374, 620), whereas the adventitial receptors with myelinated afferents respond essentially to outer circumference changes. Anyhow the less-complete resetting of C-fiber baroafferents in primary hypertension may constitute an increasingly important negative feedback in a situation where most others seem to largely accept the hypertensive state. Further analyses are certainly warranted, particularly since they might explain why, in the
course of neurogenic variants of primary hypertension, sympathetic activity appears to become less prevalent as hypertension advances. Because of left cardiac hypertrophy, stretch (volume) receptors with vagal afferents and localized to the left heart are also reset (538, 619). Thus the relationships between C-fiber discharge rates and end-diastolic pressure are so altered in SHR along with the changes in left ventricular compliance that afferent fiber activity largely equals that in normotensive controls, despite a nearly doubled end-diastolic pressure in SHR (474, 619). This resetting seems to depend at least partly on the altered structure of the left heart. The unmyelinated cardiac afferents are particularly important in the negative-feedback control of MAP and overall volume and water-salt balance (4, 164, 474, 619), as discussed further in section III D, F.

IV) RENAL LONG-TERM BAROSTAT FUNCTION. Partly based on a systems analysis approach, Guyton and co-workers (126, 127, 277-279) emphasize what they call the "long-term barostat function" of the kidneys that, by pressure diuresis and consequent volume reduction, would curtail any MAP elevation, provided renal function is not somehow also altered. At least theoretically such a renal negative feedback has infinite gain, in contrast to each individual baroreceptor reflex. These latter were denoted "short-term barostats" because they were supposed to be reset more readily in hypertension. There are also many ways to reset the renal long-term barostat function of the kidneys, however, even by means of the various short-term barostats (see sect. III D, F). The actual question here is whether the renal barostat function can also be reset by structural adaptation, in which case both long-term and short-term barostats would be adjusted to the hypertensive state in close parallel and by the same process. According to Guyton, preglomerular interferences are particularly efficient in renal barostat resetting, as amply illustrated by Goldblatt's experiments.

The preglomerular resistance section is the renal equivalent of the precapillary resistance sections in other systemic circuits. Both are sites for dominant vasoconstrictor-fiber control of resistance as well as for local functional autoregulation. These circumstances make it likely that the process of structural autoregulation would also occur in the kidneys and be largely confined to the preglomerular resistance vessels, at least to start with. If so, a highly efficient preglomerular resetting of the renal barostat function would ensue, largely in pace with structural changes at the other strategic sites of the system, including those for the short-term barostats.

Therefore paired perfusions of SHR and NCR kidneys have been performed during maximal vasodilatation to estimate arterial and tissue pressures, flow, and glomerular filtration at various pressure heads (208, 257). This allows quantitative comparisons of total as well as pre- and postglomerular resistances and also of glomerular filtration capacity. In early established SHR hypertension, filtration capacity is largely unchanged, true total renal resistance to flow is modestly increased, and the structurally determined preglomerular-to-postglomerular resistance ratio is considera-
bly elevated compared with controls. Because of largely equal plasma oncotic pressures in SHR and NCR, effective glomerular filtration pressure would be reduced even more in SHR compared with NCR at equal MAP levels in vivo. A normalization of effective filtration pressure in SHR kidneys at this stage therefore demands either a 40–50% MAP elevation (which they ordinarily have) or a corresponding postglomerular vasoconstriction (which, however, would curtail glomerular blood supply and hence also interfere with filtration).

In other words, this preglomerular structural autoregulation resets the renal barostat function in close balance with the MAP elevation in SHR. However, this structural preglomerular change hardly constitutes a primary trigger preceding other changes in SHR hypertension, since early borderline stages differ only marginally from controls in this respect (205, 208). Instead it represents another, but particularly important, expression of the early and widespread structural adaptation of the cardiovascular system, and it is therefore primary only to the extent that these structural changes are genetically reinforced, as discussed earlier.

Since this preglomerular structural autoregulation also implies an increased $w/r_g$ ratio (205), a considerable vascular hyperreactivity to neurogenic and hormonal constrictor influences also ensues (44, 130, 205, 208, 257, 421). Naturally it is most difficult to perform quantitative analyses along these lines in humans, but there are several observations in harmony with such a structurally based renal resetting also in human primary hypertension (sect. III $F$), particularly the results of intrarenal angiotensin infusions and renal nervous blockade by Hollenberg et al. (327, 328).

The effects of these preglomerular changes on glomerular filtration pressure, however, may be gradually compensated by locally induced increases of the postglomerular resistance (sect. III $F$). Then glomerular blood flow is correspondingly reduced and the increased filtration fraction is bought at the price of a raised pressure load on the glomerular capillaries. Such a situation often prevails in more advanced human primary hypertension (sect. III $F$) and also in later stages of SHR hypertension. Here the postglomerular resistance is also structurally elevated and glomerular filtration capacity per millimeter of mercury is reduced (B. Folkow and G. Göthberg, unpublished observations). Evidently these changes cause a vicious circle for renal function and vessels, often resulting in rapid deterioration [e.g., Brown et al. (95)].

Comparisons of SHR kidneys with the pressure-exposed kidney in two-kidney, one-clamp renal hypertension in rats (RHR) are of principal interest here. The RHR kidney also has an increased total resistance to flow per unit tissue weight but without any appreciable structural elevation of the preglomerular-to-postglomerular resistance ratio (257). Presumably the postglomerular vessels have been exposed to a raised transmural pressure in RHR, perhaps reflecting the preferential angiotensin constriction of efferent arterioles (sect. III $E$, $F$). Whatever the reason in this fairly early stage of renal hypertension there are no signs of any selective preglomerular reset-
ting of the unclamped renal barostat, probably contributing to the often prompt reversal of early renal hypertension in rats when the initial trigger is eliminated (422).

Incidentally these hemodynamic in vitro analyses of renal structural vascular changes also reveal how passive autoregulation, caused by parallel elevations in tissue pressure, can greatly distort the results in such studies. For example, it may mask the hemodynamic consequences of preglomerular structural autoregulation in SHR, which easily leads to partly erroneous conclusions (257).

d) Concluding remarks. Structural cardiovascular adaptation, which is per se an appropriate tissue response to increased local load, can be rapidly established. This implies an early generalization to all exposed cardiovascular sections whenever pressor influences are more sustained or repeated often. At least in some variants of primary hypertension structural adaptation may well be an expression of the hereditary predisposition if some link in muscle growth processes, or some trophic influence on them, is genetically reinforced.

The main consequences for cardiovascular function, summarized as follows, have been outlined elsewhere (205).

I) SYSTEMIC RESISTANCE. The early induction of precapillary structural autoregulation increasingly dominates the gradual elevation of resistance. By afflicting all systemic circuits it raises not only the structurally set baseline for systemic resistance control by reducing average maximal bore of the precapillary resistance section, but the $w/r$ increase caused by media thickening leads also to an unspecific vascular hyperreactivity with amplified resistance adjustments. Thus an elevated resistance can be maintained without increased smooth muscle activity. Furthermore the hyperreactivity introduces a positive-feedback interaction with triggering pressor influences, which therefore may well be only marginal in extent and intermittent in action. This explains why the triggering influences have been so difficult to trace in primary hypertension, since they are hidden behind the increasingly dominant structural autoregulation.

II) ADAPTIVE MYOCARDIAL HYPERTROPHY. By this mechanism the left heart is reset to cope adequately with the increased afterload, though with some adverse consequences for the low-pressure filling side. This is due to the concomitant effects on average end-diastolic prestretch, which is mainly compensated by an increased preload, accomplished partly by a structurally based reduction of systemic venous compliance as well.

III) CARDIAC AND ARTERIAL WALL HYPERTROPHY. This mechanism is important in resetting reflexes emanating from left cardiac (volume) and arterial (baro-) mechanoreceptors by reduced wall compliance. Consequently the so-called short-term barostats tend to maintain, rather than to counteract, the hypertensive state, though the normally high-threshold unmyelinated baroafferents may be reset less than the myelinated ones, thereby exerting an increased damping influence on hypertensive development.

IV) LONG-TERM BAROSTAT FUNCTION. This important renal function also
seems to be reset by early structural autoregulation of the preglomerular resistance vessels, a process of the same nature, rate, and extent as that resetting the short-term barostats. Later postglomerular structural changes complicate the situation, with adverse consequences for glomerular filtration capacity and renal blood supply.

Thus the intrinsically normal process of structural cardiovascular adaptation, previously much neglected in hypertension research, appears to be an all-important "missing link" in the creation and maintenance of primary hypertension. It explains how the frequently marginal functional influences of genetic and environmental elements eventually can lead to the substantial hemodynamic alterations characterizing established primary hypertension. The general character of these interacting processes appears to warrant Pickering's "quantitative" concept of primary hypertension, representing in principle the right end of the ordinary distribution curve for blood pressure, which unfortunately in the long run greatly increases risks for true cardiovascular disease with degenerative and lesional wall changes.

III. MAIN LOCATION AND NATURE OF PRIMARY PREDISPOSING ELEMENTS

A. General Considerations

Section II clearly shows that interactions between genetic elements, environmental influences, and the hemodynamic expressions of early structural adaptation are important in the development of primary hypertension. Thus its insidious development in humans, with ample chances for an early positive-feedback coupling between functional and structural components, implies that the intrinsically crucial contribution of triggering genetic elements may well be marginal in extent. Particularly when these effects are inherently variable—or even intermittent, as would be expected for, e.g., central neurohormonal influences—they may be easily masked by the effects of an increasingly dominating structural autoregulation. Perhaps the more the structural component dominates, the more the primary triggering influences become secondarily damped.

Thus the very presence of primary genetic elements has proved difficult to reveal in human primary hypertension. The best chance of identifying them in humans is at the very earliest stages, an approach pioneered by Brod et al. (88, 190) and used more extensively by, e.g., Julius, Conway, and Esler (360–362). Particularly helpful are cardiovascular expressions of primary elements that remain unaffected by structural changes, e.g., heart rate shifts due to alterations in neurogenic balance, or genetic elements that also affect other organ systems, e.g., by means of cell membrane alterations. There is also a recent, most promising increase of interest in the cardiovascular situation, salt sensitivity, and responses to mental stress in children and adolescents with a genetic predisposition for primary hypertension (60, 167,
175, 176, 187, 188, 384, 444, 469, 617), an approach utilized by Doyle and Fraser (167) in the early 1960's (sect. III B, C).

Nearly 20 years ago in Germany, Losse and co-workers (412, 413, 668, 669) observed a slightly elevated sodium content in erythrocytes from patients with primary (but not secondary) hypertension. These important early observations suggested that erythrocyte membranes in primary hypertension might be abnormally permeable to sodium, and if cell membranes also in, say, vascular smooth muscle or autonomic neurons were similarly affected, the hemodynamic consequences might be significant indeed.

In more recent extended analyses of both human and SHR erythrocytes, Postnov et al. (525, 527) found that the major difference between primary hypertension and normotensive controls seemed to be either an increased passive sodium permeability, i.e., perhaps a matter of slightly altered membrane ultrastructure, or a leaky pump system other than the Na\(^+-\)K\(^+-\)ATPase system. Thus the modestly increased membrane leakiness in hypertensives was further accentuated when the Na\(^+-\)K\(^+-\)ATPase activity, mainly responsible for active sodium expulsion (566), was depressed by ouabain. Because the difference also was present in very young SHR, or after prolonged adrenalectomy, it could not be ascribed to the hypertensive state per se. Friedman et al. (222) and more recently Canessa et al. (107) have presented similar findings. Similar permeability changes subsequently have been noted in lymphocytes (9), platelets (435), and adipocytes (528). According to Garay et al. (235, 236) the so-called Na\(^+-\)K\(^+\) cotransport system for genetic reasons seems to be insufficient, though compensated by increased Na\(^+-\)K\(^+-\)ATPase activity, whereas Tosteson's group (634) instead noted increased Na\(^+-\)K\(^+\) cotransport. Further studies should soon reveal the exact events, which may well vary in different types of primary hypertension.

It is particularly interesting that permeability is altered in normotensive close relatives of subjects with primary hypertension [Losse et al. (413), Garay et al. (237), and Henningsen et al. (301, 302)]. This greatly increases the likelihood of a truly genetic deviation, though it may also imply that additional genetic elements and/or environmental influences are needed to precipitate hypertension. The presence of increased sodium permeability in several independent cell systems further suggests that is indeed a generalized phenomenon, though often efficiently compensated for and therefore probably of little functional significance in tissues with ordinarily stable cell membranes.

However, in cells with labile membrane characteristics designed for displaying inherent activity and/or high responsiveness to environmental changes, e.g., like bulbar neurons responsible for tonic sympathetic activity, adrenergic nerve endings (sect. III D3c), myocardial cells, vascular precapillary smooth muscle, and renal tubular cells handling sodium, even modest primary alterations in membrane characteristics might have far-reaching consequences for cardiovascular homeostasis. At such sites increased sodium permeability might cause accentuated central and/or peripheral-junctional
autonomic reactivity, marginal elevations of myogenic precapillary tone, and a trend toward renal sodium retention, just to mention a few possibilities. The potentially great importance of such generalized changes in Na\(^{+}\) permeability and balance had encouraged experts like Tobian (628, 630) and Friedman and Friedman (218, 220) since the 1950's, though partly from other angles, to explore mechanisms for alterations in renal sodium handling, tissue sodium content, and transmembrane sodium gradients. These early studies dealt with influences on vascular smooth muscle tone, flow resistance, volume regulation, and pressure levels (see sect. III.C–F).

Moreover since the 1960's there has been increasing evidence of a natriuretic hormone (sect. III.E.4) with important pioneer contributions by de Wardener (654, 656) and Dahl (140). Dahl et al. (143) in 1969 suggested that in HSR such a hormonal principle might also exert a generalized “hypertensiogenic” effect. Further, based on studies of experimental secondary volume hypertension, Overbeck (490, 491) and Haddy et al. (284) proposed that a “ouabainlike” hormonal principle suppresses the Na\(^{+}\)-K\(^{+}\) membrane pump not only in the renal tubules but also in cardiovascular effectors and/or autonomic neurons, thereby perhaps enhancing their responsiveness. Obviously, if in primary hypertension there is a genetic increase in “passive” Na\(^{+}\) permeability and/or if the Na\(^{+}\)-K\(^{+}\) cotransport system or some other pump arrangement is insufficient, though ordinarily compensated for by increased Na\(^{+}\)-K\(^{+}\)-ATPase activity, a secondary hormonal damping of the Na\(^{+}\)-K\(^{+}\) pump might have particularly important hemodynamic consequences (see sect. III.C3, E2).

The responsiveness of the cardiovascular effectors ultimately depends on how such primary and secondary alterations in permeability affect \([\text{Ca}^{2+}]_{i}\), where both the influx and release and the extrusion and binding of Ca\(^{2+}\) may be influenced, as discussed by Blaustein (72, 73), Johansson and Somlyo (343, 345), and Casteels et al. (110). If, for example, salt-volume loading releases natriuretic hormone and suppresses the Na\(^{+}\)-K\(^{+}\) pump in vascular smooth muscle also, this would more powerfully increase \([\text{Ca}^{2+}]_{i}\) in smooth muscle with genetic permeability alterations. Furthermore at adrenergic neuroeffector junctions it might elevate effective transmitter concentration (114, 284, 491). However, volume increases at the same time tend to reflexly inhibit sympathetic activity (sect. III.D.3b) and to increase renal salt excretion by various routes (sect. III.F1), and the neurohormonal mechanisms then involved might also be affected by the membrane changes described. Thus there are no easy answers to what might be the net hemodynamic outcome of these generalized genetic and secondary membrane alterations. The hemodynamic results may in fact vary among individuals depending on other genetic and environmental influences, perhaps sometimes mainly affecting cardiovascular muscle and sometimes hormonal or nervous control mechanisms. It might even cause depressor effects if sensitization of, e.g., reflex inhibitory links happens to dominate the situation.

Undoubtedly the presence of a genetically increased membrane per-
meability is of greatest interest, because it brings primary deviations closer to the molecular level and because the possible hemodynamic consequences are so many. However, one must be aware that this particular membrane deviation might, with respect to cardiovascular function, in most cases represent a fairly harmless "passenger phenomenon" linked to other, more decisive genetic alterations. Its presence in normotensive close relatives perhaps indicates this or at least that other more important influences must be present as well. The different possibilities are discussed in connection with the various cardiovascular components. First, the overall hemodynamic situation in primary hypertension is scrutinized for direct or indirect signs of genetic alterations (sect. III B), followed by attempts to localize these alterations to effectors and/or to any of the major control systems (sect. III C–F).

B. Indications of Primary Elements in Prevailing Volume-Hemodynamic Balance

1. Theoretical considerations

The MAP and resistance elevations characterizing established primary hypertension may, according to Poiseuille's law, develop in two main ways: either by a) a primary resistance increase and/or b) an initial CO elevation that is secondarily transformed into a resistance increase. The various mechanisms of such changes in resistance and CO have been the focus of much speculation and theoretical analyses, most systematically by Guyton and his group in their systems-analysis approach (125, 276–279).

a) Primary resistance elevation. Theoretically this elevation can ensue from an initial increase of smooth muscle activity in the resistance vessels that is soon followed by structural autoregulation or the structural alteration might come first. An increased smooth muscle activity in turn may originate in the muscle cells themselves, either as an accentuated myogenic activity or as an increased (decreased) sensitivity to extrinsic excitatory (inhibitory) influences. Of course, increased smooth muscle activity can also be imposed from the outside by intensification of ordinary neurogenic or hormonal excitatory influences or by reduction of some prevailing humoral inhibitory influence. All these alternatives require resetting of the barostat functions (126, 277–279), which for the renal barostat would naturally follow whenever the initiating influences involve the preglomerular resistance vessels as homologues to precapillary resistance sections elsewhere.

b) Initial CO elevation. The initial CO increase that gradually shifts to a resistance elevation may also be achieved in different ways. Theoretically it could ensue from selective chronotropic-inotropic cardiac stimulation, but more likely it occurs via elevated venous return or a combination of the two (279). This in turn calls for increased filling of the system and/or reduced
capacitance-vessel volume and compliance on a structural or functional basis. Again the barostat functions must be modified so they do not entirely offset such primary events, as they normally tend to do. Alternative b furthermore demands that the increased CO soon be met by an overall resistance elevation; Guyton called this "whole-body autoregulation." As hinted at by Ewald (186) in 1877, this is the proper and immediate "myogenic" response to nonmetabolic flow and pressure increases in all precapillary resistance vessels (125, 203, 261, 278, 282, 493) when not overridden by the ordinarily most efficient reflex counterregulation (4, 164, 206, 374, 381, 619). Its long-term morphologic analogue is structural autoregulation.

c) General remarks. From a and b it is obvious that the triggering influences of genetic and/or environmental elements must somehow express themselves either directly in the precapillary resistance vessels, or indirectly via initial increases of CO, or by actions on resistance vessels and heart via the nervous, hormonal, and/or renal electrolyte-fluid controls. Guyton's group considered the renal "volume variant" as the most likely theoretical alternative in primary hypertension. It would start by a primary salt-volume retention leading to CO elevation, with a subsequent whole-body autoregulation that would soon dominate hemodynamics. Their preference was based on both experimental models and on computer systems analyses that pointed to a crucial role for the renal long-term barostat function (127, 276, 279). No doubt this is a realistic pathogenetic alternative, and it seems to be at least partly involved in, e.g., the MIIS and IISR rat models (210), though in all likelihood it is mostly reinforced by other, more complex mechanisms (sect. III E, F). On the other hand, there is no indication of any primary "volume involvement" in, e.g., the SHR and GHR variants (204, 210, 264), but the key question is, of course, what is the most common situation in human primary hypertension. The models used in Guyton's excellent analyses tend to underestimate neurogenic control mechanisms in overall balance, not only concerning their reflex efficiency in handling volume changes but particularly concerning what higher autonomic centers can accomplish (sect. III C, III D). Without prior volume expansion, central neurogenic excitatory patterns induce not only capacitance-vessel constriction and improved cardiac performance, with increased CO and MAP as results, but also neurogenic resettings of short-term and long-term barostat functions. True, this involves improved venous return and often CO increases, but these occur entirely on a neurogenic basis and should not be confused with the pure "volume alternative."

There are many ways to reset the dominating renal barostat function (sect. III F), even by means of the supposedly less efficient short-term barostats. For example, low-pressure volume receptors ordinarily cooperate so efficiently with high-pressure baroreceptors in reflex MAP regulation that the renal barostat function is often subordinated to their efferent neurohormonal links. Thus vagal cardiac C-fiber afferents in particular respond to even minor filling increases with reflex cardiac damping, relaxation of resistance-capacitance vessels, and increased renal salt-water losses via neu-
rohormonal adjustments of both glomerular filtration and tubular reab-
sorption without even allowing pressure to rise, which is the obvious pre-
requisite for pressure diuresis (4, 159, 164, 619). For example, most human
subjects respond with slight MAP reductions when tilted to the reclining
position, even though this centralizes ~500 ml of blood, which would con-
siderably increase both CO and MAP if reflex counterregulation failed.

In addition most MAP elevations ordinarily are caused by psycho-
emotional and exercise-bound central neurogenic influences. As mentioned
in section IIc3, these more or less override both barostat functions—the short-
term ones by differentiated central “occlusion” (206, 381) and the long-term
ones by neurohormonal renal adjustments (89, 159, 206, 381), which often
reduces salt-water excretion despite a pressure elevation. In other words, the
intrinsically important renal barostat function is often precluded by car-
diovascular proprioceptor reflexes and frequently subordinated to them via
neurohormonal renal adjustments, whereas both types of barostats are often
subordinated to excitatory limbic-hypothalamic patterns.

This by no means denies that pressure diuresis always serves as a final
safety valve in long-term pressure homeostasis and that the risks for hy-
pertension are serious indeed whenever this function is afflicted. The final
choice among these theoretical alternatives, however, must stem from direct
analyses of primary hypertension, where one must consider neurogenic vari-
ants, hormonal variants, and volume variants, not to mention myogenic vari-
ants in case the most decisive initial disturbance is localized to the vascular
effectors themselves.

2. Established primary hypertension

In searching for genetic and environmental influences in human primary
hypertension, it is natural first to deal with the hemodynamic situation of
the established phase, simply because it has been so extensively explored.
The older literature is excellently reviewed by Freis (214) and the more
recent references are discussed by, e.g., Frohlich (224).

In both human and rat primary hypertension this phase is characterized
by a largely normal CO with the MAP elevation essentially due to a raised
systemic resistance, though CO-resistance relationships naturally vary
somewhat, as in normotension (sect. 1B). Usually resting heart rate is slightly
elevated, suggesting a marginal neurogenic accentuation in at least a sub-
stantial fraction of cases. Stroke volume is normal or modestly lowered,
accounting for the declining CO as hypertension advances with further re-
sistance elevation (223). Because of left ventricular hypertropy, however,
over substantial periods the heart can efficiently cope with the raised af-
fterload without increasing the work load per unit myocardial tissue, but this
occurs at the expense of some preload elevation and compensatory func-
tional-structural venous adjustments, as discussed in section IIc3. Eventu-
ally deteriorating influences in the form of interstitial endowment and myocardial degeneration tend to complicate the situation (122, 123, 594, 601, 615). Because of stiffer Windkessel arteries, pulse pressure is considerably increased and, in contrast to resistance vessels, both Windkessel and conduit arteries often seem to be widened (545).

Systemic flow distribution usually is not much altered, in either human or rat primary hypertension (94, 282, 471, 493, 682), implying that all systemic circuits contribute to the elevated resistance. Muscle blood flow in hypertensive humans is sometimes (10, 92, 94, 224, 493), but by no means always (94, 224, 521, 682), mildly elevated, indicating that tonic smooth muscle activity in this vascular bed is often even lower than in normotensives. This condition is revealed by a slightly reduced $R_r/R_{\text{min}}$ ratio in human skeletal muscle in hypertensives compared with controls, despite thicker-walled resistance vessels in hypertensives. Thus $R_{\text{min}}$ is raised largely in proportion to the MAP elevation but $R_r$ somewhat less so (10, 209) in line with the considerations discussed in section II.D.5. Splanchnic and renal blood flows, on the other hand, are commonly in the lower range, with a clear trend toward further reduction as hypertension advances, particularly in the kidneys (46, 90, 456, 563). Because the intrarenal flow changes are particularly important for the overall situation, by influencing volume, electrolyte, and hormonal equilibriums, they are dealt with in more detail in section III.F. Thus the resting cardiovascular pattern is principally a raised systemic resistance, though in flow distribution and heart rate it can often resemble a marginal defense reaction, balanced so that a net elevation of resistance entirely dominates (sect. II.C.2). It then suggests a mild neurogenic accentuation that is increasingly overridden by the hemodynamic consequences of structural cardiovascular adaptation (383).

Cardiovascular adjustments during exercise are similar in hypertension and normotension, with one noteworthy and consistent exception: for equal levels of increasing work load, systemic and muscle resistances to flow remain proportionally elevated in hypertension, even at intense exercise vasodilation (11, 134, 250, 552). Evidently normal exercise adjustments are set to operate around a higher resistance and pressure equilibrium, without any “vasodilator breakthrough” at high work loads. In all likelihood this reflects the structural autoregulation, by now dominant, of the systemic precapillary resistance vessels that has also raised $R_{\text{min}}$ in rough proportion to the MAP elevation (205).

During sleep the MAP fall can be profound in primary hypertension, though it was only modest in one study where CO and resistance were also estimated (369). Cardiac output and resistance fell during sleep to about the same relative extent in hypertensive and normotensive subjects, which indicated a lack of psychogenic accentuation of sympathetic activity in the hypertensives: they would otherwise show relatively greater reductions of MAP, CO, and resistance during sleep. However, such an interpretation depends entirely on whether the respective awake control situations were
representative for the average degree of environmental stimulation in ordinary daily life for the two groups. This may not have been so, because central neurogenic influences are inherently so variable that their cardiovascular influences should be compared instead with how intermittent exercise affects locomotor function and design. Therefore these results only allow the conclusion that the raised resistance in the awake, resting hypertensives was not due to any continuously present increase of vasoconstrictor-fiber discharge, which is another matter but important in its own right.

Overall extracellular fluid content is largely normal, whereas blood and particularly plasma volumes are commonly in the lower normal range (174, 177, 405, 559, 561, 612, 614, 637). On the whole, plasma volume tends to be lower the higher the pressure (561, 612) though it often shows a modest centralization toward the heart (612, 640). The spread of values is considerable, however, and most studies seem to contain at least a small fraction of subjects in which plasma volume is clearly enhanced, as surveyed by Tarazi (612). Also in these subjects CO seems to be largely normal, whereas heart rate and renin levels are in the lower range but, in contrast to subjects with aldosteronism, mineralocorticoid levels are normal. These patterns may well reflect volume variants with respect to predisposing elements, though longitudinal follow-up studies are needed to decide whether this is really so or if the differences merely reflect stages, or transient variations, within etiologically fairly homogeneous materials. On the whole, in primary hypertension the spread of values may be more interesting, from the etiological point of view, than the statistical average because it provides hints of different variants. For example, high-volume, low-renin hypertension seems to be more common in blacks than in whites (118, 247, 418, 575).

Since total extracellular volume, exchangeable sodium, and overall electrolyte state are commonly normal (405, 561, 614), the ratio between plasma and interstitial fluid volumes is usually slightly lowered (405, 561, 612), whereas plasma protein transfer is modestly raised, both in humans (506, 637, 638) and in SHR (540). This suggests marginal pressure elevations also within capillary and venous capacitance sections, with increased filtration of fluid and proteins at largely normal capillary permeability (539, 540) and with a modest reduction of venous volume and compliance on a combined functional (411, 638) and structural (262, 263, 295, 582, 639) basis. Despite such venous wall adaptation, tilting of hypertensive subjects often leads to accentuated reductions of CO and MAP (228, 251, 677), as though reflex venous adjustments were less efficient than in normotensives. However, several factors are probably involved here, like receptor resetting (sect. IIIc) or even receptor deterioration in advancing hypertension (677). To further complicate the volume problems, it should finally be mentioned that even the compliance of the interstitial space might become altered in hypertension, probably on a renal-hormonal basis (sect. IIIE), as suggested by interesting data by Floyer (199).

Whatever the combination of initiating elements, the hemodynamic and
volume characteristics evidently are soon fairly uniform in established hu-
man primary hypertension, suggesting an increasingly dominating common
denominator for all variants of hypertension, i.e., the hemodynamic conse-
quences of structural cardiovascular adaptation (sect. II D3). This is largely
ture for rat variants as well, even though the initiating mechanisms and
ey stages certainly can differ markedly (6, 210, 337, 512), illustrating how
their impact gradually becomes masked by the rapidly established structural
alterations.

Laragh, Brunner, Bühler et al. (96, 394, 395, 397), however, have proposed
that the renin-angiotensin-aldosterone balance may also in established hu-
man primary hypertension be a useful clue to etiology and thus to prognosis
and choice of treatment as well. As mentioned, hypertension in blacks and
whites may to some extent differ in this respect. The great appeal of this
approach principle—compared with the conventional hunt for somewhat
shaky "significant differences between means" for often widely scattered
data—is the use of the very scatter as a possible clue to major hypertension
variants. This clear stand for a multifactorial, rather than unitarian, etiology
is of great interest, and the handling of data from other types of measure-
ments in primary hypertension is likely to profit from this kind of approach.
As a principle it is not belittled by the fact that the initial optimistic in-
terpretations have not in all respects stood the test of extended analyses
(166, 172, 243).

Thus the group with low-renin hypertension, first supposed to mainly
reflect benign volume hypertension (and no doubt in part containing such
variants), seems to be dominated by fairly advanced stages of primary hy-
pertension, independent of how the disease may have started, but with organ
manifestations mainly in the kidneys (45, 559, 560, 563). Here the low renin
levels may reflect a secondary renal baroreceptor suppression of renin se-
cretion (sect. III E2a) ensuing from elevated preglomerular-glomerular pre-
sures. This in turn reflects a threatened renal function where intrinsic renal
control mechanisms have somehow induced an elevation in the postglo-
merular resistance (sect. III E2), as in the unclamped kidney of advanced two-
kidney, one-clip Goldblatt hypertension (68, 95). A reflex suppression of neu-
rogenic renin release may also contribute via, e.g., unmyelinated volume-
receptor afferents in a distended left heart due to centralization of blood
volume (sect. III D) because at these later stages there are often signs of
reduced sympathetic activity, if anything (45, 48).

In high-renin hypertension, orginally supposed to represent mainly se-
vere vasoconstrictor hypertension with even vasotoxic renin-angiotensin ef-
effets, there apparently are several variants. These include early mild neu-
rogenic hypertension (183, 184) with sympathetic renin release (sect. II C3,  
III E2) and also advanced hypertension of presumably mixed etiology where
an exaggerated preglomerular resistance threatens renal function. Thus a
secondary Goldblatt mechanism is then superimposed, simulating the
clamped kidney in two-kidney, one-clip renal hypertension (95).
3. Early phases of primary hypertension

a) General aspects. There are ways to circumvent the great difficulties in tracing triggering elements in established primary hypertension, among them the epidemiologic approach. For example, prospective follow-up studies of entire population groups (49, 149, 426, 507, 521, 625), or of children with and without a family predisposition for primary hypertension (60, 145, 175, 176, 187, 384, 469), can certainly offer important information, though interpretation of the findings is often exceedingly difficult.

Much effort is presently being devoted to experimental analyses of early human primary hypertension. Here, however, the insidious and often varying onset stages offer another dilemma, simply because they are difficult to distinguish from ordinary pressure variations in normotension. Thus most cardiovascular parameters accessible in humans—whether plasma catecholamines, renin-angiotensin or aldosterone levels, heart rate, cardiac output, or pressure itself—may well vary more in the given subject with ordinary shifts in alertness or fluid balance than the variation in respective mean values between borderline hypertensives and normotensives in a given sampling. Again possible clues inherent in the scatter of values should always be considered. Thanks to the many quantitative studies now available [see, e.g., Julius et al. (185, 360, 362–364), Birkenhäuser and Schalekamp (66, 67), Frohlich (224–226), and Ferrario and Page (193)], some characteristic hemodynamic patterns can be traced in human borderline hypertension, providing interesting hints about initiating mechanisms. There is also the great help offered by the more penetrating hemodynamic analyses that can be performed on the different variants of rat primary hypertension (56, 204, 210, 227, 233, 264, 291, 337, 423, 484, 513, 588, 687–689).

Based on such studies two main concepts of initial hemodynamic events in primary hypertension are commonly discussed, though too often in an either/or fashion. It should be stressed that both seem to be of great relevance, certainly in the rat variants and most likely in humans as well, though probably more intermingled by the randomized combinations of predisposing elements. The two main patterns of early hemodynamic events may conveniently be labeled neurogenic variants and volume variants, but it might be justified to consider, e.g., myogenic variants as well. Rather than considering them in an either/or fashion, the major question for humans is whether one is very much more common than the other, simply because they are likely to reflect different predisposing combinations of importance for both treatment and preventive measures.

b) Neurogenic variants. Ideas about an early CNS involvement in human primary hypertension have a long history (sect. 1R), but really convincing experimental evidence was first presented in the late 1950’s by the pioneering studies of Brod and his group (87, 88, 92, 672). In penetrating hemodynamic analyses on young hypertensives, they found remarkable similarities between the somewhat hyperkinetic cardiovascular pattern characterizing
early human hypertension and that displayed in ordinary mild defense reactions (sect. II.C.3).

Thus very often these early cases of hypertension showed clear but modest tachycardia during rest, which was commonly associated with increased CO, distributed to favor skeletal muscle at the expense of the gastrointestinal and renal circuits. Such a hemodynamic balance is strongly indicative of the characteristically differentiated neurohormonal discharge pattern that ensues upon mild excitation of the hypothalamic defense area, as described in section II.C.3. Note that the hemodynamic situation in young SHR is strikingly similar and is further accentuated in the hyperkinetic direction, compared with controls, when the animals are exposed to alerting stimuli (204, 210, 226, 289, 290, 389, 483, 689).

The clear signs of a differentiated sympathetic activation in both humans and rats, which seems to vary with the situation, however, should be stressed—it is not necessarily a matter of any uniformly raised, continuously present sympathetic accentuation. This latter misconception has been common, however, and has much hindered an understanding of how the autonomic nervous system contributes to primary hypertension, with much off-the-point criticism during the years.

The common presence of an early, somewhat hyperkinetic stage in human primary hypertension has been further elucidated in numerous investigations [reviewed by Frohlich (224) and Julius and Conway (361)], in particular the studies of Eich et al. (178), Conway, Julius, Esler et al. (132, 183, 185, 361–364), Tarazi, Dustan, Frohlich et al. (177, 225, 613, 616), Amory et al. (10, 11), Birkenhäuser et al. (66, 67), Lund-Johansen (425–427), Levy et al. (406), and Safar et al. (546, 547). The hemodynamic situation is naturally less homogeneous in humans than in, e.g., SHR, not only because patterns of genetic predisposition are likely to vary more in humans but also because the developmental stage is far more difficult to determine and the experimental situation more difficult to standardize. Nevertheless most of these studies reveal a prevalence for a hyperkinetic circulation associated with modest tachycardia and evidently favoring muscle blood flow at the expense of splanchnic and renal supply (92, 327). The hemodynamic situation often simulates conditions during mental alertness or very mild physical exercise, except that resistance is inappropriately high for the given level of CO increase. Usually oxygen uptake is also slightly elevated (426, 427), but whether this reflects an accentuation of skeletal muscle tone as in general alertness, calorigenic effects of sympathetic activity, or some other mechanism is not known.

It must be stressed again, however, that an increased CO is not any sine qua non for an accentuated CNS engagement in early primary hypertension. Thus in acute mild defense reactions even CO is not necessarily kept high, but heart rate nearly always is. This depends mostly on whether muscle blood flow stays elevated or autoregulates back toward an approximately uniform resistance elevation (201, 206). Zanchetti and co-workers (695, 697,
have shown in awake, freely moving cats how the alertness pattern of increased sympathetic discharge seems to vary even from moment to moment.

The studies in humans by Julius et al. (183, 185, 362–364) have especially well illuminated the central autonomic involvement of both heart and vessels, with clear signs of a centrally reduced vagal tone to the heart in association with signs of sympathetic activation, which often includes neurogenic renin release and centralization of blood volume. Again the hemodynamic situation in young SHR is virtually identical in these respects (204, 210, 226, 227, 290, 423, 483, 484, 512, 689).

Lund-Johansen (425–427) made a particularly important contribution by his meticulous follow-up studies over more than 10 years of early hyperkinetic hypertension in humans. One eternal objection from skeptics has been that the defense-reaction-like circulatory state in borderline hypertension is precisely that and nothing else: i.e., a transient alerting response of little relevance for true primary hypertension. Lund-Johansen showed, however, that in untreated borderline hypertension the early hyperkinetic circulatory pattern 10 years later almost without exception had changed into a raised systemic resistance and a normalized CO, i.e., the classic pattern in established primary hypertension. Resting heart rate also tended to fall, though it remained in the upper normal range. In contrast, normotensive subjects of the same age groups showed no or only negligible changes in hemodynamic balance over the same time period (426, 427). Actually this represents one of the most important studies performed concerning the development of primary hypertension in humans. Essentially the same course of development is seen in SHR, though the far more compressed time axis makes such studies far easier to handle (6, 204, 210, 211, 224, 226, 290, 337, 512, 513, 689).

Additional hemodynamic evidence of a primary neurogenic contribution to the onset of human primary hypertension comes from most interesting studies by Falkncr et al. (187, 188). They exposed adolescents, from families with or without a history of primary hypertension, to the standardized alerting stimulus of forced mental arithmetic. Youngsters with a family predisposition to hypertension showed higher basal heart rates as well as definitely more powerful pressure and heart rate increases, which also tended to be more prolonged than in genetically normotensive controls. This increased responsiveness, expressed not only in pressure and heart rate but also in catecholamine levels, was present not only among adolescents already displaying marginal hypertension (17 subjects) but also among those still normotensive (33 subjects). This latter group in turn could be separated into high responders (21 subjects) and low responders (12 subjects), which is not surprising, partly because human genes for hypertension are likely to be heterogeneous and partly because several youngsters may not have harbored any predisposing genes at all.

Thus roughly 75% of the youngsters with a family history of primary
hypertension displayed signs of a central autonomic cardiovascular hyper-
responsiveness to alerting stimuli, again closely simulating young SHR.
Some caution is needed, however, when it comes to generalizations concern-
ing relative proportions of neurogenic versus other genetic profiles in human
primary hypertension, simply because both racial and geographical differ-
ences must also be considered (sect. 112). In any case such a genetically linked
central hyperreactivity to psychosocial stimuli must, as shown for SHR (210,
289, 290), be relevant for the gradual induction of human primary hyper-
tension as well, at least when dominant and/or triggered by a particularly
provocative environment.

This by no means denies that other genetic and environmental influences
can be important even in the same subjects and may well in others dominate
over neurogenic influences. Actually Falkner et al. (188) subsequently noted
a slightly enhanced tendency of pressure to rise also in response to salt
loading in similar subjects, resembling those of, e.g., Mark et al. (433) and
Sullivan et al. (603) (cf. sect. lllC2, 3 and lllE4, F). Further analyses of the
range of responses and whether sensitivity to salt and to stress affect the
same, or mainly different, individuals would be of great interest.

This brief summary concerning evidence of neurogenic hemodynamic
influences in early human hypertension is completed with other aspects of
neurogenic elements in section III D. However, it in no way does justice to
the many first-class studies in humans that have helped to explore the im-
portant early stages, where the borderline between normality and devel-
opment of true cardiovascular disorder is diffuse indeed. They are certainly
worthy of a review of their own, but a more detailed documentation is un-
fortunately impossible within the space allotted to the present topic.

c) Volume variants. The idea of an initiating volume, and hence CO
increase, was first suggested by Borst and Borst de Gens (79) and by Led-
ingham and Cohen (399-401), apparently putting mainly renal-adrenal
events in etiological focus. This concept has been particularly championed
by Guyton and co-workers, however, on the basis of their systems-analysis
approach (276, 279), as complemented with, e.g., subacute studies on anephric
patients and on partly nephrectomized dogs during volume expansion (125,
126, 277, 278). As outlined above, this elevates CO and thereby arterial pres-
sure, inducing a secondary resistance increase by whole-body autoregulation
mainly because of "luxury" perfusion, which leads to gradual normalization
of CO. If kidney function is preserved the increased cardiovascular filling
also returns toward normal, thanks to the elevated arterial pressure
and pressure diuresis. By such means the kidneys are supposed to exert a dom-
inating long-term barostat function because, other things remaining con-
stant, their diuretic capacity determines the MAP level finally reached (279).

This sequence of intrinsic cardiac and resistance adjustments to volume
loading is particularly evident when remote neurohormonal control of the
cardiovascular system is eliminated (125, 203, 206, 261, 279). Ordinarily, however, the combined influence of the low-pressure (volume) and high-pressure (baro-) cardiovascular reflexes can, as mentioned, efficiently balance these autoregulatory events, at least acutely if the volume loading is not excessive. When, however, a complete balance cannot be maintained (sect. III E, F), an insidious elevation of arterial pressure may ensue. In primary hypertension this can be expected whenever the genetic predisposition favors renal sodium retention and/or accentuated mineralocorticoid function, particularly during increased salt intake. The consequent isotonic volume load, rather than the Na\(^+\) addition per se, might be the critical element (sect. III E, F). It may well be that the genetic tendency (sect. III A) of increased membrane permeability in smooth muscle and/or central autonomic neurons is of particular importance here, if unmasked by volume-induced reflex release of natriuretic hormone (sect. III C–F). Less volume increase would then be needed in genetically predisposed individuals than in normotensives to cause a pressure increase. In secondary hypertension such a chain of events may be expected in clinical and experimental aldosteronism and in renal hypertension where Na\(^+\) elimination is hampered. Ouabainlike hormone effects also seem to be involved here (490, 491, 495).

The MHS (56, 58, 59) and HSR (141–143) types of rat primary hypertension offer interesting variants of such a pathogenetic development, as briefly mentioned earlier. The MHS spontaneously exhibit early mild Na\(^+\) retention, probably due to a genetic renal filtration-absorption imbalance, leading to slight transient hypervolemia and mild hypertension (56). Here the neurogenic control tends to reflexly buffer the effects of hypervolemia (291). On the other hand HSR exhibit hypertension first if provoked by increased salt intake, but then the latent predisposition can end in severe hypertension (141, 142, 233), where secondary neurogenic reinforcements, also seem to be involved (609), as further discussed in section III D–F.

The crucial question, however, is how often in human primary hypertension this type of genetic predisposition and hemodynamic development dominates early events. Authorities like Dahl (139, 140), Guyton (276, 279), and Tobian (628, 629) consider the volume variant as probably most common in humans, though Tobian considers a secondary neurogenic involvement important (233, 628). Guyton, for example, in his analytical approach by no means denies other alternatives, which is sometimes forgotten by enthusiastic subscribers to his concept. Furthermore it is often forgotten that initial CO increases are frequently part of neurogenic variants as well, though for entirely different reasons, and are by no means mandatory (92, 204, 363). On the whole, the significance of an initial CO increase has been misunderstood by some investigators and therefore neglected (sect. II C3), whereas others have overemphasized its pathogenetic relevance. Korner et al. (198, 382) have critically reviewed the situation and shown experimentally how, e.g., the induction of supposedly “volume-dependent” renal hyperton-
sion by no means calls for any initial CO elevation; the situation is certainly different in SHR as well (227). Furthermore Ferrario and Page (193) recently also criticized the view of an initial CO elevation as nearly mandatory for hypertension induction and discussed alternative mechanisms. Finally, the issue was recently brought up at a round-table discussion at the sixth meeting of the International Society of Hypertension, illustrating 1) that a "both/and" attitude seems to be the only realistic choice because both variants occur in human as well as in rat primary hypertension; 2) that initial CO elevations certainly are common but by no means obligatory; and 3) that they can then be of entirely different origins, i.e., neurogenic or volume dependent.

Note that essentially all clear-cut volume variants, like aldosteronism, MHS, or HSR hypertension, display a modest bradycardia compared with controls. This mainly reflects the reflex vagal counterregulation, which is bound to occur particularly via cardiac volume receptors on salt-fluid retention and increased central filling (619), except if central neurogenic excitation "occludes" reflex cardiac slowing (sect. II C3). This is in sharp contrast to the situation in which limbic-hypothalamic-neurohormonal influences help to trigger hypertension, where tachycardia is virtually obligatory (sect. II C3). Thus under well-controlled conditions the resting heart rate may provide a handy and reasonably reliable indicator concerning volume variants versus neurogenic variants in early human hypertension. Human volume variants should have not only a slightly lowered resting heart rate due to reflex counterregulation but also low renin levels and at least a trend toward hypervolemia, which actually occurs in early MHS hypertension (56, 291) and in human mineralocorticoid hypertension (162).

However, such signs seem fairly rare in early human hypertension (67, 161, 162, 172, 265, 612), though perhaps more common in blacks, as discussed earlier. Furthermore in a large population sample Berglund and Wilhelmsen (49) noted a positive correlation between blood pressure and heart rate. A dominance for volume variants among the hypertensive subgroup should have given an inverse relationship instead, for reasons discussed. Nevertheless, with a multifactorial genetic predisposition that varies among individuals, less dominant primary renal-adrenal-volume deviations may be fairly common but masked by more forceful neurogenic influences, as though, on the rat level, MHS and SHR had been allowed to crossbreed at random.

In addition the genetic membrane alterations may well affect both autonomic and smooth muscle responsiveness so that neurogenic and volume expressions intermingle (sect. IIIF), not to mention myogenic contributions (sect. IIIC). Concerning the latter possibility, however, primary alterations of smooth muscle responsiveness in overall hemodynamics would hardly be directly apparent but rather express themselves mainly as accentuations of neurohormonal cardiovascular responses. Therefore their disclosure calls for more specialized analyses, directed toward particular vascular regions, isolated vessel preparations, etc., as dealt with in section III C.
C. Primary Alterations in Vascular and Cardiac Muscle

1. General aspects

As mentioned in section I, in recent decades it was first more widely discussed whether vascular and/or cardiac muscles could themselves harbor genetic alterations important in the induction of primary hypertension. Earlier they were usually assumed to merely reflect whatever initiating deviations that might afflict the kidneys, the hormonal, and/or the nervous control systems.

Because of a common ontogenetic background, vascular and cardiac muscle may both be affected if inherited alterations influence any of their major functional components: membrane events, excitation-contraction coupling, the contractile machinery, and the metabolic support system (77, 78, 217, 341). As outlined in section III, the final dominance of a resistance elevation has concentrated most interest in the vessels, particularly since a rapid gain in knowledge of smooth muscle physiology greatly facilitates pathophysiological studies (77, 78, 110, 203, 217, 218, 283, 341, 343, 345, 350, 354, 447, 593). The commonly raised CO in early phases of primary hypertension is widely acknowledged, but there is little to indicate that it should to any appreciable extent be caused by a genetic alteration of the cardiac effectors themselves, which in this section is the relevant question. It rather seems imposed from the outside, either as part of a neurohormonal pattern or as due to an increased filling of the system (sect. III). This of course does not exclude the possibility that cardiac muscle may also be affected, e.g., by a generalized membrane deviation, but, if so, it hardly seems to contribute decisively to early hemodynamic events. An excellent survey of the role of the heart in hypertension is given by Tarazi, Ferrario, and Dustan (615), recommended for both its critical analysis and its pertinent literature.

The heart, however, in another way may serve as an easily studied indicator for the whole system concerning genetic alterations, namely, if they tend to accentuate muscle hypertrophy also (sect. IIID). For example, at birth SHR display an increased cardiac weight compared with WKR, involving both the left and right ventricles (M. Hallbäck-Nordlander, unpublished observations). At this early stage it seems unlikely that, e.g., sympathetic excitatory influences and/or trophic transmitter influences would be responsible, because rats are very immature at birth, and at least in venous walls adrenergic neuroeffector contacts are not yet established (410). It had been discussed in 1958 whether cardiovascular tissues might show "an inherent trend towards hypertrophic changes which become manifest even at intermittent pressure loads so moderate that they hardly can be said to exceed the normal range of blood pressure variation" (209). Some early link along the sensing and activating systems within cardiovascular muscle cells, common for both the contraction and structural adaptation processes,
may be genetically reinforced (205), perhaps because of intimate relations to the altered membrane permeability to Na\(^+\) (and probably Ca\(^{2+}\)), as recently proposed by Friedman and Friedman (218, 222). These contractile and structural muscle responses represent two sides of the same coin, as discussed in section II.D. both depend on the intensity and frequency of stimulation, as well as on the load they have to face, though the structural responses need sufficient repetition of activation over some period to develop fully. In the discussion below of possible genetic alterations, particularly for vascular smooth muscle, their importance in sensitivity, contraction, and structural adaptation should be considered.

Normal functional principles for vascular smooth muscle are summarized first, however, 1) because this effector is directly involved in what finally goes wrong in primary hypertension (namely, the resistance function), 2) because differences between normality and abnormality seem at most quantitative, and 3) because recent rapid progress in smooth muscle physiology sheds new light on what may really go wrong. Excellent reviews are available and should be consulted for details (110, 217, 343, 345, 354, 447, 593).

2. Vascular smooth muscle

a) General characteristics. These effectors are a priori likely to be differentiated because they subserve so many different functions, depending on location. Thus in 1) the Windkessel vessels they mainly control wall distensibility, in 2) the pre- and postcapillary resistance and 3) sphincter vessels their tonic activity establishes a considerable circulatory and capillary reserve also suited for rapid and precise adjustments, and in 4) the postcapillary capacitance vessels they coordinate venous return to suit cardiac demands.

Position 1 obviously calls for a stable maintenance of tone, though hardly for rapid or extensive luminal changes, whereas this is precisely what is needed in positions 2 and 3 under strict local and remote controls. In position 4, finally, the latter type of control must dominate with both speed and power, particularly in humans, where the erect position with consequent hydrostatic pressure changes poses serious problems in cardiac filling.

Studies of isolated vascular strips, mainly derived from positions 1 and 4 but lately also from 2 (77, 293, 344, 410, 503), together with hemodynamic analyses of the various consecutive vascular sections in situ (260, 410, 447, 604) and microcirculatory investigations (75, 76, 303, 315, 333) provide enough information to outline some common features of vascular smooth muscle and the three main types of differentiation.

Vascular smooth muscle is commonly characterized by a fairly low resting membrane potential, between \(-40\) and \(-65\) mV, and membrane permeability seems relatively high, particularly to sodium ions. Nevertheless the
average intracellular concentrations of K+ and Na+ apparently correspond well to those in other muscle types, being around 130–140 mM and 10–15 mM, respectively, thanks to the membrane ionic pumps (77, 110, 217, 345, 354, 593). Friedman and Friedman (218, 220) long ago emphasized the probable importance of Na+ permeability and distribution for vascular smooth muscle function and for its contribution to hypertension.

Calcium ions are, as elsewhere, of fundamental importance in excitation-contraction coupling. Vascular smooth muscle seems to contain quite small Ca2+ stores, however, so that much of this activator ion must enter from the outside on depolarization, also carrying a substantial part of the inward current. Unfortunately this important Ca2+ influx and the expulsion events are poorly understood because of the great difficulties in measuring Ca2+ and Na+ inside smooth muscle cells. However, Blaustein’s interesting concept (72, 73) may reflect the principal events reasonably well. According to this concept the Na+-K+-ATPase system that keeps [Na+] low and [K+] high, as controlled mainly by [Na+] and [K+], has in parallel a Na+-Ca+ exchange pump, which expels Ca2+. If enhanced Na+ permeability and/or reduced Na+-K+-ATPase activity increases [Na+], this Ca2+-expulsion system is correspondingly damped. In addition an ATP-dependent Ca2+-expulsion system may also be present for elimination, besides the evidently small Ca2+ fraction stored intracellularly (345). In any case, the often marked Ca2+ entrance on cell activation certainly calls for efficient expulsion systems to avoid continuous smooth muscle contraction. Any deviation of these membrane events, which at least partly couple Ca2+ to the Na+ exchange, obviously may be of great importance in hypertension.

The contractile protein arrangement is unique in smooth muscle, with each thick myosin filament surrounded by 15–18 actin filaments. However, the cyclic formation of actomyosin cross bridges is the basis for shortening, though [Ca2+] seems to directly activate the actomyosin complex, instead of the first binding to troponin-tropomysin as in skeletal muscle (345). To maintain fairly small stores of ATP and creatine phosphate in smooth muscle, energy for their synthesis is delivered mainly by aerobic breakdown of glucose and fatty acids, though often paralleled by some anaerobic glycolysis. Also the glycogen stores are small, sufficing only for 15–20 min of an unusually economical activity (341, 343).

b) Specialized types of vascular smooth muscle. Three main variants may be distinguished by differentiation along the vascular bed, though presumably with considerable overlap or perhaps rather graded shifts, where one type transfers to the other.

1) TONIC SMOOTH MUSCLE. Tonic smooth muscle characterizes predominantly Windkessel and conduit arteries, though at least in some circuits it seems to prevail relatively far out toward the true resistance section. On activation, graded membrane depolarizations have been recorded and contractions are, at least in proximal sections, quite sluggish but remarkably well sustained and metabolically economic. This muscle type is well suited
for adjusting and maintaining wall tension in supplying Windkessel arborizations, a function where there is little need of speed but high endurance and low metabolic cost are necessary. Despite often many wall layers, the adrenergic neuroeffector junctions are commonly confined to the outermost muscle sheath. Moreover, at least in the larger arteries, junction gaps are often so wide (0.1–1 μm) that little transmitter reuptake is possible. Instead the released NE may have an almost hormonelike intramural spread at increasing dilution, though evidently compensated for by an unusually high effector sensitivity (53, 54, 410, 593). This arrangement hardly favors rapid neurogenic adjustments, but they are not much needed, at least not in proximal arterial sections.

For technical reasons isolated large arteries have been abundantly used for in vitro analyses, which is unfortunate because often far-reaching generalizations have been extended to the hemodynamically more important resistance and capacitance sections. Here muscle characteristics have important differences, particularly concerning inherent activity, speed of contraction, and mode of neurogenic control.

II) PHASIC, SINGLE-UNIT SMOOTH MUSCLE. Single-unit smooth muscle displays myogenic activity and somewhat resembles spontaneously active stretch receptors with built-in contractility (203, 350, 447), because pulse and mean arterial pressures constitute important dynamic and static stretch stimuli, facilitating inherent activity (260, 344). With a presumably graded transfer from sluggish tonic muscle somewhere along the arborizations, they seem to dominate increasingly in distal precapillary resistance and sphincter sections and, curiously, in some mesenteric and portal vein sections as well, perhaps remnants of the ancient “portal heart.” This is incidentally of great experimental advantage because these veins offer handy in vitro macro-models for distal rhythmically active single-unit muscle in the inaccessible but important microvessels (344, 410, 503, 536).

Resting membrane potential is only 40–50 mV and particularly unstable in pacemaker regions, probably in part reflecting a high and varying Na⁺ permeability that is further enhanced by stretch or cell swelling (341, 350, 447). Intracellular Ca²⁺ stores are so small that contraction demands a marked influx on depolarization (604), also in this respect differing from proximal tonic smooth muscle.

Pacemaker activity seems to initiate a complete though brief depolarization and quite rapid shortenings, particularly in distal microvessels, which, on repeated discharge, fuse into tonic contractions. Contractions are often so rapid that they may peak within 1 or 2 s with quite rapid relaxation also. Depolarization can spread via nexuses over limited distances along the microvasculature, presumably resulting in a multitude of perhaps partly overlapping “single units” (203, 350, 447). Probably the pronounced precapillary basal tone is often established myogenically this way, with dynamic and static stretch constituting important but limited positive feedbacks (203, 260, 350). Moreover they are safely counterbalanced by the potentially very powerful negative feedback inherent in locally produced vasodilator metab-
olites. These two feedbacks in synergism modulate myogenic tone on pressure and flow changes enough to cause functional autoregulation of flow, capillary pressure, and perfused capillary surface area. They oppose each other only when flow is reduced by venous pressure elevation, since this raises both transmural pressure and metabolite concentration (203). This interaction between myogenic activity and the mentioned feedbacks constitutes the basic framework for local control of flow, capillary flow distribution, and capillary hydrostatic pressure.

Remote effector control, which often entirely overrules autoregulatory control, is exercised mainly by vasoconstrictor fibers, where again the adrenergic varicosities make contact only with the adventitial surface of the outermost muscle layer. Of great interest here is that the adrenergic nerve arborizations also may convey local excitatory responses, elicited mainly by distal vascular distension (304). These adrenergic "axon reflexes" reinforce myogenic autoregulation in humans, e.g., during hydrostatic elevation of transmural pressures. They are reinforced in extent once structural autoregulation is developed (305).

The neuroeffector gaps in these distal microvessels are so narrow (600-1,200 Å) that peak NE concentrations per impulse (around 10^{-5} M) must for some milliseconds almost saturate the junctional receptors, though NE seems to be eliminated rapidly by reuptake into the varicosities and only to some extent by diffusion into the intercellular space (410). Consequently transmitter concentrations in these vessels may be largely subthreshold even at nearby noninnervated muscles, which instead seem to be recruited by myogenic spread via nexuses. This distinct innervation principle with partly specific transmitter elimination allows for the necessary speed and precision of neurogenic adjustments in the all-important resistance vessels. Elimination of neurogenic microvascular responses is therefore considerably retarded if the reuptake mechanism is blocked (410). These vessels also greatly differ from the almost hormonelike sympathetic influence on the much slower, but also more NE-sensitive, tonic vascular muscle in large arteries. Finally, it should be stressed that overflow NE concentrations in plasma and tissue fluid are largely subthreshold for resistance and capacitance vessels even at intense degrees of sympathetic activity, as further dealt with in section III D.

III) MULTIUNIT SMOOTH MUSCLE. The main characteristics of this variant, which seems to dominate in substantial parts of the venous capacitance vessels and in cutaneous arteriovenous shunts (447), are a lack of myogenic tone combined with a nearly complete subordination to neurogenic control. Both aspects are a prerequisite for the precise central and reflex regulation that must be demanded of these two vascular compartments.

3. Vascular and cardiac muscle in primary hypertension

Indications of primary alterations of particularly vascular smooth muscle function in primary hypertension have emerged from very different lines
of work. The advancing knowledge of smooth muscle physiology and the important findings of genetic deviations in cell membrane function in both human and rat primary hypertension (sect. IIIA) have increasingly focused interest on membrane and excitation-coupling events. Many key problems and most of the pertinent literature were recently surveyed, e.g., by Bohr (77, 78), Friedman (217), Haddy (282), and Johansson (341, 343).

a) Altered smooth muscle responsiveness. Many investigations have been performed in humans, though often without enough controlled circumstances to allow relevant conclusions. However, some really penetrating analyses began to appear in the late 1950's. For example, Mendlowitz et al. (448, 451, 452) noted accentuated resistance-vessel responses to NE in the fingers of hypertensive subjects, which were suggested to reflect a genetic abnormality in local NE turnover. Naturally complete dose-response curves could not be obtained; however, they are almost a necessity for clear separation of effects due to smooth muscle hypersensitivity and those due to a structurally based vascular hyperreactivity (sect. IID).

Mendlowitz considered the latter alternative unlikely, because hyperreactivity was not noted in finger vessels of patients with Raynaud's disease, in which structural changes are common. However, the hemodynamic amplifying effects of even gross wall thickening can of course be entirely offset if smooth muscle responsiveness is reduced concomitantly, as it is during vascular deterioration with advanced wall fibrosis, which is also common in Raynaud's disease. Another argument was the absence of increased renal vascular responses to intravenous NE infusion, which was complicated, however, by the unavoidable pressure elevation with secondary reflex adjustments. Far fewer such disturbing effects occur on epinephrine infusion, and in response to this constrictor agent the hypertensive kidneys appeared to show a true vascular hyperreactivity, judged from the data given in this particular study by Mendlowitz (448, 450). Even if present knowledge (sect. IIID) suggests that precapillary structural changes are likely to have been mainly responsible, the results of Mendlowitz may well be ascribed partly to an increased smooth muscle responsiveness, for reasons discussed in section IIIc3b.

Other early quantitative studies on hypertensive regional vascular beds by Duff (170) and by Doyle, Fraser, and Marshall (165, 168, 169) were of particular importance, because different concentrations of intra-arterially administered constrictor agents were used during recordings of both pressure and blood flow. Duff noted some supersensitivity to epinephrine but hardly any to NE, though the relevance may be questioned because elderly hypertensive women were compared with normotensive young men. The results of Doyle et al. at first appear to indicate true smooth muscle hypersensitivity, but of an unspecific nature, since it was found for NE, angiotensin II (ANG II), and serotonin (5-HT). However, the results were plotted as percent flow reduction (100% = vascular closure), and if they are replotted instead to relate agonist concentrations to resistance elevations, the latter
clearly escalate at higher agonist concentrations in the hypertensive sub-
jects. This suggests a geometrically based vascular hyperreactivity, because
a mere smooth muscle supersensitivity should result in a leftward, parallel
shift of the resistance responses (sect. II.D8). However, an element of smooth
muscle hypersensitivity of course may be present as well. Thus a tendency
to enhanced responses was observed in youngsters from hypertensive fam-
ilies (167), though even then marginal structural changes might be involved,
to judge from findings on young military conscripts with a family predis-
position to hypertension (553).

Related findings were described by Bárány and James (33), with the
additional important observation that pilomotor smooth muscle showed in-
creased NE responsiveness in hypertensive patients. Although not cardio-
avascular, this muscle type is closely related and is certainly devoid of any
geometric complications. Again a word of caution is needed, because two
studies (330, 621) on arterial strips from hypertensive and normotensive
subjects showed no signs of vascular smooth muscle supersensitivity in the
hypertensives, and here too the geometric element is eliminated.

These examples of quantitative studies concerning vascular smooth
muscle sensitivity in human primary hypertension show how structural vas-
cular hyperreactivity easily obscures the analysis, although there may well
be a marginal increase of smooth muscle sensitivity that sometimes seems
fairly evident but cannot always be traced. It should again be stressed that
genetic deviations afflicting vascular smooth muscle will probably be so
slight as to be barely detectable. The tendency of variability might be a
consequence of the membrane events described in section III.A, where a ge-
netic permeability deviation may be to a varying degree unmasked by oua-
bainlike inhibition of the sodium pump.

Another fruitful approach comes from studies of rat primary hyper-
tension, with the obvious advantage that far more penetrating analyses can
be performed. Conversely an equally obvious drawback is that they are not
necessarily adequate models for vascular smooth muscle in human primary
hypertension. Anyhow, SHR has been most commonly used, perhaps a lucky
choice because both SHR and human primary hypertension have many sim-
ilarities (204, 226, 483, 484, 689), among them similar alterations in membrane
permeability (525–527). However, fine studies of vascular smooth muscle have
also been performed on GHR, particularly by Smirk (589), Phelan et al. (516),
and Simpson’s group (264), and on HSR by Tobian et al. (233) and Mark et
al. (609).

Experimental preparations encompass 1) subcellular fractions, much
studied by, e.g., Aoki et al. (19, 20); 2) isolated vessels, mostly aortic and
large artery strips or portal veins, particularly used by Bohr et al. (77, 78,
659), Friedman and Friedman (218–220), Jones (351–353), Spector et al. (596),
Udenfriend et al. (636), Clineschmidt et al. (119), Ljung (410, 411), Sutter and
coworkers (508, 536), and Hermesmeyer (313, 314), with McGregor (443) in-
troducing isolated mesenteric arterial trees and Halpern, Mulvany, et al.
isolated arteriolar segments; 3) isolated vascular beds, where the whole set of resistance vessels is explored, by Folkow, Hallback, et al. (205, 208, 422), Haeusler et al. (195, 287, 288), Berecek, Bohr, and Hansen (42, 43, 294), Gross et al. (44, 160), Lais and Brody (390--392), Yamori et al. (688, 689), Collis et al. (129, 130), Smirk (588, 589), Gresson et al. (264); and 4) in the total, though usually denervated, cardiovascular system, e.g., by Yamaguchi and Kopin (687) and Sokabe's group (578). All these preparations have their advantages and drawbacks, but together they provide an overview from which some general principles of deviation seem to emerge.

b) Altered membrane characteristics in vascular smooth muscle. More than 20 years ago Friedman and Friedman (218, 220) drew attention to the great importance of ionic permeability characteristics for smooth muscle tone and responsiveness, also in hypertension. With present knowledge about the effects on membrane potential, excitability, and Ca\textsuperscript{2+} entrance and elimination, the excitation-contraction coupling processes are increasingly the focus of interest.

For example, Bohr and co-workers (78, 329, 659) noted in isolated vessel strips an increased occurrence of spontaneous rhythmic contractions in SHR as well as other signs of an inherently increased membrane lability and permeability. Using different ionic transfer techniques, Jones (351--353) and Friedman (217, 218) found clear signs of an increased passive permeability to sodium and potassium in SHR vascular smooth muscle, though it was apparently more or less balanced by the active pump systems. Further, using instead an interesting electrophysiological approach in SHR tail artery smooth muscle, Hermsmeyer (313, 314) arrived at largely similar conclusions. Even gastrointestinal smooth muscle from SHR shows signs of altered membrane characteristics (7). These examples of results from quite different experimental approaches thus all suggest an increased ionic permeability in SHR vascular smooth muscle, though more or less compensated by enhanced active pumping. They are also in good agreement with the results on various blood cells, initiated by Losse's pioneer findings (sect. IIIA).

One of several possibilities is that the SHR smooth muscle membrane has a reduced ability to retain calcium in its important role as membrane stabilizer (658, 661), which is also found in isolated red cell membranes from SHR and human primary hypertension (526). Furthermore subcellular fractions from both cardiac and vascular muscles have been analyzed in SHR and controls, though the vascular samples almost always represented large-artery, tonic smooth muscle. In this variant of muscle there are signs of a reduced capacity for intracellular Ca\textsuperscript{2+} storage in SHR (19, 20, 658, 661), which might explain why findings on SHR aortic strips suggest delayed and sometimes incomplete relaxation (121). According to Aoki (19, 20), a less efficient local binding of intracellular Ca\textsuperscript{2+} could represent the major genetic background to the increased resistance to blood flow in SHR. However, the true resistance vessels depend much more than large arteries on transmembrane Ca\textsuperscript{2+} influx and subsequent active expulsion (205, 604), and both in
SHR (205) and humans (209) they relax at least as promptly and completely as normotensive resistance vessels. Furthermore SHR resistance vessels and portal veins seem, if anything, to have better intracellular stores for Ca\(^{2+}\) than normotensive ones, to judge from vascular behavior at very low [Ca\(^{2+}\)]\(_i\) (205, 503, 511).

For such reasons any inherent accentuation of resistance-vessel smooth muscle tone in primary hypertension seems more likely to depend on genetic alterations of membrane permeability (sect. II.A) than of intracellular storage capacity for Ca\(^{2+}\). Altered permeability characteristics are likely to affect also the process of Ca\(^{2+}\) influx and efflux (72), with possible consequences for average [Ca\(^{2+}\)]\(_i\) and hence for resistance-vessel tone. On the whole, any tendency toward increased Ca\(^{2+}\) influx versus efflux will increase average [Ca\(^{2+}\)]\(_i\) and thereby myogenic tone as well as smooth muscle responsiveness to neurohormonal stimuli. However, whether such a primary vascular smooth muscle change is of decisive hemodynamic significance for resistance-vessel behavior in early primary hypertension is a crucial but unsettled question. Most, perhaps all, interpretations of hemodynamic data in such a direction may rather be explained by early structural autoregulation of precapillary resistance vessels, though this process may also be genetically reinforced by means of primary membrane changes (sect. III.D).

Many studies, employing all the techniques mentioned, have approached this problem by comparing smooth muscle sensitivity to constrictor agents, to ions, or to graded sympathetic stimulation. However, much early confusion came from conclusions that reached too far among preparations and techniques, as well as from a lack of insight into the need to separate changes due to altered smooth muscle sensitivity from those due to altered vessel geometry, which calls for strict comparisons between complete dose-response resistance curves (205).

When such problems were cleared up, however, results were still confusing, because some groups noted increased vascular smooth muscle sensitivity in SHR (160, 195, 287, 294, 314, 329, 391), others found largely unchanged sensitivity (5, 119, 129, 292, 390, 464), and still others observed reduced sensitivity (577, 596). Further, on isolated arteriolar preparations, Halpern, Mulvany, et al. (464, 671) noted that blockade of the NE reuptake unmasked a higher degree of smooth muscle sensitivity to NE in SHR than in normotensive Wistar-Kyoto rats (WKR), with no difference before the blockade. Whether this represents a primary smooth muscle change or an adaptation to an altered sympathetic activity and/or transmitter handling is not clear so far.

Some investigators have suggested that the divergent results are caused by inadequate techniques or the choice of unsuitable controls (119, 658), and it is often proposed that normotensive WKR, the direct ancestors of SHR, are better controls than ordinary Wistar normotensive control rats (NCR). This may be questioned, however, because most inbred WKR may contain several of the genes that in particular constellations cause SHR

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hypertension. Therefore WKR may relate to SHR more like close relatives relate to hypertensive patients, which are not commonly preferred as the most proper controls. The best choice may be if both WKR and ordinary NCR are used, at least for some purposes. Anyhow, one group noted that although SHR vessels were not supersensitive when related to NCR ones, they were supersensitive when compared with WKR vessels, which was thought to reveal a difference relevant for SHR hypertension (391). A skeptic, however, might as well conclude from these results that the supersensitivity of SHR versus WKR could not be crucial for the hypertensive state, since NCR are then about as supersensitive as SHR in relation to WKR but remain at least as normotensive as WKR.

On closer view these differing, and at first confusing, results may have a rational biological explanation, and a pathophysiologically important one at that. As mentioned in section IIIA, there are interesting results indicating a generalized primary increase of membrane permeability, though compensated by increased active pumping. There is also increasing evidence that a natriuretic hormone (654, 656) exerts a ouabainlike effect on the \( \text{Na}^+\)-\( \text{K}^+ \) pump in almost all cells (sect. IIIA). It seems to be secreted when, e.g., the cardiac volume receptors signal increased filling (sect. IIIE). If so, such an intrinsically normal membrane pump inhibitor may produce, in individuals with a genetically altered membrane permeability, larger excitability increases in cardiovascular muscle, autonomic neurons, etc., than in controls and may also affect neuroeffector junction events (sect. IIIIDc).

If mainly controlled by cardiac volume receptors, natriuretic hormone secretion may also occur when blood volume is centralized, either for neurogenic or structural reasons, as in established primary hypertension. However, its general membrane effects, with potential increases in muscle and/or neuron responsiveness, would be normally more or less offset by concomitant reflex sympathetic inhibition (sect. IIIA). It might also accentuate basal myogenic tone and the autoregulatory power of the precapillary resistance vessels, however, particularly when genetic membrane permeability is also altered. Thus the seemingly conflicting results just described at least to some extent may reflect various levels \( \text{Na}^+\)-\( \text{K}^+ \) pump activity, depending on the current volume balance and natriuretic hormone concentrations in the experimental animals.

For example, Lais and Brody (390) noted approximately equal NE sensitivity in SHR and controls during in vitro perfusion, whereas the SHR vessels showed modest supersensitivity when perfused with blood in vivo, suggesting the presence of some sensitizing factor in blood. Pressor agents with ouabainlike effects have been traced in both secondary volume hypertension (491, 495) and in human primary hypertension (74, 656), where centralization of blood volume commonly occurs. When adult SHR, WKR, and NCR vascular beds were compared in vitro for sensitivity to NE, vasopressin, and \( \text{Ba}^{2+} \) (339), the dose-response resistance curves had largely similar ED\(_{50}\) values. However, after ouabain (10\(^{-4}\) M), which slightly shifted all curves left, this leftward shift was significantly greater in SHR for all agonists.
Similar observations have been made by Webb and Bohr (659) on isolated SHR and WKR tail arteries. These results may reflect a ouabain blockade of a compensatory membrane pump activation in SHR, unmasking an increased membrane permeability and hence leading to greater excitability increases in response to all three agonists than in the controls. In very young SHR, however, there was little sign of compensatory membrane pump increase; instead the SHR resistance vessels before ouabain tended to be slightly more sensitive to, e.g., NE than the controls (256). This also confirms several other findings in that increased sensitivity to excitatory agents in SHR seems to occur particularly in very young animals, still in the borderline phase of hypertension (160, 195, 287, 391).

c) Altered smooth muscle responses to sympathetic control. Studies on isolated precapillary microvessels with the Halpern-Mulvany technique suggest another important aspect of vascular effector responsiveness (464, 671). The isolated SHR vessels seemed to display accentuated transmitter reuptake in nerve endings, which tends to mask the true NE sensitivity, implying that it may be underestimated in resistance-vessel studies with intact nerve endings. On the other hand, in at least several studies the sensitivity (but not vascular reactivity) of the true resistance vessels is largely equal in adult SHR and controls also to vasopressin, Ba$^{2+}$, and serotonin, judged from the ED$_{50}$ of the resistance curves (5, 205, 339, 664). In any case it is not known whether the increased NE reuptake is due to genetic membrane alterations also in adrenergic varicosities or to local neuronal adaptation to accentuated sympathetic discharge in SHR (cf. sect. III@).

Of course even more important than the responsiveness to exogenous NE is how the true resistance vessels react to vasoconstrictor-fiber activations at physiological rates, since this is by far the most dominant catecholamine influence in vivo. On the other hand, it is far more difficult to perform such comparisons, particularly in small animals like SHR and control rats, since all regional adrenergic fibers must remain intact and be simultaneously excited at known frequencies to make the comparisons valid. Thus there are few such studies and they must be judged with some caution, partly because regional differences are likely and partly because of technical difficulties. In the renal vascular bed, Vanhoutte and co-workers (129, 130, 652) noted a clear exaggeration of neurogenic resistance responses in young SHR but also increased NE release per impulse. Adult SHR also show increased vascular reactivity to exogenous NE (130, 652), due to preglomerular structural autoregulation not clearly present in young SHR. Whether the increased NE release per impulse in SHR reflects genetic membrane alterations in adrenergic nerve varicosities and/or a secondary adaptation to accentuated central discharge (sect. III@) is not known. In SHR mesenteric arterial preparations, the resistance increases to both sympathetic stimulation and NE infusion were enhanced in SHR compared with controls (288).

On the other hand, in hindquarter resistance vessels of adult SHR with clear vascular hyperreactivity and some supersensitivity to exogenous NE, Lais and Brody (392) also stimulated the vasoconstrictor fibers at graded
frequencies. Curiously this did not produce accentuated SHR responses, whereas tyramine injection, which releases NE from nerve endings, did. Whether this was due to reduced NE release per impulse at these particular nerve endings, to regional differences in innervation density, or mainly to technical disturbances is not known, but direct sympathetic stimulation to rat hindquarter preparations is difficult because of the complex fiber arrangements. Clearly more studies of graded regional sympathetic activations are needed in animals and humans, not least because the vasoconstrictor-fiber influence is, besides the myogenic tonic activity, the most powerful factor influencing systemic resistance and cannot be precisely mimicked by exogenous NE administration.

d) Hemodynamic consequences. Strictly speaking, so far there is no entirely convincing demonstration that early primary hypertension is preceded or paralleled by a generalized and continuous increase of tonic smooth muscle activity in the resistance vessels proper, large enough to explain the average pressure elevation. Rather, at least in early neurogenic primary hypertension in humans and rats (SHR), remote sympathetic control superimposes differentiated resistance changes, in which that in skeletal muscle is indeed often lowered compared with normotensives, whereas those in, e.g., the renal and splanchnic circuits are enhanced. Actually there is often little or no increase in overall systemic resistance because a CO increase mainly explains the early pressure elevation (sect. III B3h). In established hypertension an overall resistance elevation dominates first, but mainly because of early structural autoregulation, where \( R_r/R_{min} \) is usually not increased, though it should be if vascular smooth muscle activity were elevated (sect. II D3, III B2).

Undoubtedly this is the most striking and important difference between primary hypertension and, e.g., renal variants of secondary hypertension, where the resistance vessels exhibit clearly increased tonic activity, particularly in early stages. In a way the enthusiasm created by Goldblatt's splen-did model of hypertension has often made it an axiom that primary hypertension should also be characterized by a considerable steady increase in resistance-vessel smooth muscle activity. However, in primary hypertension it seems difficult to trace or, when found, can usually be ascribed to central neurogenic influences that are soon replaced by structural autoregulation. In virtually all penetrating analyses of regional resistance in human primary hypertension, an increased \( R_r \) seems accompanied by a largely proportional \( R_{min} \) elevation, providing little or no room for increased smooth muscle activity, except when there are also signs of increased nervous activity.

Nevertheless several of the most convincing of these studies strongly indicate that a genetically based permeability increase is present and can express itself as increased smooth muscle responsiveness, though it may soon be offset by, e.g., enhanced membrane pump activity. Particularly if this latter activity can in turn be frequently suppressed by a volume-dependent natriuretic hormone, there should be opportunities for periods of, e.g., accentuated myogenic basal tone and autoregulatory adjustments at increases of central filling. Such events would be particularly likely in volume
variants during salt-volume loading. Thus membrane-mediated reinforce-
ments of whole-body autoregulation, both the acute myogenic component
and the subsequent structural autoregulation, may occur but so far have not
been clearly demonstrated. Rather, when such situations are experimentally
explored, the neurogenic influence seems to be predominantly reinforced, at
least in acute situations (sect. IIIA, D, E3, E4). In the long run perhaps the
most critical effect of genetic membrane-mediated influences on cardio-
vascular smooth muscle in primary hypertension may be on their structural
adaptation (sect. IID, IIIIC1). The signs of cardiac hypertrophy found in utero
in SHR by Hallbäck-Nordlander or in early sympathectomized SHR by Cu-
tilleta et al. (138) favor such a suggestion. The vascular bed also shows signs
of early wall changes, as in immunosympathectomized SHR, where the re-
sistance vessels seem to display modest structural autoregulation compared
with intact normotensive controls (664). Cerebral arteriolar vessels show
structural changes at such an early age in SHR that the minor pressure
difference from controls may not provide sufficient explanations, according
to Nordborg and Barbro Johansson (472). Furthermore the degree of struc-
tural autoregulation seems more pronounced in SHR than in genetically
normotensive rats, which by renal hypertension reach even higher pressures
(421). Finally, the venous side in SHR also displays modest wall changes at
such an early age that venous pressure measurements hardly indicate any
difference from controls, according to Greenberg's group (262, 263).

Admittedly it is exceedingly difficult to prove beyond doubt that the
degree of cardiac hypertrophy or structural autoregulation for a given load
is accentuated in primary hypertension and even more difficult to ascribe
it to intrinsic muscle processes. Only marginal differences are expected with
such genetic predisposing elements, but nevertheless they may have impor-
tant hemodynamic consequences eventually, for reasons discussed in sections
IID8 and III B. After all, primary hypertension develops gradually via several
stages, indicative of several participating components among which at least
one, which seems crucial, takes some time to be established.

Finally, even if vascular smooth muscle function also is altered by ge-
netic membrane changes, this may have less immediate hemodynamic con-
sequences than if similar membrane alterations affect the nervous control
system. This would be particularly true if the excitability of the tonically
active central neuron pools responsible for sympathetic control are thereby
affected and/or if transmitter release is increased peripherally. This pos-
sibility is dealt with in section III D.

D. Primary Alterations of Neurogenic Control

1. General aspects

Whereas myocardial and vascular myogenic activity and autoregulatory
mechanisms are the fundamentals for cardiac pumping, resistance to flow,
and flow distribution, the autonomic nervous system is by far the most powerful and fastest of the extrinsic control systems. However, there are no strict borders to, e.g., the hormonal system, since the two are often closely knit into a dual control device, exemplified by their common association into central neurohormonal patterns. Another example of interaction is the nervous control of renin release, which via angiotension II influences aldosterone release, but angiotensin II also exerts important excitatory effects on strategically important neuron sites in the brain stem (sect. III$E2$). Remote cardiovascular regulation is thus accomplished by a closely interacting dual system, where nervous control accounts for speed, differentiation, and power of adjustment and the hormonal system for sustained levels of control, often utilizing trophic-metabolic modulations of cells rather than all-or-none excitation or inhibition.

The autonomic nervous system has two major responsibilities in coordinating the various cardiovascular sections to function as an efficient unit. 1) Via pressure, volume, and chemoreceptor information, its tonic, low-frequency discharge reflexly integrates circulatory functions to maintain internal homeostasis. This occurs with great precision, exemplified by the fact that the maintenance of resting pressure and resistance levels calls for an adjustment of average vascular smooth muscle length to within a few percent. 2) Autonomic nerve activity is readily affected also by environmental influences via CNS-integrated telereceptors. The consequent psychophysiological changes are paralleled by efferent neurohormonal patterns, which are for the situation appropriate but when intense can override even reflex homeostasis, as exemplified in section II$C3$.

Naturally central reflex as well as peripheral links in neurogenic cardiovascular control have all been considered as possible sites for pathogenetic alterations in primary hypertension. As usual, however, if there are alterations in neurohormonal control, it is difficult to decide what is primary and what is secondary, once an alteration is detected. For example, most mechanoreceptors are readily reset by sustained changes, both functionally and by alterations of the wall where they are located. Further, like all tissues, nerve cells also have a remarkable ability to adapt to imposed changes. Thus when adrenergic neurons are exposed to altered drive from other sources, they rapidly also adapt transmitter synthesis, storage capacity, and release, etc., as surveyed by Burnstock and Costa (103) and experimentally illustrated by, e.g., Östman-Smith (489). Therefore if some variants of primary hypertension should exhibit changes in some central or peripheral autonomic neuron groups, this of course does not necessarily mean that precisely these nerve cells are the key pathogenetic site; the changes may as well represent neuronal adaptation to increased or decreased activity emanating from entirely different sites.

A major difficulty in studies of neurogenic control is the promptness and extent of its responses to almost any interference, including those imposed by experimenters. Autonomic control often operates with rapid on-off
activity. Thus central neurogenic contributions to primary hypertension have been irritatingly difficult to document convincingly enough to persuade skeptics, who sometimes have firm but preconceived ideas on how neurogenic influences should express themselves. Too often, for example, it has been assumed that they must then be generalized, continuously present, account for more or less the entire resistance elevation, and furthermore result in substantial increases of plasma NE levels. When experimental findings, for reasons outlined below, do not match these preconceived ideas, neurogenic contributions to primary hypertension are often dismissed entirely.

The problem is certainly not made easier by the physiological fact that not only are autonomic discharge elevations frequently intermittent by nature but they are also more or less differentiated, with increased activity to some cardiovascular regions and decreased activity to others. Finally, as discussed in sections IIA, B and IIIA, there are strong reasons to believe that functional trigger elements in primary hypertension, including neurogenic ones, need only be marginal and may well be intermittent. It is therefore not surprising that for several decades this particular issue has been, and still is, perhaps the most controversial of all in the discussion of the pathogenesis of primary hypertension. Therefore it is reasonable to critically discuss the various techniques used to evaluate neurogenic influences.

The literature and essential problems of neurogenic influences in hypertension are excellently reviewed by, e.g., Zanchetti and Bartorelli in Hypertension (241) and the central control by Korner (381) and Zanchetti (695). Finally, there are a number of good reviews and articles that critically discuss both physiological and pathophysiological facets of nervous cardiovascular control (12, 93, 103, 111, 150, 152, 157, 201, 204, 206, 232, 240, 286, 299, 363, 387, 534, 588, 689, 697, 698).

2. Methodology

Modern electrophysiological techniques at first appear to be the only appropriate choice, since it is undoubtedly a matter of solving neurophysiological problems. However, to map, e.g., central autonomic patterns with such techniques, calling for simultaneous recordings from thin fibers destined for several cardiovascular regions, borders on the impossible. Moreover it requires anesthesia or decerebrated preparations, which would distort or even eliminate the patterns to be studied. In addition action potentials in vasoconstrictor and vasodilator fibers look much the same but have definitely opposite effects on blood vessels. Likewise impulses in fibers of mixed autonomic nerves are similar whether destined for blood vessels, gastrointestinal intramural plexa, piloerectors, or sweat glands, but these fiber sets are usually involved in entirely different autonomic patterns and certainly evoke quite different responses.

Fortunately there is another, more manageable way to analyze auto-
nomic discharge patterns, namely, to record quantitatively selected effector responses, compare them with controls and/or with direct stimulation of the respective sets of fibers, and utilize the effects of regional fiber blockade (201, 206). This approach, though in a sense indirect, has great merit and simulates that used by Sherrington in his classic analyses of spinal-supraspinal somatomotor reflexes, which laid the foundations for modern neurophysiology. In fact the very arrangement of autonomic fibers offers a special advantage for this approach, inherent in the fact that pre- and postganglionic fiber bundles destined for any given cardiovascular section are somewhat fused together by extensive fiber divergence-convergence at both ganglionic and neuroeffector sites. Thus higher centers can send out differentiated commands via relatively few bulbar neurons, arranged as separate pools to direct, e.g., renal, gastrointestinal, or skeletal muscle vascular beds separately if needed (206). Within each such unit, discharge is spread fairly uniformly via the divergence-convergence arrangement to virtually all innervated effector cells, with myogenic recruitment of noninnervated ones via nexuses.

Because of this arrangement, graded direct stimulation of the entire sympathetic supply to individual vascular beds fairly well mimics the way in which higher centers control each circuit by selective variations of a regionally uniform discharge. The relationships between discharge rate and effector response form characteristic hyperbolic curves for each cardiovascular section, with high curve steepness in the lower, physiological discharge range (201, 206). An experienced investigator therefore, from simultaneous recordings of, e.g., heart rate, selected regional flow resistances, or capacitance responses, can deduce the prevailing autonomic pattern and also how intensely it is engaged. Here in particular heart rate can closely reflect the sympathetic activity during various degrees of alertness, best illustrated by the fact that concomitant recordings of heart rate and splanchnic sympathetic discharge in awake, freely moving rats are closely parallel (211, 538).

On the whole, this mode of analyzing autonomic discharge patterns and neurogenic effector adjustments forms much of the experimental basis of current knowledge about central and reflex cardiovascular control (180, 201, 206, 318, 319, 381, 695). It has also been utilized with considerable success in humans (87, 91), as well as in explorations of whether cardiovascular neurogenic control is altered in early primary hypertension, in both rats (204, 211, 290, 291, 392) and humans (91, 92, 112, 185, 188, 204, 226, 326, 362, 364).

In analyses of, e.g., cardiovascular baroreceptor reflexes in human primary hypertension, recordings of effector responses, like heart rate, arterial pressure, forearm resistance, etc., are also of great value, used particularly by Sleight et al. (524, 587) and Mancia et al. (430). Baroreceptor activation is then induced by neck suction, which involves only the carotid baroreceptors (430, 587), or by phenylephrine, which activates all arterial baroreceptors (587). Cardiac volume receptors in humans are fairly selectively engaged by lower-body compression or suction, which affects central blood volume and cardiac filling (164, 182, 619).
Of course electrophysiological techniques have also been used and complement increasingly efficiently the information based on recordings of effector responses. Anesthetized rats with primary hypertension were used, but for reasons mentioned previously this particular problem calls for sympathetic recordings also in awake and reasonably undisturbed subjects. This has recently been possible, not only in SHR (211, 359, 538) but even in humans, thanks to the admirable technique of Wallin and co-workers (643-645). However, it is very difficult to detect smaller differences in discharge rate, which hemodynamically can be quite important because of the steep frequency-response curves. Another limitation is that only brief recordings of neuronal activity to a single region can be employed, and they are therefore often complemented by hemodynamic recordings of, e.g., regional flow resistance, heart rate, and arterial pressure.

Naturally in humans neural recordings are restricted to limb nerves, implying that sympathetic discharge is recorded only in skeletal muscle and cutaneous vascular beds. The cutaneous circuit is so dominated by the hypothalamic thermoregulatory center that its sympathetic discharge reveals little about, e.g., average accentuations of overall sympathetic hemodynamic control in primary hypertension. Skeletal muscle vasoconstrictor-fiber activity is in turn usually reduced in alert responses or all-out defense reactions, whereas sympathetic discharge then increases almost everywhere else. Likewise in early hyperkinetic stages of primary hypertension the commonly increased muscle blood supply in both humans and SHR suggests that here too muscle vasoconstrictor-fiber discharge is largely unaltered or even reduced, whereas the tachycardia and the splanchnic and renal vasoconstrictions strongly indicate increased sympathetic activity to these sections, as in defense reactions (sect. IIc3).

With such a background it should not surprise even enthusiasts of neureogenic concepts that Wallin et al. (643, 644) found no clear difference in tonic sympathetic discharge to skeletal muscle vessels between controls and patients with early primary hypertension; however, induced cardiovascular reflexes could be easily traced in the expected way. Perhaps this elegant technique can be applied to recording sympathetic activity also to the heart and/or to the renal and gastrointestinal circuits, because these are the regions where substantial increases should be expected, as shown, e.g., in SHR compared with controls (211, 538).

More indirect approaches have also been used, based, e.g., on regional transmitter turnover after labeling the stores of transmitter in nerve varicosities with tritiated NE, successfully employed in young SHR by Okamoto, Yamori, et al. (484, 689). A pioneering approach along these lines was used in humans nearly 20 years ago by Mendlowitz and co-workers (248, 249, 454), when they studied the escape of injected tritiated NE and noted a more rapid elimination in primary hypertension than in secondary hypertension or normotension. At that time it was considered to reflect an abnormal NE handling at effector sites, but with present knowledge of NE metabolism it seems
more likely that the tracer was rapidly taken up by the adrenergic nerve endings, to escape as part of the transmitter release. These interesting findings therefore suggest that average sympathetic activity was indeed modestly elevated in the patients with primary hypertension, though more studies of this nature are certainly needed (204).

There is also a strong need for simple methods of evaluating sympathetic activity in human primary hypertension, for use, e.g., in larger groups with minimal interference. Since a fraction of NE released from sympathetic nerve endings normally spills over in plasma and subsequently in the urine, and sensitive methods for its measurement are now available (65, 185, 687), this approach at first appears to be the method of choice for such purposes. It has accordingly become increasingly popular, as reviewed, e.g., by Kuchel (387) and reflected in numerous publications (65, 113, 116, 157, 158, 181, 185, 306, 323, 415, 542, 645, 667, 687), and it seems to reflect fairly well the degree of sympathetic activity if this is generalized, as during spinal cord stimulation in pithed rats (687), and no exercise hyperemia is present to increase the overflow fraction of NE (211).

Nevertheless it is doubtful whether this handy method is reliable in this particular situation, for the following reasons (211). As mentioned above, sympathetic activity to the large skeletal muscle vascular bed is frequently not increased or may even be reduced in early primary hypertension, with discharge increases occurring mainly to heart, renal, and splanchnic vascular beds and venous side. The liver has a great capacity to clear plasma NE, however, so little of the transmitter overflow would be expected to enter the general bloodstream from the hemodynamically important splanchnic vascular bed. Increased NE overflow would occur mainly from, e.g., heart and kidneys, hemodynamically quite important but with a very small amount of adrenergically innervated tissue compared with the huge skeletal muscle mass (0.6-0.8 kg vs. 30 kg), though heart and kidneys per unit weight have a denser sympathetic supply.

It follows that the particular sympathetic pattern found in early primary hypertension, closely mimicking mild defense reactions, unfortunately cannot be expected to regularly increase plasma NE; sometimes it might even reduce it (211). A striking illustration is the fact that provoked defense reactions in humans with quite substantial neurogenic increases of both MAP and CO did not elevate, or increased very little, plasma NE levels, whereas they rose considerably in the same subjects after tilting (323), known to produce widespread reflex vasoconstriction especially in skeletal muscle (4, 164, 619). Actually, plasma NE correlates very closely with sympathetic muscle nerve discharge in humans (645). Therefore the vasoconstrictor fibers to the large skeletal muscle mass apparently contribute dominantly to the NE overflow into the mixed venous or arterial blood, and these fibers are much activated during tilting (116, 321, 667), “cold pressor test” (116), or exercise (542). Consequently this handy and almost noninvasive method is not a reliable indicator for detecting neurogenic contributions to early pri-
mary hypertension, because an increased sympathetic activity of the frequently involved differentiated type, with marked hemodynamic effects, may be present without increasing plasma NE appreciably. Earlier optimism that dopamine β-hydroxylase, the enzyme released in small amounts together with NE, should be a useful indicator of sympathetic activity has also largely vanished (415, 478). Moreover this protein molecule is so large that it enters the circulation first via the lymph stream. Finally, its turnover seems to be so individually variable and complex that only extensive differences in sympathetic discharge may be traced.

To know what plasma NE really means in primary hypertension, it is time to combine hemodynamic analyses of neurogenic circulatory patterns with regional NE overflow estimations from arteriovenous differences and local blood flows. After all, NE is not a hormone but a specific transmitter, and for most effector cells the subthreshold plasma levels reflect a variable spillover at innumerable discrete neuroeffector junctions with NE concentrations perhaps 1,000-fold higher and combined into often highly differentiated discharge patterns, where hemodynamic and overflow effects are by no means congruent in all situations.

3. Pathogenetic considerations

a) Limbic-hypothalamic level. Of course humans are of prime interest, though naturally also far less accessible for experimental analyses than the hypertensive rat strains. It is therefore reasonable to start with the findings in these models, notably with SHR, since most of the work on neurogenic influences has been performed on this strain.

The initial studies by Okamoto, Aoki, Yamori, and their co-workers strongly indicated that nervous elements constituted an important trigger influence in SHR hypertension, closely linked to hypophysial hormone release in a way that strongly points to a limbic-hypothalamic origin (377, 483, 484, 689, 692). Particularly when young, SHR exhibit a clear central hyperreactivity to environmental alerting stimuli compared with controls. This results in exaggerated and often prolonged defense reactions with consequent greater MAP elevations, always accompanied by more intense cardiac sympathetic activation coupled to a stronger inhibition of vagal tone (204, 210, 290). Furthermore, even during rest the young SHR clearly show a hyperkinetic circulation compared with controls, where the mildly raised pressure is mainly due to an elevated cardiac output. This in turn is a consequence of neurogenic tachycardia at largely unchanged stroke volume (211, 512, 513). Arousal accentuates this difference from normotensive controls, whether in WKR or ordinary NCR (211). The effects of selective nerve blockade, anesthesia, and direct nerve stimulation to the heart (204, 210, 211, 290) make it clear that the recorded changes are truly neurogenic and essentially of limbic-hypothalamic origin (sect. IIc3). This is further supported by the
close correlation noted between directly recorded changes in sympathetic activity and in heart rate in awake, freely moving SHR exposed to trivial environmental stimuli, where responses are more brisk and variable than in controls (211, 538). Adrenomedullary activity also is clearly raised in young SHR according to Kopin's group (266).

The close interdependence between primary central hyperreactivity and environmental influences in SHR is further illustrated by the fact that early, prolonged reduction of ordinary daily psychosocial stimuli by social isolation or light deprivation delays and attenuates the development of SHR hypertension, as paralleled by less pronounced cardiovascular structural changes (289, 389). However, such isolated SHR still display hyperreactivity to alerting influences when exposed to such stimuli, showing that it is indeed an expression of a primary deviation at the limbic-hypothalamic level (289). Conversely, when SHR are exposed to increased mental stress, their hypertension often becomes grossly accentuated, whereas genetically normotensive controls then show only modest pressure elevations (483).

With respect to other indications of a primary engagement of neurogenic mechanisms, awake or lightly anesthetized SHR display a clearly increased sympathetic discharge to the renal and splanchnic areas compared with controls (211, 359, 538), though the surgery and anesthesia involved may introduce disturbing influences. The effects of pithing also strongly suggest the presence of a centrally increased sympathetic activity in SHR (6, 337, 484, 578, 687) and structural cardiovascular adaptation as well (6).

Other reflections of a raised sympathetic activity in SHR, at least in young rats, is the increased NE turnover in the heart (484, 689) and also the many interesting signs of altered catecholamine metabolism in central monoaminergic neurons (27, 151, 152, 232, 285, 286, 299, 484, 534, 544, 689). The precise meaning of the latter changes is not fully understood, because too little is known about exact physiological roles of the various pools of central monoaminergic neurons, at least when it comes to cardiovascular control (111, 150, 152, 299, 594). Ascending monoaminergic pathways with limbic-hypothalamic projections, however, seem to facilitate sympathetic discharge, whereas others also exert inhibitory influences, presumably at medullospinal levels (150, 152, 299, 534). These mainly bulbar monoaminergic neurons evidently serve as powerful neuronal modulators in both descending (111) and ascending directions (299) and can thereby reset many fundamental CNS mechanisms, including those responsible for mental alertness and psycho-emotional balance (150-152, 299). For such reasons they must considerably influence also autonomic suprabulbar and bulbar mechanisms, their reflex modulation, and hence also tonic efferent sympathetic activity. Interesting work on hypertension problems is being done by the groups of, e.g., Chalmers (111), Fuxe (232), Haeusler (285), Henning (299), de Jong (151, 152), and Reis (534).

Possibly some of these central monoaminergic neurons are primarily responsible for the increased central hyperresponsiveness characterizing
early SHR hypertension. This has also been repeatedly discussed (151, 299, 484, 534, 689), though the old problem of primary and secondary is particularly difficult here, considering the immense complexities of central neuronal arrangements. For example, much interest has been devoted to the bulbar neuron groups utilizing epinephrine as transmitter (232); Saavedra et al. (544) and Fuxe et al. (232) have presented evidence of an important involvement in central sympathetic control, as well as of alterations in early SHR hypertension. Furthermore findings by Haeusler (285, 286) suggest that the reactivity of autonomic hypothalamic centers may depend on ascending facilitatory monoaminergic pathways. Such a facilitating influence might explain the central hyperreactivity to environmental stimuli in SHR, which also show other signs of accentuated "emotional charge," like increased explorative behavior, etc. (210, 484, 689).

Beyond reasonable doubt, therefore, some genetic alterations influencing central sympathetic control in SHR must exist, but a word of caution is needed concerning their exact nature and location. Perhaps the central monoaminergic neurons have been the focus of too much interest, simply because there are so many good methods of studying them. In all likelihood they are importantly involved in, e.g., the increased central hyperreactivity, but whether they here mainly convey deviations starting elsewhere or really are true initiators remains unknown. After all, brain stem mechanisms utilize millions of neurons with a great variety of transmitters, and a priori it is not impossible that some other neuron type is even more important than the catecholamine ones for initiating the increased central reactivity of neurogenic cardiovascular control, in both rats and humans.

It is clearly too soon to go into details concerning exact locations and primarily involved neuron types, and at present it is enough to conclude that at least one important, genetically linked trigger mechanism of SHR, and often also human, hypertension results in an accentuated reactivity of limbic-hypothalamic-bulbar autonomic centers, tending to elevate sympathetic activity in response to a variety of stimuli, particularly environmental ones (cf. sect. III.B.3.b). For this reason increases of average sympathetic activity in hypertension should exhibit considerable variability and rather be more intermittent than stable and continuous. Another strong indication that limbic-hypothalamic levels, with their psychoemotionally directed neurohormonal response patterns, are influenced is the fact that young SHR show elevations also of hypophysal ACTH content and secretion of thyroid-stimulating hormone (377, 483, 484, 692).

Finally, it should be discussed whether genetic alterations of membrane permeability (sect. IIIA) might be involved. If generalized they could of course afflict the CNS, though significant effects on excitability may perhaps be expected only in such neurons that normally are particularly sensitive to stimuli or are even inherently active. This seems to be the situation particularly for neuron pools in the brain stem structures, where sympathetic tonic activity originates and where even central chemoreceptor activity oc-
curs (206, 318, 363, 381, 534, 695). Ultimately it might be such genetic membrane alterations that express themselves in some critical neuronal pools that normally accentuate arousal and central autonomic activity. At the present stage, however, this remains pure speculation.

Hypertension in GHR seems to display an early accentuation of central autonomic activity, as studied by Smirk (589) and Phelan et al. (516) and reviewed in Hypertension (210), though comparatively few studies of this nature have been performed on this interesting variant. However, early stages of GHR hypertension are, like SHR, characterized by an increased heart rate that is no doubt neurogenic. Furthermore the rising pressure shows much more variability than it does in controls, which again indicates an important neurogenic contribution (210).

As outlined in section IIIb1b, the hemodynamic situation in early human hypertension often shows such close resemblances to ordinary mild defense reactions that CNS influences offer the only reasonable explanation (92, 185, 188, 204, 224, 226, 363, 364). Thus the hyperkinetic circulatory state with increases of arterial pressure, heart rate, cardiac output, and muscle blood supply is a common finding, but, as noted by Brod, a resistance increase may also dominate the pressure elevation. Again a CO elevation is certainly not an obligatory sign of neurogenic influences of this kind. The dominance of a resistance increase is indeed often seen also in experimentally elicited defense reactions and simply depends on the balance between current central-hypothalamic, reflex-bulbar, and local influences on the CO-resistance relationship (206, 381, 695). Shifts in this balance determine whether CO and muscle blood supply both increase in mild defense reactions or whether a modest muscle vasoconstriction adds to the more powerful ones in other circuits, with little or no output increase. Then plasma NE is likely to increase (cf. sect. IIIb2).

Depending on which variant prevails at a given central neurogenic pressure elevation, the vasoconstrictor-fiber engagement within the large skeletal muscle mass thus may vary from mild accentuation to inhibition, which must greatly influence net plasma NE levels, as discussed earlier. Another disturbing influence is that, for a given vasoconstrictor-fiber discharge to skeletal muscle, the NE overflow increases considerably whenever muscle activity adds an element of hyperemia (211). Quite likely such factors to a great extent explain the many conflicting results concerning plasma NE levels in human primary hypertension and for "wrong" reasons led investigators to disregard CNS effects. There is certainly a great need for simultaneous measurements of regional NE release by means of arteriovenous differences and blood flows in, e.g., kidneys, heart, and skeletal muscle in human primary hypertension.

Thus a given central neurogenic activation can result in substantial variations of the balance between CO and resistance, and with that also in NE overflow to the mixed blood, but these central autonomous activations nearly always lead to increased heart rate, which seems to closely parallel
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sympathetic activity to the hemodynamically important renal and splanchnic regions (211, 538). Section III B2b describes how, e.g., Julius and co-workers (364) in their hemodynamic analyses utilized this much more reliable indicator of increased sympathetic activity in human borderline hypertension, as was the case also in the important studies by Falkner, Onesti, and co-workers (188), in addition to the revealing findings in Lund-Johansen's excellent follow-up studies (425–427). Together these and many other findings provide convincing evidence of the common participation of a centrally accentuated sympathetic drive on the cardiovascular system in early human hypertension, and furthermore this element is, as in SHR, genetically linked. It is hardly possible to explain the findings of Falkner et al. (188) any other way.

Apart from the heart rate changes and more or less hyperkinetic circulation, early neurogenic variants of human hypertension often show modest elevations of plasma renin activity as well, presumably reflecting a central nervous engagement also of the kidney and its renin cells (183, 184). Hollenberg and co-workers (327, 328) in such patients found strong evidence of an accentuated sympathetic activity in many cases by utilizing local effects of α-adrenergic blocking agents (sect. III F2).

It is also known that cardiac volume receptors with unmyelinated afferents exert a particularly effective reflex damping effect on renal sympathetic activity (164, 619) and also on neurogenic renin release (183, 373). Furthermore early primary hypertension in both humans and SHR exhibits a centralization of the usually modestly reduced blood volume (183, 362, 423, 547, 612, 613, 640), which would tend to activate cardiac volume receptors. Competition between a centrally increased sympathetic drive and a preferential volume-receptor reflex damping of renal sympathetic activity may in early neurogenic hypertension cause variations in renin secretion over a considerable range (183, 184, 373).

It was briefly mentioned (sect. III B3b) that Falkner (187) noted another interesting difference in other studies of youngsters from families with and without primary hypertension. When both groups were given 10 g of NaCl daily beyond their usual intake, those who had a family predisposition to hypertension showed somewhat more pressure elevation than the controls. This evidently volume-dependent pressure rise was not associated with further tachycardia, however. The question then arises whether this accentuated response to salt loading also reflects the presence of, e.g., genetic renal-adrenal abnormalities (sect. III E, F), whether it is secondary to a prevailing accentuation of renal sympathetic activity (sect. III F), or whether both might be more or less indirect expressions of generalized membrane alterations (sect. III A). Volume loading might then, e.g., via reflex release of natriuretic hormone, increase excitability in vascular smooth muscle, reinforcing myogenic tone, or accentuate the effects of autonomic neurons, both in CNS and peripherally, as discussed by Overbeck et al. (491, 495) and Haddy et al. (284). In 1969 Axelrod et al. (27, 112, 114) showed that salt loading in rats increased NE turnover in adrenergic neurons, where the induced volume
increase is probably responsible. In line with this finding Takeshita and Mark (609) recently observed that the vasocostrictor-fiber influence increased when HSR were exposed to salt loading, in a way suggesting increased NE release per impulse, whereas forearm resistance increased in borderline human hypertension (433).

Findings of this nature in early human and rat primary hypertension indicate how such apparently different influences as neurogenic and renal-volume elements might after all have several connections and perhaps even common denominators at the molecular level. The two interact not only via central neurohormonal influences on renal excretion and incretion, with angiotensin serving as a positive feedback on the brain stem (sect. IIIE2), but also in the hypothalamic–brain stem centers for sympathetic control and NaCl and volume homeostasis (12–14, 240), which is discussed further in section IIIE2, E4, F and in a review by Brody et al. (93).

Finally, the presence of a genetic predisposition, which at the limbic-hypothalamic levels leads to accentuated increases of sympathetic activity in response to environmental influences, raises the question of whether it is reflected also at the psychic level in terms of, e.g., an altered mental equilibrium. A priori this is of course not necessarily so, because functional consequences may be restricted to lower brain stem levels only, here facilitating some of the efferent expressions of otherwise ordinary corticolimbic psychophysiological events. However, SHR are reported to also show signs of psychophysiological changes, judged from observed behavior alterations, characteristic of increased mental alertness (210, 484, 689). In humans difficulties in identifying possible changes are far greater, particularly because any genetic alterations are likely to be subtle and moreover nearly impossible to distinguish from effects of environment and earlier experiences. These aspects of possible hereditary traits in primary hypertension are reviewed by, e.g., Weiner (662), Henry and Cassel (307), and Harris and Singer (296) but go beyond the scope of the present topic, interesting as they are.

b) Reflex control level. Theoretically the generally acknowledged resetting of cardiovascular proprioceptor reflexes may represent a truly primary alteration or be entirely secondary. Furthermore it may be due to changes of the receptor endings per se, of the walls in which these are situated, or of the bulbar reflex centers. In fact these alternatives may all contribute to a variable extent, which may also depend on the current phase of hypertension. Therefore this brief survey concentrates on the principal types of changes that seem to be particularly common and dominant in their effects and on whether primary influences contribute. Many studies have been devoted to this problem [e.g., Kezdi and Kordenat (367, 368), Pickering and Sleight (524, 587), Mancia, Zanchetti, et al. (430, 696), Korner (380), Brown and co-workers (17, 557), Reis and Doba (584), and Salgado and Krieger (385, 548, 549); for reviews, see Pickering and Sleight (524) and Zanchetti (696)]. The cardiovascular reflexes and their resetting were also dealt with in great detail in a recent symposium (587).

Apart from the ordinary cardiovascular proprioceptor reflexes and their
generally inhibitory effects on sympathetic activity (4, 164, 206, 252, 374, 619), except for the myelinated atrial afferents (206, 366), another variant with clearly excitatory effects should be mentioned, since it may be important in hypertension. Malliani et al. (429) have analyzed the functional significance of a special group of nonnociceptive cardiac afferents running together with the cardiac pain fibers in the sympathetic supply. These afferents are activated during, e.g., myocardial stimulation, and they exert an excitatory influence, primarily on the spinal sympathetic centers. They might be the myocardial equivalents of the thin afferents in skeletal muscle that are activated during exercise and then tend to accentuate sympathetic discharge (206). There might also be situations in primary hypertension, perhaps in the early hyperkinetic stage with increased cardiac stimulation, when these interesting cardiac afferents and their apparent positive-feedback influence on sympathetic control might reinforce the increased sympathetic drive, though little is known at present.

Concerning a possible primary resetting of the baroreceptor nerve endings, earlier proposed particularly by Heymans (sect. IIB), recent findings by Brown et al. (17, 557) in young SHR may suggest such a change, and it was considered to reflect an altered receptor membrane permeability. However, with a primary increase of membrane permeability like that discussed in section IIIA, an increased receptor sensitivity might have been expected instead. The phenomenon, however, may also reflect an early secondary receptor adaptation but is hardly then likely to be of dominant importance for increasing sympathetic activity, because a different type of hemodynamic pattern would then be expected in early primary hypertension. Thus reduced cardiovascular mechanoreceptor activity commonly produces the possibly most intense type of reflex vasoconstriction in skeletal muscle (4, 164, 206, 374), but in early primary hypertension this vascular bed is usually the least constricted one, for reasons discussed in section IIIB, D3a.

There are, however, intimate mutual connections between the different control levels along the brain stem, apart from the fact that they are also modulated by the central monoaminergic neurons. For example, the cardiovascular proprioreceptors exert important actions not only via the nucleus tractus solitarii and the medullary reflex arches (374, 381, 534) but also influence considerably the limbic-hypothalamic centers (318, 320, 381). These in turn, via the defense reaction, can centrally adjust the medullary reflex arches (206, 318, 320, 381, 695, 696) and entirely suppress at least their vagal cardiac link (206, 318, 320, 381). Thus Haeusler's results (285, 286) on the central and reflex nervous control in SHR suggest that medullary baroreceptor reflexes are centrally modulated, presumably by influences emerging from still higher levels, where possibly both are in turn adjusted via central monoaminergic neurons. Anyhow such central resettings of the reflex control must be considered in primary hypertension whenever limbic-hypothalamic centers are involved, where the principles are amply illustrated by, e.g., Hilton and Spyer (318, 320) and Korner (381).

In such a central resetting of the reflex homeostasis in primary hyper-
tension there is an important contribution of secondary peripheral alterations, suggested by most studies since the classic paper in 1956 by McCubbin, Green, and Page (438). Earlier it was not known whether such peripheral resetting was due to a true receptor adaptation, to an altered vascular wall, or perhaps even to receptor degeneration. Again all these elements are likely to contribute, varying individually and with the stage. However, the studies by Aars (1, 2) and Angell-James (18), where both wall distension and receptor activity were measured simultaneously, strongly suggest that an adaptive wall change reducing distensibility is of great importance, occurring largely in pace with structural adaptation elsewhere (sect. II D). Most findings in both SHR (476, 477, 555) and human primary hypertension (524, 587, 696) agree with such a view, but quite likely other elements also contribute. Thus purely functional influences in the respective vascular walls must be considered, since neurogenic or hormonal changes of smooth muscle activity in large arteries, for example, no doubt affect the wall distensibility and thereby the regional receptor activity. This provides possibilities also for an element of more acute receptor resettings, which may best explain the very rapid changes noted by Krieger's group (385, 548, 549) in experimental rat hypertension.

In conclusion, several elements probably contribute to the necessary resetting of the cardiovascular proprioceptors in primary hypertension, and they may well vary in relative importance with different stages and among individuals. First, the receptor nerve endings per se probably to some extent alter their excitability, but it seems less likely that this is a major determinant of the long-term reflex resetting. A more important functional element seems to be a bulbar resetting of the reflex arches, occurring whenever central excitatory influenc...
to a less efficient elimination of the transmitter, e.g., by reduced neuronal reuptake. However, changes in transmitter release and elimination may as well reflect ordinary neuronal adaptation to activity alterations that originate at still higher levels. Alternatively they may be caused by extrinsic local influences on the neuroeffector junctions, induced by local hormones, by angiotensin, by natriuretic hormone, etc.

With respect to human primary hypertension, Mendlowitz and his group (453) interpreted their findings, discussed in section III D2, in terms of a primary (enzymatic?) disturbance of transmitter handling at the neuroeffector site. However, other interpretations may now appear more likely, e.g., the presence of increased sympathetic activity. This of course does not exclude the possibility that neuroeffector disturbances of the proposed type might contribute, though recent results by Manger et al. (431) concerning the NE metabolism in peripheral vascular beds in human primary hypertension seem to leave little room for such mechanisms. On the other hand, alterations in local NE turnover may indeed be induced by salt-volume shifts, according to the discussed results of Axelrod, de Champlain, et al. (27, 112, 114), perhaps causing changes in the direction proposed by Mendlowitz.

In SHR, Vanhoutte et al. (129) found evidence of an increased release of adrenergic transmitter per impulse in the kidneys. This, however, might be secondary to the centrally increased drive evidently acting on these sympathetic neurons (211, 538), because Lais, Shaffer, and Brody (392) in SHR skeletal muscle vessels, where sympathetic discharge may if anything be attenuated (sect. III D3a), noted signs of a reduced transmitter release. A truly primary alteration at this site would be expected to be generalized to all peripheral adrenergic neurons, which, however, also readily adapt their transmitter turnover to both regional and more sustained changes in activity (103, 489).

With the numerous processes that can modulate the peripheral transmitter release and reuptake, reviewed by Langer et al. (393), Starke (559), and Vanhoutte et al. (652), there are ample chances for both direct and indirect alterations, primary as well as secondary. These interesting problems call for intensified experimental studies of primary hypertension, and so far there is not much firm evidence that, e.g., genetic alterations at this peripheral site of adrenergic neurons are an important etiologic element. Possibly, however, the interesting findings of Vanhoutte's group, Halpern, Mulvany, et al. (464, 671), and Haeusler and Haefely (288) at least partly reflect such a change, even though a secondary neuronal adjustment may seem more likely at present. However, genetic membrane alterations (sect. III A) might also be important for transmitter release and uptake in peripheral adrenergic varicosities. As mentioned earlier (sect. III A), Overbeck, Haddy, and co-workers (284, 491, 495) found evidence in secondary volume hypertension of an increased secretion of ouabainlike agent, presumably natriuretic hormone, and suggested that it might influence neuroeffector events as well, presumably reflecting the changes noted by Axelrod et al.
(27, 112, 114). If genetic membrane changes also occur at this site in primary hypertension, the net effects on local transmitter concentrations could be marked when volume increases or blood volume centralization induces a release of the ouabainlike hormone. The results during sympathetic nerve stimulations in salt-loaded HSR by Takeshita and Mark (609) mentioned earlier are of great interest here because they seem to reflect events along these lines. Much more work is needed, however, and this area is certainly one of the more interesting in current research on hypertension.

E. Primary Alterations in Hormonal Systems

1. General aspects

The important findings by Goldblatt, Braun-Menéndez, Page, and associates (sect. 1B) concerning the relationships between pressure, kidney blood supply, renin release, and angiotensin formation led to strong emphasis on hormonal mechanisms in the search for the origin of primary hypertension. Particularly when angiotensin proved to be an even more potent pre-capillary smooth muscle stimulant than the vasoconstrictor transmitter NE, blood-borne pressor influences were for long widely supposed to explain the chronically raised resistance, particularly since neurogenic mechanisms at that time seemed to be ruled out, as outlined in section 1B.

It is therefore hardly surprising that studies of hormonal pressor (and depressor) mechanisms, particularly of renal and adrenal origin, have numbered in the thousands, together making up perhaps the largest single sector of research on primary hypertension. This has greatly increased knowledge about hormonal control in general, its links to neurogenic mechanisms, and how these systems jointly dominate cardiovascular and volume regulation, as surveyed in many reviews (34, 63, 99, 146, 148, 153, 235, 236, 241, 243, 246, 274, 281, 284, 325, 365, 396, 404, 479, 499, 508, 529, 533, 550, 569, 650, 654).

Physiology, however, has in a way profited more from these efforts than has the problem they intended to unravel—the etiology of primary hypertension—which has proven about as elusive to hormone purists as to proponents of other unitarian concepts. These studies have produced many surprises concerning the functional significance of the respective blood-borne agents. This has been particularly true for angiotensin after Gross (270) in 1958 suggested that the kidneys must somehow, perhaps via renin-angiotensin, control the adrenal mineralocorticoid function (270). Soon afterward it was shown by various methods that angiotensin is indeed a powerful stimulator of aldosterone release and that the kidneys therefore serve as important regulators of aldosterone secretion via renin-angiotensin [Davis (146), Denton (158), Genest (241), Page and Bumpus (499), Reid and Ganong (533)]. Bickerton and Buckley (61) further showed that angiotensin also ex-
erts stimulatory effects within the brain, though it took a long time before the importance of this finding was fully realized.

It is necessary here to limit the survey of the very interesting hormonal influences on cardiovascular homeostasis, and in a way it is also justified because there is far less evidence of a common, truly initiating involvement of hormonal factors in primary hypertension than there is for secondary hypertension. This by no means denies that the various hormonal mechanisms are indispensable regulatory elements also in primary hypertension, that their resetting is often a prerequisite for its maintenance, and that they, in some variants at least, may contribute to its initiation. These mechanisms are outlined below with a discussion of their role in primary hypertension and relationships to other control elements, starting with the kidneys as a source of both pressor and depressor humoral agents.

2. Incretory functions of the kidneys

a) Renin-angiotensin system. This hormonal component is by far the most studied among the various blood-borne agents affecting cardiovascular control and certainly is the most widely considered candidate for a key role in primary hypertension. For details the reader referred to numerous reviews and books devoted to this favorite topic for research (148, 235, 274, 324, 325, 396, 499, 508, 510, 529, 550, 569, 606, 622, 650).

I) SOURCES OF RENIN. Renin was long thought to be unique to the kidneys, but there is not increasingly firm evidence that this angiotensinogen-splitting enzyme is also formed elsewhere. This is true for at least some parts of the brain (234, 235, 236), though the almost uniformly present "brain renin" may in most places simply be the lysosomal protease cathepsin D. Furthermore most vascular walls display reninlike activity, as demonstrated in the 1950’s by Dengler (see 606). More recent analyses of vascular renin by Swales and co-workers (606, 624) and Barrett, Eggena, and Sambhi (37) suggest that at least one fraction is formed locally, but apparently kidney renin also penetrates vascular walls to become locally somewhat bound and therefore has a longer half-life than blood-borne renin. With converting enzyme apparently present in all vascular walls, at least in the endothelium, there should be a good chance for intramural angiotensin II (ANG II) formation, serving more like a local hormone.

These new findings greatly broaden the cardiovascular significance of the renin-angiotensin system, in the brain presumably serving as a local modulator of central cardiovascular control and in vascular walls perhaps as a modulator of myogenic activity and/or of neurogenic NE release. Finally, at least in some species like mice and rabbits, considerable amounts of "isorenins" are found in salivary glands and uterus, respectively (64, 529). They probably subserve local functions, so far little understood, and at any rate contribute little to blood-borne angiotensin concentrations.
In the kidneys—the classic site for renin formation—it emerges as an inactive precursor (mol wt 50,000–60,000), but in the secretory granules it is stored as active renin (mol wt ~40,000). It is released in this form (529) from the granular myoepithelial cells, which are preferentially concentrated in the polar cushions of the afferent arterioles, though some may occur in efferent arteriolar walls as well. By far the major renin fraction in the blood therefore comes from the abundant preglomerular stores, though some may instead enter renal interstitial fluid, perhaps causing some angiotensin formation with functions as local hormone. For example, this might occur with the minor renin amounts that may be formed by the efferent arterioles, which, as a denominator in the preglomerular-to-postglomerular resistance ratio, is a major determinant of glomerular filtration (see below). Furthermore plasma also seems to contain substantial amounts of large-molecular-weight inactive renin in both humans (569) and rats (529), which may be activated by certain plasma factors (550) though it is not clear what its physiological significance and origin are. There are also biogenic inhibitors of renin (550), and by various experimental interferences with renin and renin actions, Haber and co-workers (281) have developed promising diagnostic and therapeutic tools.

II) MODES OF RENIN RELEASE. Renin release can be induced in at least four different ways, of which two are remote and two strictly local and any might be of pathogenetic significance in some situations (148, 274, 324, 396, 506, 650). In the first mechanism, specific sympathetic secretory nerve endings contact the juxtamedullary myoepithelial cells via \( \beta_1 \)-adrenergic receptors. This direct neurogenic route causes considerable renin release at discharge rates below 1 Hz, too low to affect overall renal vascular resistance significantly (146, 379, 649, 699). Like sympathetic renal control in general, this neurogenic renin release seems to be under the particular reflex inhibitory influence of cardiac volume receptors with unmyelinated vagal afferents (373, 619). Further, particularly since the renal preglomerular resistance vessels are controlled by \( \alpha \)-receptor mediated vasoconstrictor fibers, these fibers influence renin release, but first at somewhat higher discharge rates and more indirectly, perhaps by modulating the renal baroceptor control of renin (146, 379, 649, 699). These two neurogenic modes of renin release, with quite different frequency-response relationships, probably are executed via separate adrenergic neurons and higher centers may therefore modulate their discharge independently.

These control arrangements suggest a predominant role of the renin-angiotensin system in overall volume regulation, in which the hypothalamic sodium receptors (osmoreceptors) are also importantly involved (13, 14, 36, 93, 154, 197). In addition these neurogenic routes of renin release form part of the widespread hypothalamic-neurohormonal adjustments elicited by, e.g., alerting environmental stimuli (70), which almost implies an anticipatory renin release with consequent early measures to retain sodium chloride and volume. Furthermore renin release occurs whenever volume receptors and
baroreceptors are unloaded because of reflex sympathetic activation, though this mode of neurogenic renin secretion is probably reset during hypertension along with the respective cardiovascular reflexes (380, 524, 696). Finally, nonnociceptor afferents from the kidneys themselves seem to be able to cause reflex release of renin, according to Zanchetti's group (106, 699), a mode of control that might reflect another important connection between kidneys and brain. Clearly the links between nervous and hormonal influences are particularly intimate here, and a primary increase of, e.g., central sympathetic activity may therefore substantially engage the renin-angiotensin system as well.

The second type of remote control of renin release is exercised by a variety of blood-borne agents (148), where particularly epinephrine from the adrenal medulla causes increased release via the β1-adrenergic receptors and thereby reinforces the direct neurogenic influence. It is more doubtful whether the normally very low transmitter overflow concentrations in the plasma are significant compared with the far higher local NE concentrations in the junction gaps at the renin cells whenever the secretory nerve fibers are active.

Most, perhaps all, other blood-borne agents are inhibitory, where, e.g., angiotensin and antiuretic hormone by direct suppression of the myoepithelial cells reduce renin release. Also increases of aldosterone, sodium, and potassium suppress renin please, though probably more indirectly via the macula densa region (see below). These latter effects constitute a variety of humoral negative feedbacks on renin release, of considerable efficiency and versatility, which complete the reflex neurogenic ones initiated from cardiac and baroreceptors (164, 374, 619). Together they may forcefully counterbalance the positive feedback arrangement that exists between sympathetic renin release, ANG 11 formation, and ANG 11-stimulating effects on central control of sympathetic activity, as outlined below.

The other two mechanisms for renin release into the bloodstream are strictly local, because their sensing mechanisms are situated within the kidneys. The third type is the best known, because it was utilized experimentally by Goldblatt, and it is under the control of an interarenal baroreceptor principle, as first suggested by Tobian (see 148). The exact arrangement is not known, but in essence increased renin release occurs whenever pressure at the preglomerular site of the baroreceptor arrangement is reduced and vice versa. Thus most changes threatening to lower glomerular filtration pressure and blood supply lead to increased renin secretion. Such renal baroreceptor unloading can be accomplished by arterial pressure reduction, renal artery obstruction, and/or renal preglomerular vasoconstriction, if this mainly occurs upstream of the baroreceptor site (148, 324, 650). Perhaps in this latter way the renal sympathetic innervation also more indirectly, via α-receptor-mediated vasoconstriction upstream of the baroreceptors, contributes to renin release.

The fourth mechanism of renin release is located in the interesting mac-
ula densa region, at which point the distal tubules and their contents establish very close contact with the renin-secreting cells. According to Barajas the association with the efferent arterioles seems, if anything, to be even closer than that with the afferent ones (sec 148). Thus perhaps the local servocontrol from the distal tubules to the renal vascular bed also includes modulation of the postglomerular resistance and hence of the preglomerular-to-postglomerular resistance ratio, which would be far more efficient than control of the preglomerular resistance only. Anyhow, in a way that is not fully understood, apparently a decreased sodium chloride delivery to this specialized tubular section leads to increased renin secretion, possibly via the decreased amount of chloride passing the macula densa cells. The macula densa region thereby functions as a tubular “natriastat” (sect. III F) with important influences also on renin release (148).

There is considerable controversy, however, concerning the mechanism by which the macula densa region influences renin release as well as the renal vessels. One reason is that this region is very inaccessible to micro-puncture, a technique that might have clarified the local chemical situation and thereby its influence on renin release. For example, Thurau (629), who in elegant single-nephron studies showed how increased NaCl delivery to the macula densa region causes preglomerular constriction, suggested that this vascular response was due to renin release and angiotensin formation, which latter, by local hormone action, should keep renal blood supply and hence glomerular filtration balanced to tubular reabsorptive capacity. If, however, angiotensin were involved in this way it would probably constrict the efferent arterioles even more, since these vessels seem to be more sensitive to angiotensin than the afferent ones (148, 325). Furthermore renin levels can be reduced 1,000-fold without hampering the macula densa feedback (467).

This, however, by no means belittles Thurau’s finding of an efficient macula densa-mediated control of renal blood flow, also proposed by Guyton et al. (280) but without involvement of the renin-angiotensin system. For example, osmolar or ionic changes may well mediate the proposed vascular adjustments, reinforcing the myogenic autoregulatory principle (25, 370), and Thur’s important observations on single nephrons may be explained along such lines. Possibly it is instead the preglomerular-to-postglomerular resistance ratio that is under macula densa control, though then calling for inverse effects on the pre- and postglomerular vessels, which would greatly reinforce the vascular modulation of glomerular filtration pressure (sect. III E). Moreover it is not impossible that the renal prostaglandins and kinins (see below) are somehow involved in these local events, where the macula densa arrangement allows the nephrons to sample their own excretion for induction of appropriate corrections, among them influencing renin release.

In summary, these four mechanisms of increasing renin release all depend on signals directly or indirectly derived from reduced cardiovascular filling and lowered contents of sodium chloride, though balanced by negative feedbacks as well. This strongly supports the view that the renin-angiotensin
system is predominantly a powerful and far-reaching link in the organism's volume regulation, rather than merely a system for arteriolar constriction as originally assumed.

III) ANGIOTENSIN FORMATION AND ACTIONS. By the action of renin on its plasma substrate α2-globulin angiotensinogen, the decapeptide ANG I, which in most respects is less potent, is split off. When, however, ANG I passes the pulmonary vascular bed it comes in intimate contact with the ANG I-converting enzyme, predominantly located in the pulmonary capillary endothelium as in endothelial cells generally. This strategically placed enzyme, which by deamination also rids the blood of polypeptide vasodilator kinins before they reach the systemic circulation, splits off another two amino acids from ANG I to form the highly potent octapeptide ANG II (499, 508). At least in the adrenal cortex another amino acid can be split off to form ANG III (84, 508).

Per mole, ANG II is approximately 10 times more potent as an arteriolar smooth muscle constrictor than NE, whereas venous smooth muscle is far more responsive to NE than to ANG II. Yet it is apparently not as a direct precapillary smooth muscle constrictor that ANG II exerts its predominant role in vivo. Thus the dose–response relationship for ANG II stimulation of the aldosterone-producing zona glomerular cells, where the heptapeptide ANG III may be even more potent, shows the highest sensitivity among the various ANG II effects, with an ED_{50} just above 10^{-10} M (508). At an ED_{50} around 10^{-9} M ANG II causes catecholamine release from the adrenal medulla, but first at an ED_{50} just below 10^{-8} M arterial smooth muscle constriction is achieved (508). A parallel may be drawn to another classic pressor agent, “vasopressin,” which was also detected by its vasoconstrictor power and was first baptized accordingly. However, it was later rebaptized to “antidiuretic hormone” (ADH) because it primarily adjusts renal water losses and only constricts blood vessels at exceptionally high blood concentrations.

At very low concentrations ANG II activates the sympathetic nervous system also centrally (99, 192, 300, 487) from the bulbar area postrema and/or from third ventricle regions, like the organum vasculosum and the subfornical organ. According to Buckley, Jandhyala, and co-workers (100, 340) these sympathostimulatory effects are conveyed by central α-receptors, and they seem to particularly engage the sympathetic supply in producing renal and splanchnic constriction, a differentiated sympathetic discharge similar to that in the defense reaction. At the mentioned CNS sites the capillaries are fenestrated, thus constituting “windows” to the bloodstream for the otherwise semiclosed (by the blood-brain barrier) CNS. Across these capillaries blood-borne polypeptides like ANG II reach local chemosensitive neurons and can thus exert far-reaching CNS effects. Thus it is not impossible that other blood-borne agents with either pressor or depressor affects might elicit at least part of their effects via these CNS regions, e.g., Muirhead's depressor material, natriuretic hormone, etc. (see below). In humans Johnson, Henning, and Åblad (300, 349) showed that ordinary pressor con-
centrations of infused ANG II exert cardiovascular effects mainly by means of sympathetic activation, certainly centrally and perhaps also at neuroeffector junctions. Thus regional sympathetic α-blockade abolished these ANG II effects, whereas the same intravenously administered ANG II amounts constricted veins in a forearm that was entirely excluded from the circulation. Furthermore to induce direct ANG II constrictor effects in a sympathetically blocked forearm the local blood concentrations had to be raised roughly 10-fold above those causing centrally mediated vasoconstriction (300, 349). There may well be species differences in the relative sensitivity of the various ANG II effects, but the data for humans are undoubtedly the most relevant. Furthermore vascular smooth muscles in the kidneys, particularly those of the postglomerular resistance vessels, appear to be so sensitive to ANG II that constriction may occur at blood pressure concentrations too low to raise, e.g., blood pressure (325). Particularly during salt depletion in humans, ANG II seems to be very important, also for the control of the renal vascular bed (see below).

Thus blood ANG II concentrations apparently are, at least in humans, only occasionally high enough to contribute to systemic resistance by direct arteriolar smooth muscle constriction (except in the kidneys), and, when they are so high, the CNS-mediated neurogenic effects are also enhanced and hence still likely to dominate. In situations like sodium depletion where renin release is greatly increased via the many feedbacks safeguarding volume—or in shock and certainly in secondary renal hypertension—these neurogenically mediated ANG II effects become increasingly important and direct arteriolar ones are added.

Barger et al. (34) have elegantly shown how in such situations neurogenic and renin-angiotensin effects interact and even “substitute” for each other. Thus in sodium depletion the neurogenic vascular effects appeared to weaken but not those in response to exogenous NE, suggesting depressed neurogenic NE turnover, as noted by Axelrod’s group (27, 114). Angiotensin II blockade during sodium depletion caused a profound pressure fall but with signs of failing venous return. Since ANG II has only weak direct effects on venous smooth muscle, these reactions suggest a considerable ANG II reinforcement of neurogenic control of capacitance vessels, perhaps both centrally and at neuroeffector junctions (300, 349). Findings by Guyton’s group (124) on salt-depleted rats and by Conway et al. (133) on dogs are also perhaps best explained by an ANG II-mediated, overall reinforcement of sympathetic cardiovascular activity. In the sodium-replete situation, on the other hand, neurogenic cardiovascular control was found to be highly efficient, but renin ANG II levels were low and it was even difficult to provoke renin release by regional kidney hypotension (34). Exactly how alterations in sodium-volume balance influence neurohormonal effector control is not clear but was discussed briefly earlier and also in section III.4, F.

Such findings again emphasize that the renin-angiotensin system is mainly involved in volume regulation, where the first line of defense is in-
creased aldosterone secretion, whereby sodium chloride is conserved and hence volume maintained. The second line of defense then is the central sympathetic activation by ANG II, probably reinforced at neuroeffector junctions as well. These indirect but powerful ANG II influences also subserve volume regulation by reinforcing sympathetic effects on, e.g., venous capacitance vessels, gastrointestinal salt-water uptake, and renal excretory and incretory functions (sect. III F). At this latter point, nervous and hormonal influences are linked to form a positive feedback, because the central ANG II reinforcement of sympathetic discharge would also increase renin release, with further ANG II formation, and so on. As usual in biological positive feedbacks, however, there are plenty of negative feedbacks, both nervous and hormonal, as outlined above.

IV) RENIN-ANGIOTENSIN SYSTEMS OUTSIDE THE KIDNEYS. There is growing evidence that renin is also formed elsewhere, with regional ANG II formation perhaps influencing cardiovascular function as a local hormone. A recent symposium (99) and several reviews (234–236) deal with most aspects of cerebral ANG II influences. First, the plexus chorioideus has a high renin content, with possibilities for ANG II formation and cerebrospinal fluid access to hypothalamic and bulbar cardiovascular centers, besides blood-borne ANG II acting via these CNS regions with fenestrated capillaries. Furthermore some cranial brain stem regions evidently form their own "true" renin for local ANG II formation, perhaps to modulate CNS circuits involved in thirst, sodium conservation, overall volume control, etc., though experimental evidence is still mainly indirect (234–236, 470, 488). For example, ANG II strongly facilitates the sodium receptors of the hypothalamic thirst center, from which nervous and hormonal influences on volume, cardiovascular, and renal homeostasis are modulated as well (13, 14, 36, 62, 93, 154, 197). Whether such effects are also elicited by a strictly local nonneuronal renin angiotensin system is not proved but seems increasingly likely (236, 470, 488). In addition ANG II might be one of several polypeptide neuronal transmitters that seem to abound in higher brain stem sections (236), but again unequivocal evidence is lacking.

Furthermore the vascular media seems to form its own renin, hence allowing for some ANG II local hormone production (37, 606, 624) that possibly modulates precapillary myogenic tone, NE release from adrenergic varicosities, etc. After all, vascular smooth muscle synthesizes both elastin and collagen (486, 636), making renin formation not too surprising, particularly since the juxtaglomerular renin cells originate from vascular smooth muscle. If smooth muscle formation of renin is enhanced by sympathetic stimulation as in the juxtaglomerular cells, at this local level there would also be chances for a positive-feedback interaction, because ANG II facilitates NE release from nerve varicosities (499, 599). However, again it is too early to decide what would be the significance of such intramural ANG II formation relative to blood-borne ANG II.

V) PATHOPHYSIOLOGICAL SIGNIFICANCE. It is now time for the really im-
important question in this context: are any of the various renin-ANG II systems involved in the induction of primary hypertension and, if so, how often and how extensively? Clearly since there are several variants of primary hypertension, both in humans and rats, there cannot be any unequivocal answer to this question and it has been difficult to tackle experimentally. Because ANG II is the final “executive arm” of these systems, however, specific interferences with the various ANG II effects, or with its formation, should best reveal whether it is responsible for any hemodynamically relevant abnormality in early primary hypertension. This calls for specific ANG II blockers to be used during quantitative hemodynamic analyses and standardized circumstances in early hypertension, which is asking a lot, particularly in humans. Most promising improvements are on their way, however, like increasingly potent converting-enzyme blockers (34, 133, 334, 335, 428), though misleading side effects may still be a nuisance. This approach is particularly suited for the analysis of a restricted number of cases, compared with matched controls.

A screening of larger groups by plasma renin estimations in early primary hypertension, as initiated by Laragh’s group, may provide valuable hints of a possibly initiating renin-angiotensin involvement. However, single values must be judged with great caution, not least because transient renin alterations may ensue from even slight shifts in, e.g., sympathetic discharge caused by, e.g., changes in alertness or alternatively from accidental deviations in salt-volume balance.

Based on renin levels in early primary hypertension, it can only be concluded that there is indeed little to suggest that the renin-ANG II system, except for a few cases, should be of any initiating importance on a wider scale, either in humans or rats (32, 67, 166, 184). This may sound like heresy to enthusiasts of this fascinating control system, but there is really very little evidence, if any, from such data. For example, in most instances of human primary hypertension renin levels are normal or even low (67, 166, 172, 395). Furthermore most, if not all, early hypertensives with raised renin levels show clear signs of a centrally increased sympathetic activity (183-185), which via the mentioned nerve connections should also increase renin release. Here the signs of sympathetic accentuation generally remain after pharmacologic interferences with the renin-ANG II system (183, 184, 373), suggesting that the increased sympathetic activity is primary and not caused by raised ANG II levels that theoretically could have induced increased sympathetic activity via CNS actions. This of course by no means denies the great homeostatic importance of the renin-ANG II system in hypertension, as in normotension, but this is another matter. In fact the normally accentuated role of ANG II for maintaining pressure during salt restriction (see above) should be of great therapeutic advantage during combined treatment with, e.g., diuretics or salt restriction and ANG II-blocking agents, in line with the results of Barger’s group (34).

Enthusiasts for a primary role of ANG II might argue that both renin
and volume levels may seem inappropriately high when related to the raised arterial pressure. Had nothing else happened, both should have been correspondingly lowered. However, this most likely reflects a mere resetting of renin-ANG II control, just as barostat functions (sect. III D3b, F), resistance vessels, and heart (sect. II D3) are all reset in various ways in chronic hypertension. After all the cardiovascular reflexes as well as the renal preglomerular resistance (and thus renal barostat function) have all “accepted” the raised pressure equilibrium, and they all strongly influence renin release and ANG II formation. It would therefore be strange if the volume-controlling renin-ANG II system had not also adapted to the chronic arterial pressure elevation, because otherwise the much more important volume control would be jeopardized. Nature apparently cares far more about such risks than about gradual pressure elevations that are hardly dangerous until postreproductive phases of life.

In rats, and probably also in humans, some variants of primary hypertension appear to be volume induced (sect. III B3c), and at least some of these might depend on a primary increase of renin-ANG II formation (or delayed elimination). Most, if not all, such variants generally exhibit correspondingly low renin levels, however, which rather indicates that the volume increase has another origin. Thus it may be due to altered renal sodium and water excretion, as in MHS and HSR, where renin regulation responds appropriately to the primary volume expansion by apparently being reflexly suppressed via cardiac volume receptors, etc. (56, 210, 376, 531).

Enthusiasts for the renin-angiotensin system may also cite the important effector functions controlled by ANG II that may exhibit increased sensitivity and therefore respond with exaggerated reactions to normal renin-ANG II concentrations. This sometimes seems to occur in human primary hypertension with aldosterone, since ANG II infusions can produce greater increases of aldosterone in hypertensive subjects than in normotensive controls, as discussed in section III E3. However, aldosterone levels that are mildly increased in human primary hypertension are usually caused by slower elimination and not by increased formation, according to Genest’s group (sect. III E2). Therefore this altered angiotensin effect, which may also be secondary, is evidently somehow compensated for. It may also be argued that pressor or vasoconstrictor effects of angiotensin are enhanced in subjects with primary hypertension (sect. II C), but then it should be recalled that they are bound to display an unspecific vascular hyperreactivity due to the presence of structural autoregulation of the resistance vessels (sect. II D3).

Finally, if primary increases of renin-ANG II formation, and/or inherently increased responses to ANG II of the mentioned types, were common in primary hypertension and decisive for the pressure elevation, they should all respond with clearly exaggerated reductions of pressure when given specific and potent converting-enzyme inhibitors, even when the potentiating influence of structural autoregulation is compensated for. However, comparisons of the average blood pressure reductions in groups of normotensive
and hypertensive subjects, when given such converting-enzyme inhibitors, so far have shown largely equal percentage pressure reductions (428). This is exactly what would be expected if the relative contribution of ANG II to cardiovascular homeostasis and pressure control is about the same in the average case of primary hypertension as in normotension. (Unfortunately, greater absolute pressure changes in hypertensives have often been misunderstood to imply that the factor under study is specifically accentuated, but simple hemodynamic considerations show that it is the percentage change in pressure, or systemic resistance, that should be compared.)

Therefore such findings do not suggest any accentuated ANG II involvement in average groups of human primary hypertension but of course do not exclude this possibility in subgroups of a larger material. This again emphasizes the potential value of subdividing the results in such materials for further individual analyses, instead of using only mean values for comparisons. However, even then increased ANG II effects in some individuals may not be strictly pathogenetic, since they may well be a consequence of e.g., a primary accentuation of sympathetic activity or due to a later, superimposed Goldblatt state.

In the hypertensive rat strains the renal volume variants (MHS and HSR) commonly have low renin levels. Normal or slightly elevated renin levels are usually noted in SHR (32, 210) but are then likely to reflect the centrally accentuated sympathetic activity or to reflect later stages (32). Some recent findings in SHR with a converting-enzyme blocker by Doyle's group (334, 335) should be mentioned, however. The blocker caused relatively greater MAP reductions even in anephric SHR than in controls and also on CNS intraventricular administration, in agreement with reports by Ganten et al. (235, 236). With reservations for unspecific drug effects, these interesting observations might suggest accentuated local ANG II effects in CNS and perhaps also in vessel walls in SHR. However, Elghozi et al. (179) blocked central ANG II effects with two different antagonists and found no difference in blood pressure effects between SHR and controls. Certainly more work is needed in this interesting field, but such approaches may provide new aspects on the complex nervous-hormonal interactions in primary hypertension, both centrally and peripherally. However, even if central angiotensin effects really are more pronounced in SHR than in normotensive rats, this does not necessarily mean a primary ANG II role in SHR hypertension. It may just as well be secondarily induced from central autonomic neurons controlling sympathetic discharge and represent an interesting central variant of the interactions between the renin-angiotensin and sympathetic systems discussed earlier.

On the whole, however, emphatic yes-or-no statements should be avoided whenever the possibility of an early involvement of individual mechanisms is considered in primary hypertension. As outlined in section II.4, only minor additional excitatory influences may be enough to start the ball rolling, provided they are reasonably persistent in action, whether continuous or in-
termittent. For example, prolonged infusion in animals of initially subpressor ANG II amounts may gradually result in substantial MAP elevations (437), perhaps due to aldosterone-induced volume increases with secondary reinforcement of neurogenic influences, etc. (sect. IIIE3, 4). Furthermore it should be emphasized again that subgroups of human primary hypertension might have early increases in renin-ANG II involvement, though hidden behind the averaged values from larger groups. Finally, the contribution of the renin-ANG II system may often increase gradually as primary hypertension advances, at least when Goldblatt mechanisms are superimposed because of renal preglomerular vascular deterioration, where even malignancy may ensue (95, 105, 246).

In conclusion, earlier enthusiastic attempts to find a key initiating role for the renin-ANG II system in primary hypertension have been rewarded, though mainly by increased physiological knowledge. With respect to the disorder they aimed to unravel, they instead indicate that primary increases of renin-angiotensin formation are rarely of etiological importance. It is quite another matter that renin release may often be modestly increased as one of many expressions of an accentuated central neurohormonal activity, but such an involvement should not be mistaken for a primary renin-angiotensin involvement. Studies during the last few decades, however, have confirmed that the renin-angiotensin system is a vital link in the organism's powerful and far-reaching homeostatic control of volume and electrolyte regulation, which would grossly fail in depleted states if the various ANG II effects failed. Thus ANG II may become even more important in primary hypertension as volume-salt regulation and reflex pressure homeostasis may become increasingly vulnerable. This drastic shift in emphasis concerning physiological-pathophysiological roles of the renin-angiotensin system somewhat resembles the situation for another potent vasoactive agent, serotonin (5-HT), in which some 25 years ago enthusiasm for its assumed involvement in almost everything from shock to hypertension was intense. Today 5-HT is perhaps mainly acknowledged as a central neurotransmitter of key importance in maintaining optimal mental balance and psychomotor functions, for species ranging from mice to humans.

b) Renal depressor substances. About 40 years ago Goldblatt, Braun-Menéndez, and Fasciolo et al. were aware of the antihypertensive role of the kidney (189), and Wollheim and Grollman postulated that there might even be reduced formation (or increased destruction) of a depressor hormone in hypertension (sect. 1B). This approach, in a way a deprivation theory, has recently developed in several directions with the identification of at least three groups of substances formed in the kidneys that can exert vasodilator influences: 1) Muirhead's antihypertensive renomedullary lipids, 2) the renal prostaglandins, and 3) the closely coupled renal kallikrein-kinin system.

1) MEDULLARY DEPRESSOR LIPIDS. Muirhead and co-workers (461-463) have concentrated on the medullary interstitial cells, localized between the tubules particularly toward the renal papilla. These cells (402, 463, 631),
which occasionally form tumors and can be multiplied in tissue cultures, produce prostaglandins (230, 402, 403, 463) and also vasodepressor lipides, by Muirhead called "antihypertensive neutral renomedullary lipid" (ANRL) and "antihypertensive polar renomedullary lipid" (APRL), which seem to be alkyl ethers of phosphatidylcholine (462, 463). Both induce powerful and—particularly ANRL—prolonged MAP reductions and vasodilatation and are also active by mouth. There is much evidence that the medullary interstitial cells are truly secretory in producing these agents and that this secretion is somehow regulated.

For example, whereas renal cortical blood flow is autoregulated, the medullary circulation changes much more with pressure, which, according to Tobian et al. (631), might somehow be sensed by the interstitial cells because their granulation decreases in experimental hypertension. Quite recently Muirhead (462) showed that renal declipping releases large amounts of ANRL in the renal vein to exert powerful and prolonged depressor effects. Analyses of how these putative medullary depressor hormones participate in pressure-volume homeostasis generally suggest that they help to counteract, e.g., volume-provoked hypertension, i.e., that their secretion is then enhanced, whereas their absence from otherwise intact organisms would hardly alone cause pressure elevation (462, 463). Quite likely they participate in cardiovascular control also in normotensive organisms, at least in some situations.

This important line of work is also relevant here by providing another potential link, perhaps also serving as an attenuating influence depending on the current events in the renal vascular bed. There must be some negative feedbacks that are not easily reset in primary hypertension, hindering escalation of the potential vicious circuit (sect. IIID8), and this might be one, besides the unmyelinated baroafferents (sect. IIIID3b). However, the precise physiological significance of these hormonelike lipids cannot yet be evaluated, making their role in primary hypertension uncertain. It could well differ among different variants. After chemical identification, with perhaps synthesis of specific agonists and antagonists, rapid progress can be expected in this area. For example, it is not impossible that these agents could be involved in the presumably humoral renal influence on the compliance of the interstitial space, according to Floyer's interesting findings (199; sect. IIIIB).

II) RENAL PROSTAGLANDIN-KALLIKREIN-KININ SYSTEMS. There are good reasons for discussing these factors under a common heading, since they are in part closely connected within the kidneys, at least for distal tubular events. A balanced view of this highly complex and fairly new research field is next to impossible, however, simply because it is developing so rapidly that even reviews by true experts (135, 171, 229, 230, 402, 439-442, 459, 558, 660) run the risk of being outdated upon printing. Particularly the nearly explosive developments in prostaglandin (PG) research resemble a rapidly shifting battle where outsiders are waiting for the smoke to settle to separate the survivors from the dead.
First, the formation and stepwise degradation of the PG variants are often extremely rapid; second, virtually all tissues may form PGs, though perhaps mainly when challenged by excessive stimuli, trauma, etc. Thus PG release often seems to represent a "cry of despair" from threatened cells, and it should be realized that "physiological" experiments often utilize stimuli and environments far in excess of what tissues normally have to face, simply to provide more accentuated and hence clear-cut effects. However, it is then particularly difficult to distinguish between physiology and pathophysiology when the inherently very labile PG system is studied. For example, in the cardiovascular system as a whole, all vascular walls, particularly the endothelium, apparently can form the potent vasodilator and antithrombocyte aggregating substance prostacyclin (PGI₂) (230, 459, 558). Furthermore local PGE₂ formation, presumably in the vascular media and perhaps serving as a negative feedback for NE release at constrictor nerve endings, has been demonstrated (230, 298), though its physiological relevance is not known. It is not surprising that such findings have led to enthusiastic suggestions of local hormones or even of a circulating role for PGI₂ because it is not destroyed in the lungs, as are PGE₂ and PGF₂α. If so, PGI₂ might also be of particular interest in primary hypertension and suggestions in this direction have been made.

However, just like a possible ANG II involvement in primary hypertension can now be scrutinized by the use of fairly specific antagonists such as saralasin or converting-enzyme blockers, Vane (459) has demonstrated that PG synthesis from arachidonic acid is blocked by indomethacin and related anti-inflammatory drugs, among which aspirin certainly is used profusely. This most useful tool has helped to outline the physiological participation of the various PG substances [mainly PGE₂, PGF₂α, and recently PGI₂, as well as the thromboxanes (the functional contrast to PGI₂, which cause vasoconstriction and thrombocyte aggregation)].

The results of these blockade experiments have somewhat cooled the initial enthusiasm for a more generalized, truly physiological role of the PG system in blood pressure and general cardiovascular control. The closer one approaches undisturbed normal homeostasis, as in resting intact humans, the less significant are the cardiovascular and blood pressure effects of PG synthesis blockade (230, 402, 459, 558). Moreover if PG really affects blood pressure control in humans substantially, more such results would have been reported, considering the abundant use all over the world of, e.g., aspirin. Indeed there is little to indicate that, e.g., PGI₂ should normally serve as a blood-borne vasodilator hormone with significant effects on resistance and pressure. Possibly, however, intramurally formed PGI₂ and PGE₂ in some situations may exert strictly local effects, whereby, e.g., vascular myogenic activity and/or neuroeffector events might be modulated (230, 298, 459).

In the kidneys, however, the PG system is more firmly established as a truly physiological component, where it apparently functions in close cooperation with the kallikrein-kinin system, though it is also linked to the
renin-angiotensin system (171, 229, 230, 402, 439-442, 459, 558, 660). The highest renal capacity for PG synthesis is found in the medulla, where it is mainly derived from the interstitial cells, which predominantly form PGE$_2$ and PGF$_{2\alpha}$. Thanks to the specific tubular and vascular arrangements in the medulla, the readily diffusible lipophilic PGs seem to reach and influence also the renal cortex, which has a much higher PG-inactivation capacity than the medulla. The renal cortex also has a modest but probably quite important PG-synthesizing capacity of its own, perhaps located mainly to the endothelium of the specialized cortical vasculature and where PGI$_2$ may be the dominating product (230, 440, 442, 459, 558).

Both PGE$_2$ and PGI$_2$ are powerful renal vasodilators with a preference for the efferent arterioles, thus being nearly precise antagonists to ANG II. At least in some situations they are involved in the complex intrarenal control of blood flow, where they might help to modulate the important preglomerular-to-postglomerular resistance ratio (sect. 111F). Furthermore PGI$_2$ seems to facilitate, or might even largely mediate, the renin release induced from the macula densa region and by the renal baroreceptor mechanism (230, 439, 660), whereas the neurogenic $\beta$-receptor-mediated renin release seems independent of PG (230). On the other hand, PGF$_{2\alpha}$ appears to inhibit renin release, and Weber et al. (660) have discussed whether, e.g., salt loading could modulate the PGF$_{2\alpha}$/PGE$_2$ balance toward increased PGF$_{2\alpha}$ formation and thereby cause renin suppression. Renin levels are very low during salt-volume loading, when it can even be difficult to provoke renin release by pressure reduction (34). Weber et al. (660) also discussed whether similar influences might be involved in some low-renin variants of primary hypertension, but little is known at present.

The renal kallikrein-kinin system has been studied mainly by Croxatti and his group, who have also reviewed the field (135). Generally the kallikrein-kinin system is organized very like the renin-angiotensin system, but the origin of these two renal enzymes and their effects on renal function are quite different. The precise site for kallikrein formation is not known, but much evidence points to the tubular cells themselves, with a preference for distal tubular parts (135, 439, 487), which explains why kallikrein readily enters the urine. Increased kallikrein formation is induced, e.g., by salt-volume loading but also by raised mineralocorticoid levels. For example, high urinary levels are noted in primary aldosteronism (440). This latter effect probably represents a negative feedback to locally balance renal mineralocorticoid effects.

In a way not fully understood, but probably by more than increased medullary blood flow, the kallikrein-kinin system reduces sodium reabsorption in distal tubular sections, possibly in the ascending Henle loop. Furthermore the polypeptide kallidin, split off from plasma kininogen by kallikrein, is, like PGE$_2$ and PGI$_2$, a powerful vasodilator and will, particularly in the inner cortex-medulla regions, increase blood flow, which per se tends to increase sodium excretion. Moreover increased kallikrein-kallidin for-
nformation stimulates further PG release, which reinforces renal vasodilatation; furthermore PGE$_2$ itself suppresses the increased water permeability induced by ADH in distal tubules (135, 439, 440, 558).

Therefore this mainly medullary engagement of the kallikrein-kinin-PG systems helps to increase both salt and water excretion and also balances tubular effects of mineralocorticoids and ADH. Similarly a mutual stimulating effect on release between renin and PGF$_2$ in the renal cortex may balance their opposite intrarenal influences on, e.g., cortical blood flow, preglomerular-to-postglomerular resistance ratio, etc. Thus effective feedback systems for the modulations of glomerular and tubular functions by intrarenal hormones seem to be organized, though only some general outlines can at present be recognized.

Therefore the most likely possibility for participation of the renal PG-kallikrein-kinin systems in primary hypertension, if any, would be as local modulators of renal water-salt excretion. However, even by such local effects they may have far-reaching effects on exchangeable sodium content, plasma, and interstitial fluid volumes and thus might be important, perhaps particularly in volume variants of primary hypertension. Influences by way of generalized vasodilator effects, on the other hand, are unlikely, not the least because both the medullary PGE$_2$ and the kinins are cleared in the lungs if they escape from the kidney. Whether disturbances of intramuraually formed PGF$_2$ in the kidneys (and elsewhere in vessel walls) might be important in primary hypertension remains to be seen, and its normal role must be settled first.

The consequences of a disturbed intrarenal function of the PG-kallikrein-kinin systems for overall volume regulation are perhaps most logically discussed below in section IIIF, but here it should be mentioned that a reduced urinary excretion of kallikrein is common in established primary hypertension in humans and in, e.g., SHR and MHS (172, 440). In humans it was first noted in 1934 by Elliot and Nuzum (172), and the early findings by Wollheim (sect. 1B3; 681, 683) of the relative lack of a vasodilator factor in urine from patients with primary hypertension ("depressan") might at least partly have reflected reduced kallikrein excretion. Furthermore salt loading increases kallikrein excretion less in established primary hypertension than it does in normotensives (440). In most cases this probably represents a secondary renal adjustment to alterations in overall and renal hemodynamics, because there seems to be no clear evidence of altered kallikrein-kinin functions in early phases of primary hypertension (172, 440, 700). However, it has been proposed that an early deficiency in the PG and/or kallikrein-kinin systems might contribute to the pressure rise, at least in some variants of primary hypertension (440), presumably by contributing to renal salt-water retention in volume variants. Direct evidence in humans is lacking, but detailed analyses of patients with early reductions of kallikrein excretion might prove rewarding.

A relative deficiency of intrarenal PG inactivation in the GHR variant
of rat primary hypertension has been described (23) and was suggested to be of pathogenetic importance, particularly because the PGs in rats are vasoconstrictors and reinforcers of NE effects. However, early phases of GHR hypertension do not show any signs of salt-water retention (264); had this proposal been correct, GHR hypertension would have been easily curtailed by early indomethacin treatment, which apparently was not tested. Furthermore recent findings (31) do not support any important involvement of renal PGs in the initiation of GHR hypertension.

Dopamine can be traced in the kidneys and might indicate the presence of specific intrarenal dopaminergic neurons. This catecholamine is also of considerable interest because it induces both renal vasodilatation and natriuresis, the very opposite effects of NE and epinephrine (254). Dopamine might therefore represent yet another link in the multifaceted regulation of renal blood supply and sodium handling, but so far nothing is known about its possible involvement in primary hypertension.

3. Adrenal mineralocorticoids

a) General aspects. The great physiological importance of the mineralocorticoids was first revealed by the serious disorders caused by hyposecretion and hypersecretory states. For example, severe salt and volume depletion with often fatal hypotension was noted in Addison’s disease, whereas Cushing’s disease resulted in hypervolemia, hypertension, and extensive metabolic disturbances.

Loeb, Grollman, and Selye and their co-workers showed during the 1940’s how excess mineralocorticoids could lead to chronic hypertension in animals, particularly when extra salt was given [for reviews see, e.g., Davis (146) and Genest et al. (241–244)]. Dean and Masson noted there was often a zona glomerulosa enlargement in experimental renal hypertension, and Denning and Luetscher found greatly increased amounts of a sodium-retaining substance in the urine in human disorders with salt-water retention.

These and similar observations indicated a specific mineralocorticoid hormone, and in 1953 Simpson et al. isolated and identified aldosterone. A few years later Conn elegantly showed how a rare but interesting variant of secondary hypertension, Conn’s syndrome or “primary hyperaldosteronism,” ensues from tumors or hyperplasia of the zona glomerulosa. Finally, around 1960 findings by Gross, Genest, Davis, Laragh, Ganong, Mulrow, Blair, and Denton et al. made it clear that the kidneys efficiently control aldosterone secretion by the renin-angiotensin system and thereby their own sodium-potassium excretion (sect. III F). Knowledge about aldosterone, its control, and its effects has since increased rapidly, mainly due to greatly improved methodology [for reviews see, e.g., Denton (153), Reid and Ganong (533), Davis (146), Genest et al. (241–244), and by Laragh and Sealey (396)].

Basically aldosterone secretion is stimulated by low plasma sodium and particularly by increased potassium concentration, as first shown by Laragh.
and Staere in 1957 (146, 396). Perhaps the most powerful and sensitive control of aldosterone secretion, however, is exerted by ANG II and, at least in some species, by ANG III (sect. III.E.2a). As shown in humans by Oelkers et al. (481), the efficient ANG II stimulatory effect is further enhanced during sodium-depleted states, whereas the ANG II pressor effects are then attenuated, both alterations tending to facilitate sodium conservation.

The question arose quite early whether the zona glomerulosa, like the zona fasciculata, was under a specific central control of hormonal and/or neurogenic nature. Adrenocorticotropic exerts a trophic influence on the glomerulosa cells and can, at least transiently, increase aldosterone secretion substantially (146, 533). Nevertheless the possible presence of a specific “adrenoglomerulotrophic” hormone has been considered for two decades after it was first suggested by Farrel. For example, during their thorough studies of sodium control and aldosterone function, Denton and co-workers (568) and also Guyton and his group (436) accumulated evidence of an additional factor controlling aldosterone secretion, presumably of hypophyseal origin. Recently Sen et al. (571) identified a specific aldosterone-stimulating factor and also localized special cells in the anterior hypophysis for the synthesis, storage, and release of this new hormone. Its release is probably in turn influenced by, e.g., the central Na+ receptors (osmoreceptors) and by the cardiovascular volume receptors, though nothing is proved so far.

The adrenal cortex releases another mineralocorticoid hormone, 18-hydroxy-11-deoxycorticosterone (18-OHDOC), which is roughly 100-fold less potent than aldosterone. It is interesting nevertheless, because it seems to be directly controlled by ACTH, although opinions differ as to what extent it is affected by ANG II (243, 244, 479, 673). For example, 18-OHDOC might be important in the ACTH-induced variant of hypertension in sheep, extensively studied by Denton’s group. However, ACTH also releases some hypertensinogenic steroids, the progesterone derivatives 17-hydroxyprogesterone (17-OHP) and 17α,20α-hydroxyprogesterone (17α,20α-OHP), which apparently do not act by way of mineralocorticoid or glucocorticoid effects. These two agents might add a new type of adrenocortical pressor influence, though evidently complex because they have only minor pressor effects when given alone (567, 568).

The partly different central controls of aldosterone and 18-OHDOC may well indicate that their functional roles are somewhat differentiated, which is also supported by the fact that they are not always secreted in close parallel (242, 479, 531, 673). For example, the common anticipatory neurohormonal adjustments to alerting environmental stimuli (sect. II.C.3) involve an often powerful ACTH release accompanied by 18-OHDOC and possibly also 17-OHP and 17α,20α-OHP secretion. Aldosterone may in turn be mainly engaged by the important intrinsic stimuli that reflexly control volume homeostasis, though both ASF and the sympathetic control of the renin-angiotensin link might allow aldosterone engagement also by environmental excitatory stimuli (sect. II.C.3).

The presence of these powerful sodium-retaining hormones is vital, par-
particularly for species adapted to salt-poor environments, which includes humans, who also must cope with losses via thermoregulatory sweating (154, 240). Thus with the aldosterone renal effects concentrated in the distal tubules, virtually all filtered NaCl may be reabsorbed at intense aldosterone secretion; at the same time renal potassium excretion is enhanced. In salivary and sweat glands aldosterone can, by reinforcing uptake, almost abolish NaCl excretion, accompanied by a facilitation of intestinal NaCl absorption (36, 154, 240). Thus cardiovascular control, blood pressure, cardiac output, and plasma volume can be surprisingly well maintained in chronic sodium depletion, but only because of increases of more than 10-fold in ANG II and aldosterone release, often combined with accentuated sympathetic activity. This is clearly demonstrated when, e.g., converting-enzyme blockers are given in salt-depleted states (34, 124, 133). However, in such situations our capacity to cope with, e.g., bleeding and other accidental salt-fluid losses must be substantially curtailed, simply because the regulatory mechanisms are already considerably taxed in maintaining ordinary homeostasis.

In addition to the vital aldosterone facilitation of active NaCl uptake at key excretory sites, the adrenal corticoids may affect the cardiovascular system more directly, e.g., via the muscle cells. Corticoids seem to be "permissive" in maintaining normal myocardial function, and aldosterone also seems to exert a mild positive inotropic influence, at least in concentrations of $10^{-8}$ M and above, as reviewed by Lefer (404). It is doubtful, however, whether such effects are significant at ordinary physiological aldosterone concentrations.

Likewise mineralocorticoids can directly enhance vascular smooth muscle responsiveness to, e.g., NE in isolated preparations (404). Again, however, it is doubtful whether ordinary plasma concentrations are relevant here, except perhaps at the very high levels present in severe sodium depletion or in experimental deoxycorticosterone (DOC)-salt hypertension. In the latter situation smooth muscle responsiveness to NE is considerably enhanced also in vitro and membrane permeability to cations is increased in smooth muscle [for review see, e.g., Jones (353)].

The question arises, however, whether this enhanced responsiveness is due to specific mineralocorticoid effects directly on the cardiovascular effectors or whether it is somehow secondary to the induced salt-volume expansion. Friedman (219) recently showed on isolated vascular smooth muscle that aldosterone directly stimulates the membrane pump, which, if anything, tends to cause hyperpolarization and muscle relaxation. Furthermore if direct mineralocorticoid effects on, e.g., vascular smooth muscle had been the major cause of the substantial hemodynamic effects, they should also occur at the extremely high aldosterone concentrations during chronic salt-volume depletion when the organism by no means "borders on cardiovascular shock," though a marginal hypovolemia is present. However, the cardiovascular responses to neurogenic influences and to ANG II are then attenuated, and those to exogenous NE are largely the same as in salt-repleted states, despite extremely high aldosterone levels (sect. III E 2u).
These findings seem to indicate that the potentiated cardiovascular responses occurring when raised mineralocorticoid levels are combined with salt-volume increases (in the normally controlled organism these two almost always go in opposite directions) are secondary to the salt-volume increase per se. A ouabainlike agent, probably natriuretic hormone, seems to be released in such situations (sect. IIIA, E4). A generalized damping of the membrane Na\(^+\)-K\(^+\) pump would be expected to increase responsiveness in, e.g., cardiovascular effectors and perhaps also in tonically active sympathetic neurons, in addition to possible influences on their transmitter turnover (sect. IIIA, C, D).

b) Involvement in primary hypertension. Obviously, among the so-called permissive factors in hypertension, aldosterone is certainly mandatory in any variant of this disorder and is causative in some, like Conn's syndrome. Furthermore in variants where aldosterone is not responsible for initiation of hypertension, aldosterone regulation must be gradually reset, like that of sympathetic control, renin regulation, etc. Otherwise, normal negative feedbacks would efficiently suppress aldosterone secretion and thereby reduce sodium content and blood volume well below normal, which is certainly not common in established primary hypertension.

Furthermore, based on animal experiments, on studies of Conn's syndrome, and on the finding of Distler et al. (162) that experimental mineralocorticoid hypertension can also be induced in normotensive human beings, excess aldosterone clearly can induce what begins as volume hypertension. Likewise it is clear, particularly from Biglieri's studies (63), that there are several ways in which corticoid synthesis may deviate, resulting in increased mineralocorticoid formation from which hypertension often ensues.

Hemodynamic analyses in the human experiments with mineralocorticoid additions, performed by Distler's group, suggest a course largely along the lines proposed by Guyton and co-workers. Cardiac output is initially raised due to increased stroke volume while heart rate is reduced, reflecting neurogenic counterregulation via volume receptors and baroreceptors. A secondary resistance elevation follows, after which output returns toward normal. As reviewed by Brody et al. (93), however, recent studies of experimental mineralocorticoid hypertension reveal that this supposedly classic type of volume hypertension also involves a substantial neurogenic component by way of increased central sympathetic activation and perhaps also via increased NE release at neuroeffector junctions, according to the studies by Axelrod (27) and de Champlain et al. (112, 114). Again an influence of ouabainlike factors, probably in the form of natriuretic hormone, may be suspected—perhaps like angiotensin partly acting via the fenestrated CNS capillaries in regions like the area postrema as well as at peripheral nerve endings.

The most relevant question, however, is whether increased mineralocorticoid levels are decisive for the initiation of human primary hypertension (and in the rat models) and, if so, to what extent and how often. Genest et
al. (242–244, 479) have made the perhaps most important and consistent contributions during the past two decades by their thorough explorations in humans of virtually all aspects of the problem. Using advanced techniques in well-controlled situations, they noted a clearly significant but modest (30–40%) elevation of average aldosterone levels in stable (established) primary hypertension. Analyses of average secretion and elimination rates suggest a largely normal aldosterone release, whereas elimination seems slightly retarded, perhaps partly due to a modestly lowered splanchnic-liver blood flow and partly to firmer plasma protein binding. The aldosterone responses to volume changes were also often blunted compared with normotensive controls. However, the spread around the means was considerable and might include different variants at the extremes.

In contrast, early labile phases of primary hypertension did not differ much from normotensive controls, though again a considerable spread of values makes it possible that aldosterone might be more decisively involved in at least some early cases. The secretion rate of 18-OHDOC, on the other hand, in about two-thirds of the cases was substantially elevated both in early labile and in stable primary hypertensives. This is of principal interest, though perhaps not so much in connection with mineralocorticoids because the low potency of 18-OHDOC presumably means little addition to the effects of aldosterone alone. However, it suggests an increased ACTH secretion in most patients with early primary hypertension, which may be but another facet of the mildly increased neurohormonal activity resembling the defense reaction that often seems to prevail (sect. III B, D). Genest and his group (242, 387) are also inclined to conclude that a CNS involvement may be common in early phases. Obviously the effects of the hormonal links of such central neurohormonal patterns should not be neglected, even though the direct neurogenic influences may be more interesting to the investigator of hemodynamics. The corticoids may contribute more long-range effects, like affecting volume regulation with all its consequences, adjusting metabolic processes, and exerting trophic influences. However, the important point is that higher brain centers are responsible for initiating influences, rather than primary endocrine deviations, though the interactions between nervous and hormonal links are intimate indeed. In rat primary hypertension, 18-OHDOC secretion increases somewhat, probably reflecting the genetic predisposition of the HSR (531).

The modestly raised aldosterone concentrations in established primary hypertension might also depend somewhat on CNS engagements, partly because renin release is controlled by sympathetic fibers and thereby by the CNS, partly because the defense reaction often implies some neurogenic restriction of splanchnic-liver blood supply. Such hemodynamic effects are perhaps reinforced by structural autoregulation of the resistance vessels, which seem particularly pronounced in this vascular bed (580, 605). Together such influences would tend to reduce aldosterone elimination and thereby raise plasma concentrations.
Since elevated aldosterone levels seem to prevail more regularly first in established human primary hypertension, they are likely to often represent a resetting of aldosterone control to maintain, despite the pressure rise, a sufficient volume equilibrium to cope with other cardiovascular challenges like exercise, maintenance of the erect position, etc. No doubt the mineralocorticoids are thus very important in maintaining the chronic high-pressure state, though mainly for the same reasons as when they help maintain cardiovascular homeostasis in normotension. This is clearly demonstrated by, e.g., salt depletion in essential hypertension linked to therapeutic interferences with aldosterone release or action.

Of course there are other explanations for the modestly elevated mineralocorticoid activity in both early and established human primary hypertension, particularly since the situation may vary substantially among patients. For example, the possibility of primary deviations in adrenocortical functions should be seriously considered at least in some groups, as also discussed by Genest and co-workers (242–244, 479). Several groups have found that ANG II usually induces a modestly accentuated release of both aldosterone and 18-OHDOC in essential hypertension compared with controls (213, 244, 533), perhaps suggesting primary alterations of the ANG II–adrenal cortex relationship. However, aldosterone production seems fairly normal in primary hypertension according to Genest’s group (242–244), with a slower liver elimination usually accounting for the mildly elevated levels often seen in established hypertension, perhaps at least in part due to a mild restriction of splanchnic blood supply (456). Therefore the slight increase in ANG II sensitivity of the glomerulosa cells is evidently somehow compensated for in most cases, and it might be secondary. At least in some cases, however, the mineralocorticoid secretion may indeed be “inappropriately high” in relation both to the prevailing Na⁺ volume and to the concentrations of renin and ANG II, as suggested by Luetscher et al. (see 241). Genetically linked initiating influences may well be quite marginal, if only fairly persistent, because of early positive-feedback interactions with structural autoregulation at the precapillary resistance level (sect. IID3, II4). A primary alteration in mineralocorticoid influence might therefore be so minor that it is difficult to detect against the background noise, but nevertheless in the long run it could exert a push toward hypertension.

Such primary increases of mineralocorticoid secretion would particularly be expected where early phases of primary hypertension show high aldosterone and low renin levels, reduced neurogenic activity, and a trend toward volume increase. The spread in aldosterone levels is considerable, and there may well be subgroups where increased aldosterone release is of decisive importance for the initiation of primary hypertension. For example, Fraser et al. (213), based on the elegant comparative analyses of Conn’s syndrome, nontumor aldosteronism, and ordinary primary hypertension, have suggested that a small group of the latter variants, quite distinct from Conn’s syndrome, has such a background. This also led them to stress that
the multifactorial background of primary hypertension provides several human variants, and they christened the common though mistaken belief among investigators in an entity "Mill's disease" (434). Anyhow, most of the group with low-renin hypertension, originally thought to mainly represent volume variants on a mineralocorticoid-renal basis, in reality have a heterogenous background (sect. III B2, E2a). Thus among younger patients this variant generally constitutes well below 10% of the group, according to Genest et al. (243). Most low-renin hypertensives instead represent advanced stages without evidence of either primary salt-volume retention or hyperaldosteronism but with increasing renal deterioration (sect. III B2, E2a, F2).

In summary, mineralocorticoids are a prerequisite for any type of hypertension, since here, as in normotension, they are vital for maintaining appropriate cardiovascular filling. They therefore have a natural maintenance role in primary hypertension, and their control must be reset to the chronically raised pressure equilibrium, like other important cardiovascular regulatory elements. As for possible initiating influences, early borderline primary hypertension in humans often shows a clear elevation of the mainly ACTH-controlled 18-OHDOC; this perhaps largely reflects the common slight accentuation of the central neurohormonal alertness pattern, which involves ACTH release and often seems to prevail in early human (and also SHR) primary hypertension (sect. III D). Aldosterone levels are then usually normal but have a wide range. However, at least a fraction of early human cases, particularly with raised aldosterone release and with volume levels in the upper range at normal or even low renin-angiotensin levels, may represent variants with a primary deviation in mineralocorticoid release, but they are probably fairly rare. Otherwise the often modestly elevated mineralocorticoid levels in established primary hypertension may rather reflect secondary resetting to keep volume normal despite the raised pressure or express central neurohormonal influences.

4. Natriuretic hormone

a) General aspects. During the last two decades much evidence of a specific natriuretic hormone, primarily studied by de Wardener et al. and also by Laragh's group in the 1960's, has accumulated [relevant literature recently reviewed by de Wardener and MacGregor (654, 656), Overbeck (491), Haddy et al. (284], and Blaustein (73)].

Thus both in humans and in animals volume loading causes the release of a plasma factor, also entering urine, that in a variety of test preparations causes prolonged diuresis and increased sodium excretion (570). This natriuretic principle now seems clearly separate from other known mechanisms influencing sodium excretion. It evidently acts by suppressing active NaCl uptake in the tubules, and according to Harris et al. (see 654, 656) it also
inhibits active sodium transport in preparations like the toad bladder epithelium. Such findings indicate that a generalized damping effect on membrane sodium pumps may be induced, i.e., a ouabainlike action predominantly on the Na⁺-K⁺-ATPase pump system (566).

Further, since one major stimulus for release of this natriuretic principle is volume expansion, it is probably importantly influenced by the cardiac volume receptors. Actually evidence has accumulated (165, 240, 366) that, e.g., local left atrial distension, besides causing release of ADH as shown by Gauer and Henry (240), leads to the release of another blood-borne factor of unknown nature that seems to increase diuresis and natriuresis also in the denervated kidney. Any blood volume expansion—or increased centralization of a largely unchanged blood volume (182), which often occurs in primary hypertension—would then be expected to enhance the release of the putative natriuretic hormone (182). Furthermore the kidneys themselves would seem to be another likely source of control, but little is known so far.

Neither the chemical nature nor the origin of natriuretic hormone is known exactly, and in fact there may be two substances, one small molecule (around 500 daltons) and one larger molecule (around 10,000 daltons). Several reports indicate that it may come from the CNS (196, 654, 656), but it is not known from exactly which region. However, the findings [e.g., Andersson et al. (12–14), Denton et al. (71, 154)] concerning the important hypothalamic Na⁺ receptors and their role in overall sodium homeostasis fit such a view, and topical lesions in these areas can greatly impede the organism’s ability to excrete a salt load (14). Recent results surveyed by Brody et al. (93) also lead in the same direction. For example, topical hypothalamic lesions greatly reduced or even abolished the pressure elevation in experimental volume-dependent secondary hypertension, but not the hypernatremia and volume expansion.

This latter fact also indicates that increased sodium content and hypervolemia per se do not necessarily induce hypertension and that something else is often needed; both a natriuretic, ouabainlike hormone and a secondary neurogenic influence may be involved (93, 233, 284, 433, 491, 656). In fact such extrinsic influences are likely to reinforce the basic hemodynamic events, which Guyton et al. have proposed occur on volume expansion. Here the acute whole-body autoregulation may often be facilitated this way (233), and structural autoregulation soon takes over and dominates the resistance elevation.

Another important aspect of this type of hormonal action, particularly relevant in hypertension, emerges from other interesting observations. In 1969 Dahl and co-workers (143) noted in the salt-sensitive rat strain (HSR) that sodium loading (and hence volume expansion) led to the release of a “hypertensionogenic substance,” evidently quite stable and of long action, since it could be transferred via parabiosis. They assumed the release of a “sodium-excreting hormone” to be responsible. Furthermore Overbeck et al. (sect. IIIA; 490, 491, 495) found in dogs with renal hypertension and volume
expansion a selective attenuation of $K^+$-induced vasodilatation, which latter
is mainly due to a stimulation of the electrogenic $Na^+-K^+$ membrane pump
in vascular smooth muscle. In these animals plasma contained a factor with
a ouabainlike action on the membrane pump, enhancing vascular smooth
muscle responsiveness. It was further suggested that this factor might also
influence sympathetic activity and/or the junctional NE release (sect. III D3c;
284, 491, 495). It seemed to be fairly stable and to bind to the tissues, since
its effects could also be traced during in vitro conditions.

The evidence from these different lines of work suggests the presence
of a natriuretic hormone (or hormones), supposedly formed in the upper
brain stem–hypothalamus and released when, e.g., cardiac receptors are
stimulated by volume expansion or centralization of blood volume. It seems
to exert a generalized ouabainlike damping of electrogenic $Na^+-K^+$ mem-
brane pumps, which in the kidneys have the advantage that tubular sodium
reuptake is correspondingly reduced, hence favoring volume reduction. In,
e.g., vascular cells or in tonically active autonomic neurons, on the other
hand, such an action would tend to enhance excitability and responsiveness
to excitatory stimuli. However, in most normal situations this would not
matter much, because volume expansion also leads to reflex sympathetic
inhibition, generally overriding the presumably mild excitatory effects of
the membrane-induced changes by the released natriuretic hormone. There-
fore in most subjects volume expansion would hardly lead to increases in
either pressure or resistance, unless the volume load is marked, though the
situation may often differ in hypertension, as exemplified by the different
responses to salt-volume loading in HRR and HSR (233, 632).

b) Involvement in hypertension. For example, in volume-expanded renal
hypertension, where release of natriuretic hormone seems to parallel the
increased renin-angiotensin levels and angiotensin cardiovascular stimula-
tion, a general damping of the membrane pump would have an additive
excitatory action on, e.g., vascular smooth muscle. Overbeck (491) and Blau-
stein (73) have therefore proposed that this element may be of key impor-
tance whenever volume is expanded in hypertension and thus also in volume
variants of primary hypertension. Furthermore de Wardener and MacGregor
(656), mainly studying human primary hypertension, also stress the impor-
tance for the induction of hypertension of ouabainlike effects that appear
to be secondary to volume expansion or volume centralization. In fact plasma
from subjects with primary hypertension often seems to contain factors that
enhance vascular smooth muscle responsiveness (74, 390, 458, 656) or reduce
the vasodilator response to $K^+$, which acts by stimulating the $Na^+-K^+$ pump
(494). This may well reflect a reflexly released natriuretic hormone via, e.g.,
cardiac receptors, which with respect to renal excretory function would be
quite appropriate.

However, since less of such a factor seems to be present in plasma from
equally salt-loaded normotensive individuals (74, 458, 656), the question
arises whether there is a primary accentuation of its release in hypertensive
subjects or whether they simply respond with more powerful reflex adjustments from, e.g., cardiac volume receptors to given volume loads. In humans this is very difficult to elucidate, but at least in SHR a given volume addition elicits more powerful cardiac receptor activation than in WKR and hence stronger reflex sympathetic inhibition (538). In other words, this difference between hypertensives and normotensives might merely be one of a lower venous compliance in chronic hypertension, which has been demonstrated by many investigators (sect. II D8c; IIIB2, D8a).

Overbeck and de Wardener have also discussed whether the electrogenic Na⁺-K⁺ pump might be genetically defective in primary hypertension. However, as mentioned in section III A, most studies of isolated cells in primary hypertension in humans and SHR rather indicate that this membrane pump is, if anything, compensatorily stimulated to overcome what may—according to Postnov et al. (525, 527)—be, e.g., a genetic "passive" increase of sodium permeability and/or—according to Garay, Meyer, et al. (237, 238)—a relative deficiency of the Na⁺-K⁺ cotransport system. Of course both these and other components in the complex membrane events (684) might independently show genetic alterations (sect. III A).

Whichever proves to be the most common and/or important alternative, they both mean that for genetic reasons cell membranes are more leaky to sodium in primary hypertension, with consequences also for Ca²⁺ concentrations in, e.g., smooth muscle, when not compensated for by increased membrane pumping. If a secondary damping of the Na⁺-K⁺ pump via a volume-induced release of natriuretic hormone occurs (which may in turn be more pronounced due to reduced venous compliance), this would produce relatively greater increases of sodium influx and potassium efflux than in controls, hence accentuating more in hypertensive than in genetically normotensive individuals the responsiveness of vascular smooth muscle, of sympathetic neurons, etc. (sect. III A). Such a chain of events would help to explain why organisms genetically predisposed to hypertension often seem to respond with stronger pressor and vascular responses if salt-volume loaded, which also seems to involve neurogenic excitatory influences (187, 233, 433, 458, 632, 656). Furthermore such events might help to explain why increased K⁺ intake attenuates the pressor effects of NaCl loading, as stressed by Dahl and other investigators (139, 455). Besides facilitating aldosterone secretion, raised plasma K⁺ levels also stimulate Na⁺-K⁺-ATPase (283, 494) and might thereby partly offset effects of natriuretic hormone on the membrane equilibrium in smooth muscle, autonomic neurons, etc. Furthermore, by such membrane effects increases in K⁺ normally dilate vessels and participate in, e.g., exercise hyperemia (283, 447). The many influences of K⁺ in hypertension are excellently reviewed by Tan and Mulrow (611).

Finally, such interactions at the membrane level may well explain the many apparently contradictory studies on vascular smooth muscle sensitivity in humans and SHR, some reporting increased effector sensitivity and others unchanged or even reduced effector sensitivity (sect. III C). Rather than being
errors in measurements, they might simply reflect the prevailing degree of cardiovascular filling (or blood volume centralization) and consequent alterations in plasma-tissue concentrations of the ouabainlike natriuretic hormone. This would correspondingly damp the membrane pump and thereby unmask to different degrees genetic increases of membrane sodium (and Ca) permeability, with greater consequences for smooth muscle responsiveness in primary hypertension. This is illustrated in the interesting findings by Webb and Bohr (659), by the ouabain effects on SHR and WKR arteries, and also in a recent comparison of the complete dose-response relationships of NE, vasopressin, and Ba²⁺ in the resistance vessels of SHR and normotensive controls before, during, and after ouabain administration (339). For all these constrictor agents, which act very differently on smooth muscle, ouabain caused a greater left-hand shift of the dose-response curve in SHR, thus unmasking a greater effector sensitivity than in normotensive controls, whereas no clear difference in sensitivity between hypertensive and normotensive resistance vessels was seen before ouabain.

Certainly studies along these lines, converging from several different starting points and findings, open up important possibilities concerning initiating influences in primary hypertension, providing a potentially important role also for natriuretic hormone. However, much remains to be done to identify, locate the site of release, and elucidate the control of this new hormonal principle and its proposed ouabainlike action and to investigate its precise interactions with genetic cell membrane deviations in primary hypertension. However, because neurogenic influences tend to centralize an initially normal or even slightly reduced blood volume—even without a single element of “primary” volume expansion present—a reflexly increased release of natriuretic hormone may well occur even in neurogenic variants of primary hypertension, where blood volume centralization often occurs (sect. IIIB3, D9). This might add a ouabainlike influence here also, perhaps reinforcing both smooth muscle and autonomic nervous activity, in situations where the latter is already marginally increased for other reasons. Thus there are many interesting new possibilities for interaction between renal, hormonal, and neurogenic elements, which, together with genetic membrane alterations, may combine into different patterns of triggering influences: primary hypertension is certainly not a topic for unitarian concepts.

F. Primary Alterations of Renal Excretory Functions

1. General aspects

Although renal incretory functions are important in primary hypertension, the role of the kidneys as final executors of salt-water excretion is even more significant. For good reasons Guyton et al. (126, 127, 279) have emphasized the renal contribution to long-range volume and pressure control.
by using the expression "long-term barostat function" of the kidneys. It is therefore not surprising that genetic alterations in renal sodium handling have often been proposed as the true culprit in primary hypertension, a view particularly championed by Dahl (139, 140) and by Guyton et al. (127, 276). Likewise authorities like Tobian (627-629), Peart (509), and Brown et al. (95) stress the great importance of renal incretory-excretory functions in primary hypertension, though with a more multifactorial outlook and acceptance of many variants (434). To experts on central neurohormonal influences, like Brod (90, 92) with his wide knowledge of renal engagement in both primary and secondary hypertension, the kidneys are instead involved secondarily in most patients with primary hypertension, mainly by virtue of their consistent engagement in the accentuated neurohormonal drive that encompasses the entire cardiovascular system (87, 91).

Thus the experts generally agree that the important renal excretory function must be altered in primary hypertension, but opinions certainly diverge concerning what comes first. As so often happens in biology, however, either/or questions tend to end up with both/and answers; for example, studies of HSR and MHS clearly illustrate a triggering influence of the kidneys, whereas results for SIIR, and perhaps also GIIR, just as clearly point to the CNS as the main trigger. Primary hypertension in humans also probably includes various mixtures of these (and other) variants (sect. II A, B), though most studies seem to favor a secondary renal engagement in most cases. The great importance of the kidneys for the maintenance and later development of primary hypertension probably has everyone's agreement today.

Because both primary and secondary abnormalities of renal sodium handling might afflict almost any of the many links involved, normal NaCl excretion is outlined first. For details concerning the many intricate problems and the vast literature, readers are referred to reviews like those of Brod (89, 90), de Wardener (653, 655), and Jørgensen (358). To illustrate the dimensions of renal salt-water handling: human kidneys filter roughly 1.5 kg NaCl/day, some 10 times the total contents of the body, but take back about 1.49 kg across the tubular walls. Thus an extra daily salt load of 10 g reduces active reuptake from 1.49 to 1.48 kg/day; if anything, this is a relief for hard-working tubules, though humble indeed. Nevertheless the seemingly inappropriate but common expression "salt load" is not always without sense, because increased salt intake may pose serious homeostasis problems, with renal excretory capacity often the focus, particularly in hypertension. However, when things go wrong the kidneys may not always be the real culprit, or at least not the only one, as discussed later.

a) Control of glomerular filtration. The renal excretory function is characterized by the remarkable stability built into the system, and yet it has a great capacity to swiftly deal with accidental disturbances. Glomerular filtration, which in humans is 170-180 liters/day, is kept surprisingly constant by a series of local vascular controls (25, 35, 370, 685). Remote influ-
ences, mainly neurogenic renovascular adjustments, can be powerful indeed but are usually intermittent in connection with exercise, psychomotional episodes, or accidental fluid-salt losses.

The relative constancy of glomerular filtration is even more remarkable, because effective glomerular filtration pressure seems to be lower than had been assumed previously, perhaps only 15–20 mmHg (85, 372, 407). This calls for especially high precision in the intrinsic control of the preglomerular-to-postglomerular resistance ratio, because a shift of only a few percent, accomplished by a shift of a few pro mille in average smooth muscle length, would alter filtering pressure by about 10%! Filtration occurs across a most complex membrane and according to principles that are not fully understood [for reviews, see Latta (398) and Brenner et al. (85).]

The myogenically based, preglomerular autoregulation of renal blood flow responds promptly and over a wide range to shifts in arterial and intrarenal pressures, caused by, e.g., tubular distension, thereby tending to keep glomerular filtration pressure constant also (25, 89, 370). This myogenic autoregulation is superimposed by the tubuloglomerular feedback from the macula densa region (sect. IIIE). Thus accidental shifts in lower-nephron NaCl delivery can be corrected by appropriate adjustments in preglomerular resistance, mediated by ionic changes and/or by local hormones (280, 372, 407, 467, 623, 685). Perhaps these preglomerular effects are complemented by reciprocal postglomerular adjustments, which would greatly increase the sensitivity of this local control and minimize interferences with glomerular blood supply.

Should renal blood flow and consequently glomerular pressure and/or filtration rate nevertheless tend to fall, intrarenal compensatory mechanisms seem to induce somewhat selective elevations of postglomerular resistance. Exactly how this is accomplished is not known, but the macula densa region may be involved because of its particularly close connections with the efferent arteriole, according to Barajas (35, 407, 685). Possibly such effects are conveyed by local hormone formations of PGI₂ and of ANG II, which seem to exert their strongest effects on postglomerular vessels (sect. IIIE3a, b). For example, Leyssac (407) has proposed that such a local ANG II formation is involved in the glomerulotubular balance. A particularly strong chronic engagement of the postglomerular resistance vessels occurs in advancing primary hypertension, maintaining the filtration rate by increasing the filtration fraction as renal blood supply declines (sect. IIIF2).

Finally, due to the comparatively low filtering pressure and a filtration fraction as high as 20%, the steep rise of plasma oncotice pressure in distal capillary sections (to around 35 mmHg) helps to keep glomerular filtration rate constant by purely physical means. It also facilitates proximal reabsorption (see below) by high oncotice pressures in tubular capillaries, thereby aiding fluid absorption from paracellular tubular spaces. Therefore the inevitable plasma protein dilution upon increased salt-volume intake correspondingly aids in excreting the extra volume via the kidneys, as discussed by O'Connor (480).
The delivery of filtrate to the tubules is kept surprisingly constant during the steady state, both in normotension and in most cases of primary hypertension. It can, however, also be readily adjusted to, e.g., imposed changes in salt-volume balance, physically mainly by the consequent alterations in plasma oncotic pressure (480) and physiologically mainly by reflex adjustments of renal blood supply and glomerular capillary pressure (25, 89, 685), as modified by the many local humoral and myogenic controls (25, 280, 325, 370, 467, 623, 685), where perhaps also local (neurogenic?) dopamine effects (254) might be involved.

b) Control of tubular reabsorption. Proximal tubular reabsorption is also normally kept surprisingly constant, with the osmotic uptake accounting for approximately two-thirds of total reabsorption. This proximal uptake also adjusts remarkably well to changes in filtered volume, the so-called glomerulotubular balance (101, 358, 371, 378, 407, 623, 653, 655).

The Henle loop is responsible for the fascinating concentration-dilution events that are driven by active NaCl uptake in the thick ascending limb with exclusion of water. This results in the well-known countercurrent exchange between descending and ascending limbs, creating an increasing hydromolarity toward the loop end and a delivery of hyposmolar fluid to the macula densa region and distal convoluted tubules. The proximal tubules and Henle loops together account for about 85% of total uptake. In the Henle loops active uptake also seems able to adapt to a changed filtrate delivery, which is again adjusted from the macula densa region.

In the distal convoluted tubules and collecting ducts, the final, facultative adjustments of salt-water excretion take place, mainly directed by remote control rather than by proximal nephron events. The remote control derives predominantly from cardiovascular volume receptors, central Na⁺ receptors (osmoreceptors), and the associated neurohormonal reflexes (sect. II.2). These involve ADH, aldosterone, and probably natriuretic hormone, but with local modulation via the kallikrein-kinin-PG systems. However, in recent years proximal tubular sections have also been shown to be under remote control, after Muller and Barajas had demonstrated a direct adrenergic innervation of these tubular cells (see 159). DiBona (159) and Gottschalk et al. (258) found an important α-receptor-mediated facilitation of sodium uptake, mainly based on direct effects of sympathetic fibers but probably also influenced by blood-borne catecholamines at more intense activations of the adrenal medulla.

Another relevant question is how NaCl uptake is accomplished in the various tubular sections, because this may well be important for alterations of sodium excretion in primary hypertension. Since Skou discovered Na⁺-K⁺-ATPase in 1957, intense research has been devoted to its fundamental importance for cells and cell membranes in general. In principle, one Na⁺-K⁺-ATPase molecule expels three Na⁺ ions from the cell in exchange for two K⁺ ions, at the energy cost of breaking down one molecule of ATP to ADP (358). This pump is stimulated by high [Na⁺], and high [K⁺], and is inhibited by digitalis glycosides, like ouabain, and evidently by natriuretic hormone.
No doubt the renal tubules have many membrane pump systems besides Na\(^+\)-K\(^+\)-ATPase. However, the mere magnitude of their NaCl handling has directed interest to this ionic pump system, especially because no other mammalian tissue contains as much Na\(^+\)-K\(^+\)-ATPase as the tubules, particularly the ascending Henle tubule, as reviewed by Jørgensen (358).

Attempts to entirely block renal Na\(^+\)-K\(^+\)-ATPase by ouabain indicate that roughly half of the tubular NaCl uptake may be ascribed to this pump. However, with some 85% of total sodium uptake taking place in proximal tubules and ascending Henle tubules, at most only 33% of that in proximal tubules seems to depend directly or indirectly on Na\(^+\)-K\(^+\)-ATPase compared with the greater part in ascending Henle tubules, distal tubules, and collecting ducts. This has evoked much discussion of how the extensive NaCl uptake as well as the glomerulotubular balance are organized in the proximal tubules, particularly since energy costs seem to be lower here than in the Henle section, according to Kiil (371, 372).

In principle NaCl must first somehow enter the cells via the luminal surface, because the Na\(^+\)-K\(^+\)-ATPase is mainly placed to expel Na\(^+\) from the cells into the paracellular spaces. Several ouabain-insensitive pump systems along the luminal brush-border surface have been suggested (101, 371, 378, 455, 653, 655); moreover this cell surface seems fairly permeable to both Na\(^+\) and Cl\(^-\). Kiil (371, 372) has also suggested that an important driving force is created by the carbonic anhydrase-dependent bicarbonate formation and absorption, where Na\(^+\) exchanges with H\(^+\). The expulsion of bicarbonate into the paracellular space would allow a substantial osmotic influx of water and NaCl via intercellular junctions. This interesting theory, still open to debate, may explain the relatively low energy costs and why carbonic anhydrase blockers considerably reduce proximal uptake and disturb the glomerulotubular balance, which would then mostly depend on the filtered bicarbonate load. Kokko (378) prefers a more multifactorial background, where, e.g., high active absorption of organic molecules increases the luminal NaCl concentration and thereby also favors its passive uptake. Furthermore oncotic and hydrostatic pressures in tubular capillaries may indirectly, but substantially, influence fluxes across the proximal tubular walls, though opinions vary considerably (370, 378, 407).

Leyssac (407) proposes that proximal reabsorptive capacity may vary independently of the filtrate load and that it helps to check the latter by a feedback influence via proximal tubular pressure. With a low effective filtration pressure and a fairly high distal tubular resistance, increased filtration may also raise proximal intratubular pressures, where an increase of only a few millimeters of mercury implies substantial filtrate reductions. Angiotensin II as a local hormone is supposed to serve as a stabilizer, partly by inhibiting proximal reabsorption (hence amplifying the proposed back-pressure feedback), partly by constricting mainly the postglomerular resistance vessels. According to Leyssac this would further stabilize delivery to the Henle loop, which is necessary for optimal control of osmolar regulation.
Thus there are several interesting explanations for the remarkable stability of filtrate formation and proximal reabsorption; quite likely several different control mechanisms are involved in this important process. All the proposals discussed may therefore be valid, though with relative contributions varying with the situation.

The ascending Henle limb contains the highest Na\(^+\)-K\(^+\)-ATPase concentration of any mammalian tissue, but here this pump seems to be concentrated in the cell surfaces bordering the paracellular spaces. Furthermore these tubular cells, as well as their intercellular junctions, are almost impermeable to water, and a question arises about how luminal NaCl enters them to become accessible for active expulsion into the paracellular spaces. Burg (101) and Kokko (378) suggest that a specific chloride pump is responsible for bringing NaCl into the cells, but other alternatives are also discussed (358, 653, 655). These active transfers against considerable electrochemical gradients may explain the high metabolic demands of the ascending Henle segment (371), and the high concentrations of Na\(^+\)-K\(^+\)-ATPase may explain how uptake readily adapts to increased delivery.

In the distal tubules and collecting ducts, where both the final facultative NaCl uptake and selective water uptake occur, reabsorption is principally independent of proximal NaCl delivery. The NaCl uptake is very dependent on Na\(^+\)-K\(^+\)-ATPase, upon which aldosterone presumably exerts powerful facilitation, with natriuretic hormone as a probable inhibitor. Here ADH opens membrane pores for water, so that the initially hyposmolar tubular content becomes available for water absorption when it passes down the collecting ducts close to the increasingly hyperosmolar Henle loops. The kallikrein-kinin-PG system probably serves as a local modulator, tending to offset mineralocorticoid and ADH actions (sect. IIIE2b).

2. Situation in primary hypertension

Combinations of reduced renal function and water-salt loading can certainly cause hypertension. This classic volume type of hypertension starts largely according to the concept of Guyton et al. (125-127, 279), though the events are probably more complex than originally assumed (sect. IIIE1). For example, in Dahl rats, salt-volume loading increases cardiac output also in HRR, but resistance is proportionally lowered instead of the apparent whole-body autoregulation and pressure rise occurring in HSR (sect. IIIB3b, E4). Evidently other mechanisms are also involved, as outlined below.

In any case the handling of extra salt loads may pose serious problems, at least in advanced primary hypertension; furthermore even in fairly early phases the renal excretory function becomes reset along with the rising pressure level, more or less independently of how this is induced. This is evident, e.g., from the approximately parallel right-hand shift of the relationship between arterial pressure and sodium excretion in both human and
SHR primary hypertension (22, 28, 90, 208, 257, 326, 365, 475), to begin with mainly for functional (neurogenic?) reasons. However, the renal long-term barostat function, like most other important control systems as well as the cardiovascular effectors proper, is quickly reset structurally to operate around a higher pressure equilibrium (205, 208, 257). The various aspects of renal alterations in primary hypertension have recently been discussed in a symposium (57).

a) Primary renal involvement. The critical questions here are whether and how often in human primary hypertension alterations of renal excretory function are truly primary, in the sense that they are genetically bound and responsible for the initiation of a chronic high-pressure state. Excellent models of such a situation are presented by HSR and MHS, though HSR must also be challenged by the environmental influence of increased salt intake (sect. II C 2c). On the whole, whenever salt loading is important in primary hypertension, it has seemed natural to investigate the kidneys as the real culprit, and quite often they do contribute, as in MHS and HSR, to judge from cross-transplantation experiments (58, 142).

However, considering the increasing evidence of a ouabainlike natriuretic hormone, combined with genetic increases of membrane Na⁺ permeability (sect. III A, 64), the kidneys are not necessarily the real, or at least not the only, critical point during increased salt loads. For example, salt intake in humans is ordinarily concentrated at a few daily meals and is usually accompanied by appropriate water intake. The ensuing postprandial bouts of salt-fluid absorption are bound to cause transient, mild volume expansions, though their extent certainly increases if salt intake is raised. However, normal cardiovascular systems seem to handle even large salt intakes efficiently and without significant pressure increases, mainly because of reflex neurohormonal adjustments of heart, vessels, and kidneys, the latter after some inevitable delay causing appropriate excretion. Concomitant reflex release of natriuretic hormone facilitates excretion and, with normal cell membranes for sodium permeability, generalized ouabainlike hormone effects on, e.g., smooth muscle and adrenergic neurons would be more than offset by reflex sympathetic inhibition. For example, salt loading is of little consequence in HRR, and normotensive humans can also accommodate fairly massive increases of salt intake without significant pressure elevations (375, 420, 603). This is in general agreement with Simpson’s recent critical survey of the literature on the relationships between salt intake and blood pressure for population samples in which he could trace no such relationship, with the possible exception of the very extremes of intake (sect. II C 2b, 584).

However, the situation may be different in at least some groups of genetically predisposed individuals, if afflicted by alteration of membrane sodium permeability, even if their kidneys are not hampered in their handling of salt loads and actually often excrete them more rapidly than hypertensives (sect. III F 2b). The same episodic volume expansions may here—by ouabainlike effects of the reflexly released natriuretic hormone—unmask
the raised membrane leakiness enough to enhance, e.g., smooth muscle and/or sympathetic responsiveness transiently. If this overcomes the concomitant reflex inhibitory adjustments, it would cause net elevations of daily average pressure as a result of such intermittent bouts of volume-dependent pressor effects. It was mentioned in sections IIIC2b and IIIB3c, E4 how salt loading, at least in some cases of human primary hypertension and in HSR, may cause resistance elevations that seem to involve accentuated neurogenic effects, according to Mark, Abboud, et al. (433, 609). This is in direct contrast to what would be expected from uncomplicated volume expansions, showing reflex inhibition of sympathetic activity. In comparisons of HRR and HSR, Tobian and his co-workers (233, 632) concluded that something else besides the mere salt-volume load was involved in raising systemic resistance in HSR.

Such possibilities in no way deny that coexisting genetic renal abnormalities in excretory function would help to create trouble with increased salt intake, best exemplified by HSR. On the other hand, during the first few months of their early pressure rise, SHR can be exposed to marked increases (or real deprivations) of NaCl intake without really affecting their pressure rise (21, 210, 416). Once established, however, SHR hypertension is also aggravated by extra salt loading. In contrast, stroke-prone SHR, evidently with an aggravated genetic predisposition that might involve renal elements, are more sensitive to early salt loading, according to Dietz et al. (160). In their thorough studies of this SHR variant, these investigators also noted that renal sympathetic denervation considerably delays hypertension development, illustrating how central autonomic influences can indeed importantly affect primary hypertension via the kidneys. The spectrum of genetic variants and the combinations of interactions with environmental influences are certainly impressive and far from unified concepts of pathogenesis.

It should be possible to distinguish between a membrane-dependent pressure rise in response to volume loading and one caused by a primary renal excretory abnormality. The latter, but not the former, is likely to cause exaggerated and prolonged volume expansions for given salt loads, which indeed seems to be true for HSR and probably also MHS. Apparently HSR has a reduced medullary blood flow, which would favor salt-water retention (210, 632). In MHS glomerular filtration capacity seems to be slightly reduced, presumably with the same end result of increased salt-water retention (30, 56, 58). For both strains the predisposition for hypertension accompanies the kidneys in cross-transplantations with normotensive controls. This has been claimed also for SHR, but here cross-transplantation was performed first at an age when the kidneys must have been structurally reset (sect. IIID8), thus giving no information about any initiating renal involvement.

There are probably subgroups like HSR and MHS in human primary hypertension, i.e., with genetic alterations of some of the links in renal sodium handling, but the difficult question is how common and pure such human variants are. This requires detailed renal analyses in very early cases,
well before any secondary renal resetting has started, ideally in normotensive youngsters from families with a strong genetic predisposition. Bianchi et al. (60) studied such youngsters and noted that up to 40% have an increased renal blood flow compared with genetically normotensive controls. What this means is difficult to say, but it might reflect a compensatory renovascular adjustment to keep, e.g., glomerular filtration normal. Further experimental work is certainly needed, but it is here of great interest that other investigators, studying young hypertensive subjects, have also distinguished a subgroup with increased renal blood flow, as reviewed by Hollenberg and Adams (326).

However, according to Hollenberg et al. (327, 328), at least two-thirds of the subjects with early primary hypertension show clear signs of increased sympathetic activity in the kidneys with reduced renal blood flow, in general agreement with, e.g., Brod’s early findings (sect. II.C-2, III.A.3b). Furthermore, Hollenberg’s analyses of the renal vessels in human primary hypertension also provide evidence of an increased vascular hyperreactivity, suggesting a considerable structural autoregulation of the renal resistance vessels, as in SHR (130, 208, 257, 421).

Moreover in a similar group of genetically predisposed youngsters, like those in which Falkner, Onesti, et al. noted exaggerated and prolonged defense reactions to forced mental arithmetic (sect. III.B.3), there was a tendency to respond with slightly greater pressure elevations than genetically normotensive controls when exposed to similar salt loads (187). However, it is not known whether this is really due to a primary renal alteration or is merely a renal expression of the accentuated central neurohormonal drive via sympathetic effects on vessels and tubules; alternatively it may be an effect of exaggerated ouabainlike effects of reflexly released natriuretic hormone. After all, central autonomic control can affect the kidneys and their excretory function by many routes and in ways that may simulate primary renal abnormalities, as exemplified by SHR and stroke-prone SHR (129, 130, 160, 205, 421, 538).

Parfrey, Wright, and Ledingham (504) recently compared young individuals who were genetically predisposed to hypertension with normotensive controls for patterns of salt-water excretion after a standardized isometric work load. In early primary hypertension there were signs of a delayed salt-water excretion in the hypertensive group. However, no such delay was found in normotensive youngsters with a strong genetic predisposition for primary hypertension, leading to the conclusion that their altered sodium excretion was an effect rather than a cause of primary hypertension.

Together these interesting though unfortunately too few studies of the earliest prehypertensive stages of human primary hypertension suggest that there may be at least a few subjects with genetic alterations of renal excretory function; whether this alone is enough to trigger hypertension is still an open question. Apparently, however, in most cases of human primary hypertension the kidneys are involved first secondarily, but with signs of a
gradual resetting quite early along the pressure rise, which is in good agree-
ment with findings in SHR. It also seems clear that neurogenic influences 
on renal function are often marked in early human primary hypertension, 
again like SHR (sect. IIID8). Expanded studies are much needed, however, 
and they might be facilitated if simplified tests for genetic markers, like the 
altered erythrocyte handling of sodium (sect. IIIA), can be used on a wider 
scale for identification of potential risk families. This would, for example, 
allow extended early explorations, e.g., of primary renal abnormalities and 
of increased sensitivity to salt and/or to environmental stimuli in predis-
posed individuals, in addition to concentrating preventive measures on those 
really needing it instead of exposing whole populations to somewhat futile 
drives against salt and stress.

b) Secondary renal involvement. This provides a natural transition to 
the important question of how renal excretory function is secondarily reset 
in primary hypertension. Again the rat models have been helpful by allowing 
detailed longitudinal studies. Whereas relationships between arterial pres-
sure and glomerular filtration are still largely normal in young borderline 
SHR, at 3-4 mo of age this relationship is reset some 30-40 mm along the 
pressure axis (208, 257). It reflects a structural renal vascular adaptation 
that in this early established phase considerably increases the preglomer-
ular-to-postglomerular resistance ratio but at only modest increases of total 
renal vascular resistance at maximal vasodilatation, compared with controls 
(sect. IIID8).

Such a change represents perhaps the most efficient way of resetting 
renal long-term barostat function, to judge from Guyton’s computer simu-
lation analysis (126, 279), because now a higher pressure is needed to main-
tain glomerular filtration, in case postglomerular resistance is not compen-
satorily raised, which would only further reduce renal blood supply, raise 
the filtration fraction, and increase glomerular filtration pressure. Actually 
this occurs with further advancement of SHR hypertension, again on a struc-
tural basis. At 12-14 mo of age postglomerular and hence also total renal 
resistance is much increased, whereas glomerular filtration capacity is re-
duced by about 40% /g renal tissue (G. Göthberg and B. Folkow, unpublished 
observations). When ordinary functional renal vascular adjustments are su-
perimposed on such structural alterations, they may well further accentuate 
the adverse consequences for glomerular pressure and filtration.

In fact these events in the SHR model seem to closely mimic the far 
more gradual changes occurring in human primary hypertension, where it 
is much more difficult, however, to separate structural and functional 
changes. First, glomerular pressure and filtration largely remain normal 
despite a rising arterial pressure and signs of a neurogenic renal resistance 
increase (90, 327, 328). In later stages renal blood flow decreases further, 
with clear signs of raised glomerular pressure and filtration fraction, sig-
naling an increasing postglomerular resistance. This is commonly associated 
with a presumably renal baroceptor–induced reduction of renin release (low-
renin hypertension; sect. III B2) and with signs of decreasing sympathetic activity (46, 48, 68, 90, 96, 560, 563). These changes in human kidneys have often been assumed to reflect only changes in vascular smooth muscle activity, but, to draw parallels to the SHR model, early structural vascular adaptation is most likely to lay the foundation for these alterations also in humans. At this stage the kidneys are increasingly dominant and are facing real trouble: they now resemble the unclamped kidney in advanced two-kidney, one-clamp renal hypertension, as pointed out by Birkenhäuser et al. (68), Schalekamp et al. (562, 563), and Brown et al. (95) in elegant studies of various stages of human primary hypertension.

In the later stages of primary hypertension it is easy to recognize the great importance of the kidneys and their troubled excretory function. It has been suggested, for example, that the reduced blood supply with increased filtration fraction also causes increases of peritubular oncotic pressure, thereby facilitating proximal sodium reabsorption, not to mention that medullary blood flow reductions tend to favor distal reabsorption as well. Somehow the low kallikrein levels may be involved, since the kallikrein-kinin system tends to favor sodium excretion. Perhaps the low kallikrein is a local renal compensation to counteract the tendency toward exaggerated natriuresis (see below).

Nevertheless true volume expansion is rare, and plasma volume is usually in the lower normal range in these stages, though increasingly centralized mainly because of reduced venous compliance in the systemic circulation (sect. III B2). Furthermore at these later stages there is often hardly any evidence of increased salt intake; rather, habitual salt intake may be slightly reduced, to judge from urinary analyses in untreated subjects, perhaps reflecting some automatic negative feedback on salt appetite when salt intake becomes a problem (48). A reduced salt appetite is noted also in the stroke-prone, salt-sensitive substrain of SHR (160), illustrating that increased salt intake is not always the culprit (sect. II C2).

A most interesting and puzzling phenomenon is the exaggerated natriuresis displayed in established primary hypertension, both in humans and SHR, for which there are many explanations, and probably several causes, partly depending on the type and stage of hypertension (265). Simply, when given salt loads, the hypertensives get rid of them more promptly than normotensive controls—not quite favoring the concept that hypertensive kidneys are increasingly helpless in facing salt loads. Kil (370) stresses that largely the same phenomenon occurs in normotensive kidneys during acute pressure elevation by, e.g., baroreceptor unloading. One argument is that the increased filtration raises tubular pressure, which further reduces preglomerular resistance, whereas tubular capillary oncotic pressure may fall and hydrostatic pressure may increase. Lowenstein et al. (417), via renal wedge pressures in salt-loaded normotensive and hypertensive subjects, have traced higher intrarenal pressures in the hypertensives during salt loading, probably reflecting exaggerated arteriolar adjustments with their consequences.

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for filtration, etc. Brown et al. (95) and Schalekamp et al. (562) found no relationship to renin-angiotensin levels but greater natriuretic responses the more advanced the primary hypertension; they suggest as a major cause greater hydrostatic pressure increases in tubular capillaries. Ricksten et al. (538), working on SHR, noted that a given volume load was more centralized and produced more volume-receptor-induced reflex sympathetic inhibition in SHR than in normotensive controls. This accentuated sympathetic inhibition in SHR also involved the renal sympathetic supply, and to some extent at least the increased natriuresis in SHR may therefore be ascribed to a stronger reflex suppression of the α-receptor-mediated facilitation of tubular sodium uptake. However, all the discussed elements presumably participate to some degree in this apparently paradoxical phenomenon.

This short survey shows that in most instances of human primary hypertension, genetic alterations of renal excretory function are probably not a decisive trigger influence, though the kidneys are early and importantly modified by functional means, mainly by neurohormones. Furthermore quite early a gradual structural resetting of the renal preglomerular-to-postglomerular resistance ratio also occurs, and then the renal excretory function increasingly exercises a decisive influence on further development. Gradually the postglomerular resistance begins to rise to keep filtration up, and then the glomerular capillaries become more exposed to pressure, which invites deterioration and initiates a fall of maximal filtration capacity. This calls for further postglomerular constriction, glomerular capillary pressure rises still more, and a rat race is started, one of the several deleterious positive feedbacks that seem to develop in primary hypertension. Particularly the excellent work of the Glasgow group (95) has greatly contributed to the understanding of the renal role in human primary hypertension.

With respect to truly primary renal deviations in humans, which no doubt occur but probably not too often dominate early events, much further work is needed, particularly investigations on normotensive individuals from a genetically strongly predisposed group, as started by Bianchi et al. (60) and Falkner et al. (187).

IV. SUMMARY AND CONCLUSIONS

For nearly 100 years great efforts have been made to elucidate how human primary hypertension is initiated and maintained. Progress was greatly stimulated by Goldblatt's introduction of experimental secondary hypertension in the 1930's; unfortunately enthusiasm for the developed unitarian models also delayed the realization that human primary hypertension is basically of multifactorial origin. A new attitude slowly emerged in the 1950's and 1960's, greatly facilitated by the introduction of polygenetic variants of rat primary hypertension, which also provided researchers with better experimental models.
Together with experimental, genetic, and epidemiological studies in humans, the investigations of the rat models have made it clear that primary hypertension ensues from variable combinations of initiating, reinforcing, and stabilizing elements. Each element may be fairly harmless alone, but when combined in particular constellations they induce various degrees of a slowly developed pressure elevation, at least in humans, so that primary hypertension in population surveys simply constitutes the right-hand part of the normal distribution curve for blood pressure levels. The raised pressure level alone would perhaps be of little consequence if only heart and vessels had been genetically designed to tolerate prolonged elevations of load, but unfortunately deterioration slowly ensues in most individuals, with organ damage and manifest disease as the final result.

The insidious onset of human primary hypertension, nearly indistinguishable from ordinary pressure variations in normotension, has considerably hampered studies of the etiologically interesting early stages, though recent long-term follow-up analyses have provided important information clearly linking different stages together in a continuous change. The rat models have also been invaluable because of their compressed time axis, easily controlled environment, and uniform genetics within strains but important differences between strains.

These studies have revealed three major, strongly interdependent causative elements in both human and rat primary hypertension. I) A polygenetically transferred predisposition: this represents the sine qua non which in humans may vary individually in balance and power, whereas within each hypertensive rat strain it is uniform because of inbreeding but shows important differences between strains. II) Environmental factors: here at least two major elements can be distinguished—1) excitatory psychoemotional influences and 2) habitual salt intake. They reinforce and sometimes may even precipitate the hemodynamic expressions of I, though their relative importance also depends strongly on the nature of I. Their cardiovascular actions may in fact show considerable interactions at both the renal and volume control levels. III) Early structural adaptation of heart and vessels: this element, which is in principle a normal and rapid tissue response to any stimulatory pressor effects like those of I + II, might also be genetically reinforced. 1) At the resistance level a positive-feedback interaction is introduced with I + II; 2) in the heart and capacitance vessels contractile strength is increased and compliance is reduced; and 3) volume-receptor and baroreceptor reflexes as well as the renal barostat function are reset to operate at higher pressure levels, by altering cardiac, arterial, and preglomerular vessel design.

These multifactorial interactions have some important consequences. The pressor influences of the various I + II constellations need only be marginal and may even be intermittent, because whenever persistent enough they will initiate III. This structural adaptation is so rapid in onset and establishment that it becomes intertwined with the functional excitatory
influences of $I + II$, particularly since these mostly seem to be fairly insidious, both in extent and mode of action. Here $III(I)$ will ensure a gradual rise of systemic resistance to ultimately high levels due to its positive-feedback interactions with $I + II$, and $III(II)$ and $III(III)$ will also adapt proportionally. It is something of a paradox that the morphological alterations of the left heart, large arteries, and arterioles were recognized more than 100 years ago—in fact before blood pressure was ever measured in humans—but the functional consequences of these most palpable alterations were largely disregarded until fairly recently.

These various functional expressions of $III$ will increasingly dominate hemodynamics and, besides contributing importantly to the gradual pressure rise, they will also be the essential element maintaining the chronic high-pressure state. Thus the structural adaptation of precapillary resistance vessels, with a reduced inner radius and a thickened media, results in an unspecific vascular hyperreactivity whereby a raised resistance can be maintained also at normal levels of smooth muscle activity. At this stage it is often quite difficult to trace any direct influence of $I$. Further, if also genetically reinforced, $III$ might even develop in response to quite ordinary levels of excitatory influences on the cardiovascular system. Thus thanks to $III$ the cardiovascular system soon becomes redesigned to function at a higher pressure and resistance equilibrium, also with respect to the major barostat mechanisms, and the hypertrophic structural alterations must be forced into regression by, e.g., prolonged pharmacological pressure reductions if a truly normotensive homeostasis is to be regained. The more cardiovascular muscle hypertrophy is also complicated by, e.g., collagen infiltration and outright degeneration and lesions, the more difficult it is to normalize the situation.

Genetic deviations may in principle exert their triggering hemodynamic effects via the nervous and hormonal control systems, via the renal excretory control of cardiovascular filling, and/or via the cardiovascular muscle effectors themselves. At this latter level they might in parallel influence both function and cell design, since these two represent different time facets of how muscles respond to stimulation and load and probably have important initiating links in common. With a polygenetic background, several of these main components may well be affected simultaneously in different combinations and degrees, depending on the individual genetic setup and environment.

Analyses of early phases of primary hypertension in humans—and, among rats, in SHR and probably also GHR—strongly suggest that central neurohormonal influences are a common and important trigger influence, reinforced by ordinary psychosocial stimuli that tend to increase the average level of alertness. In prehypertensive stages, predisposed individuals have been found to already show, e.g., exaggerated and prolonged defense reactions in response to graded alerting stimuli. This type of CNS influence illustrates the futility of either/or attitudes when considering nervous and
hormonal factors in primary hypertension: both are combined into common reaction patterns prompted from the highest CNS levels, though greatly modified at the reflex and peripheral levels. Also in the resting state these neurogenic—or perhaps better neurohormonal—variants often display the hemodynamic characteristics of very mild defense reactions with a hyperkinetic cardiovascular balance, though with a gradual shift toward normalized cardiac output and raised resistance when hypertension reaches the established phase.

The rat strains HSR and MHS, in contrast, represent genetic variants in which primary hypertension starts along quite different routes; once the established phase of hypertension is reached, however, largely the same hemodynamic balance prevails, dominated by an elevated systemic resistance. Here the kidneys seem to be a major starting point, presumably because of genetic deviations in the glomerular filtration/tubular reabsorption balance, or its control, with a tendency to salt-water retention, where at least in HSR salt loading is a necessary precipitating element. Human primary hypertension probably also contains related volume variants in which renal influences dominate or at least importantly contribute to the initiation of primary hypertension. However, in pure form such volume variants seem to comprise only a minority in humans, though elements of this nature of course may be blended with, e.g., neurogenic elements.

As primary hypertension advances, however, the reset kidneys more and more tend to dominate the situation and to counteract normalization largely for the same reasons as they strongly counteract on induction of hypotension in normotension. Furthermore, because the renal circuit and the glomerular filtration capacity seem particularly vulnerable when exposed to pressure elevation, the kidneys in advanced stages of primary hypertension will have an even more dominating influence on the increasingly disturbed pressure and volume homeostasis.

There also seem to be variants where an initial increase of mineralocorticoid release helps to start the pressure rise, but again they seem fairly rare in human primary hypertension, except as links in the CNS neurohormonal influences mentioned above. Earlier assumptions that increased renin-angiotensin levels should be a common initiating element in primary hypertension, as in secondary renal hypertension, seem to have very little support except, again, as integral parts of the neurogenic variants, where a sympathetic renin release is one of many adjustments constituting the far-reaching central neurohormonal influence.

This by no means denies the great importance of the renin-angiotensin system in overall volume homeostasis, which particularly in established hypertension seems to be increasingly vulnerable and where the extensive effects of angiotensin can be most important as a maintenance factor, also utilized in modern therapeutic variants. Furthermore the aldosterone-producing zona glomerulosa cells often show increased sensitivity to angiotensin in primary hypertension, but evidently this sensitized control link is somehow compensated for, because early increases of aldosterone secretion are
fairly rare in early primary hypertension. However, in the established phase of human primary hypertension there is often a mild mineralocorticoid elevation, presumably due to delayed elimination and/or perhaps representing a compensation for maintaining plasma volume, which at this stage is often in the lower normal range.

In both rats and humans there are often signs of marginal increases in vascular smooth muscle sensitivity, but the extent to which such a primary effector deviation directly contributes to the initial pressure rise is not clear because superimposed neurohormonal influences often mask such changes. It is not impossible that the finally most important consequence of a mildly increased effector responsiveness is an accentuated trend toward structural adaptation, for which there are several indirect signs in, e.g., SHR.

On the whole it seems likely that mild deviations in different parts of the circulation and its control systems often coexist in various combinations. Furthermore several of them might be expressions of a deviation in cell membrane, an interesting possibility originally observed more than 20 years ago but recently explored in more detail. Finally, genetic deviations must express themselves as alterations in design and function of macromolecules like enzymes, carriers, membrane constituents, contractile proteins, etc.

This membrane deviation has been traced in patients with primary hypertension as well as their close relatives (but not in secondary hypertension), in SHR, and probably in some other rat strains. Thus evidence strongly suggests a truly genetic deviation, which seems to express itself as a slightly increased "passive" permeability to Na\(^+\), perhaps as a reduced Na\(^+\)-K\(^+\)cotransport activity, though being somewhat compensated for by increased Na\(^+\)-K\(^-\)-ATPase activity and active Na\(^+\) expulsion. There is much to indicate that this slight membrane deviation, the exact nature of which is not settled and may even contain several variables, is generalized to all cells, though being mostly compensated for by the ATPase pump. However, if affecting cells that already normally have labile membranes and high permeability to sodium ions, like vascular smooth muscle and central and peripheral autonomic neurons with their neuroeffector junctions, the excitability and/or inherent activity of such cells might thereby be at least potentially increased.

There is also increasing evidence of a natriuretic hormone that seems to exert a fairly generalized, ouabainlike depression of the Na\(^+\)-K\(^+\) pump, besides its particular depression of renal NaCl uptake. Therefore the ordinarily well-compensated increase in membrane leakiness to Na\(^+\) (and probably to Ca\(^{2+}\)) may become to some degree unmasked when natriuretic hormone is released, perhaps induced via cardiac volume receptors in response to salt-volume loading and/or at increased blood volume centralization, which seems common in, e.g., neurogenic variants of primary hypertension. Such events might explain why, e.g., salt loading in some variants of primary hypertension (e.g., IISR) can induce considerable pressor effects. They are probably not just consequences of a volume-induced increase in cardiac output with secondary resistance autoregulation, because few such effects are
seen in, e.g., the genetically normotensive HRR, and a secondary accentuation of neurogenic and/or myogenic vascular influences seems to occur as well. There are reasons to suspect an unmasking of a primary, increased membrane permeability via released natriuretic hormone, which might influence the responsiveness of both autonomic neurons and smooth muscle effectors.

Such apparently mild genetic deviations in cell membrane ultradesign and function, perhaps of several different types, might prove to be a common denominator behind trigger influences in primary hypertension that at first appear so different—central nervous hyperreactivity with accentuated neurohormonal cardiovascular effects, altered release of mineralocorticoids, deviations in renal function, etc.—but only future research can elucidate these most interesting possibilities. Simplified tests of these membrane alterations in, e.g., blood cells may help in the early identification of risk groups, allowing more penetrating early experimental analyses with opportunities for adequate preventive measures directed to those who really need it.

If it really is true, as several findings seem to indicate, that the genetic triggering elements are fairly mild, they might perhaps also be offset by relatively modest countermeasures, if only they can be identified well before they have started the ball rolling and initiated structural adaptation of both heart and vessels. Another indication that the genetic predisposition for primary hypertension, which after all encompasses well over 10% of most population samples, hardly implies any massive abnormalities or genetic defects (in the ordinary sense of this word) comes from epidemiological studies. Thus it is reported that isolated population groups, which have remained little exposed to some important influences of modern technological society—a more vivid psychosocial environment and liberal salt intake—seem to have particularly low blood pressure levels with little rise with age. When such populations are exposed to the mixed blessings of the industrial world, however, they soon seem to catch up in blood pressure profiles, suggesting that the genetic elements may have been there but are largely latent until challenged by the proper environmental influences. This is a field of great interest that needs further studies.

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