# Arterial Hypertension

Pathogenesis, Diagnosis, and Therapy

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Pathogenesis, Diagnosis, and Therapy

*Edited by*

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Foreword by Irvine H. Page

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The illustration on the front cover is based on
Page's mosaic theory of hypertension.

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*To my mother and the memory of my father*

# Contents

# Foreword

It has been a little more than half a century since serious, organized research on hypertension began. Public and even physician interest in the subject remained minimal until the early forties, and even then there were not more than a dozen "fulltime" investigators worldwide. The first organization devoted to communicating regularly the results of hypertension research was created in Cleveland in 1945; it became the Council for High Blood Pressure Research of the American Heart Association in 1949.

The early history of hypertension is not a story of progressive achievement. Richard Bright is given great credit, followed by Mahomed, Allbutt, Riva-Rocci, Bergman and Janeway, but it was not until Volhard, Fahr and Allen that some semblance of order emerged. They were followed by a younger, much more vigorous group of investigators who in fact initiated modern research in hypertension. Two more generations have followed.

In the course of some fifty years, we have seen emerge a magnificent body of evidence that has prescribed good treatment and contributed a considerable understanding of the many complex mechanisms involved in the hypertensions. Treatment is now actively promoted by public health agencies, including the World Health Organization. This is another case of treatment preceding full understanding of the nature of the disease.

The secondary hypertensions have received by far the greatest attention. It has become cliche to state that "the cause and mechanisms of essential hypertension are unknown." The early investigations all sought single causes and mechanisms, and all ended up with one or another aspect of secondary hypertension, such as aldosteronism or renal hypertension. But it has at last become apparent, I believe, that essential hypertension, like arteriosclerosis, has no single cause or mechanism. It has been called a "disease of regulation," because so many of the body's systems are involved in the regulation of blood pressure in order to regulate tissue perfusion. This principle has been pictured as a mosaic, which depicts the interrelatedness of the regulatory functions. This was the analogy used by Willard Gibbs to describe the Phase Rule in physical chemistry.

While people found it difficult to accept the principle of dysfunction of regulatory mechanisms, it has received almost unconscious sanction in current attempts to quantitate each of the varied facets of hypertension to show the "modulating effect" of each mechanism on the other.This has allowed for the current range of thinking on the subject.

A second generality in which I now believe, after 45 years, is that the core mechanism of hypertension involves angiotensin, either of renal, neural or angiogenic origin. Determination of the structure of inhibitors to angiotensin and the ability to synthesize them have disclosed an extraordinary picture: angiotensin and salt-water metabolism, both of which involve the nervous and endocrine systems, act to modulate one another. So we now have a body of knowledge that lends itself admirably to experiment, and we are on the threshold of taking the next large step: deepening our research to the molecular level, a step taken by the chemists and geneticists only a few years ago with the development of molecular biology.

Dr. Rosenthal and his colleagues have worked diligently, and I believe successfully, in compiling this volume. It is a particular pleasure for me to introduce this valuable work, which I feel sure will contribute significantly to further understanding of this very important subject.

Irvine H. Page, M.D.

# Preface

In the past few years, the explosion of information contributing to our understanding of hypertension has made it all but impossible for any one physician to keep thoroughly up-to-date. The practicing physician must apply principles of diagnosis and therapy that are evolving from the research and clinical experience of many specialists. It was my purpose, therefore, in asking my colleagues to contribute chapters in their various areas of expertise, to distill a practical and critical review of the mechanisms, diagnosis, and therapy of hypertension as we presently understand them. Experimental data have been included only where they are necessary to the understanding of fundamental principles directly relevant to clinical practice. Data that have yet to be confirmed have been included only marginally. Our goal was to present information that has been proven to be clinically useful and practical. As each contributor is treating the subject from his particular angle, an overlapping of information is, by necessity, entailed in some instances.

In order to shed light on certain factors responsible for the development and maintenance of high blood pressure, individual chapters are devoted to psychosomatic, metabolic, endocrine, neurogenic, and cardiovascular functions in hypertension. Besides contributions on the renal and urologic aspects of hypertension, we have explored the apparent connection of hypertension to atherosclerosis, obesity, and diabetes mellitus. We also felt it important to include a chapter on the increasingly visible problem of adolescent hypertension. Each of the steps involved in the diagnosis of hypertension, including techniques for measuring blood pressure, the basic work-up of a patient, and radiologic and nuclear medicine evaluation, are covered in separate chapters. Finally, problems that arise in treating hypertensive patients, including those with mild and resistant forms and those with the geriatric form, are discussed thoroughly, along with some relevant aspects of clinical pharmacology.

My most sincere thanks are due to all the contributors for their excellent work and for their patience. They both supported and challenged me as this volume developed, and for their suggestions and criticisms I am indebted to them. My particular thanks are due to the staff of Springer-Verlag New York, and above all to my wife Regine, who unfalteringly supported me with patience, wisdom, and active cooperation.

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*Ulm/Donau, 1982*

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# An Overview of Current Concepts Regarding the Pathogenesis and Pathophysiology of Hypertension

1

W. M. Manger, I. H. Page

## The Problem and Its Magnitude

Although significant strides have been made in understanding the mechanisms of secondary forms of hypertension, the etiology of essential hypertension remains an enigma. The term "essential" is a misnomer since it was originally, and erroneously, believed that elevated blood pressure was "essential" to ensure adequate tissue perfusion in patients with hypertension. Since the initiating cause, or causes, of essential hypertension are not established, a more appropriate designation would be "idiopathic" hypertension. At least 90% of the hypertensive population with both systolic and diastolic pressures elevated have this latter type of hypertension.

Hypertension is worldwide and of epidemic proportions. It is present in 15% to 20% of all adults. It is the most common serious chronic health problem, since it carries a high risk of cardiovascular complications. As an indication of the magnitude of the hypertension problem in the United States, it is estimated that it afflicts 40 million Americans (one in every five adults!) and another 25 million have borderline hypertension. It costs the nation about 20 billion dollars in medical bills, lost wages, etc. and is responsible for 52 million working days of productivity lost each year. Today it is estimated that roughly 26 million adults in the United States have diastolic hypertension; the remainder have only systolic hypertension, caused mainly by atherosclerosis or occasionally an elevated cardiac output or an increased stroke volume. An insidious and ubiquitous disease, which is particularly virulent in the black population, hypertension and its complications may contribute to the death of 1½ million and the disability of another 1½ million Americans each year. Perhaps less than half of the hypertensive population of Americans know they have this disease; and of these, probably 50% or less are receiving adequate treatment, which has proved so effective in reducing morbidity and mortality. In one sense it is extremely unfortunate that the vast majority of hypertensives are "symptomless," since irreversible cardiovascular damage and death may occur before the condition is recognized.

The magnitude of this health problem is especially evident when one appreciates that approximately 95% of persons with diastolic hypertension are incurable (except very rarely by renal transplantation). It is estimated that 5% of all cases of diastolic hypertension result from bilateral renal parenchymal disease, whereas 90% are due to essential hypertension. Only 5% of patients have other causes of hypertension which are sometimes curable (Table 1).

The fact that marked variability occurs in both the systolic and diastolic blood pressure of normotensive and hypertensive individuals during a 24-h period of observation (Fig. 1 A, B, and C) makes it mandatory to repeat blood pressure determinations on different days in order to establish whether sustained hypertension is present. Unfortunately, some people who do not have sustained hypertension are mistakenly treated for a transiently elevated blood pressure.[279] The prevalence of hypertension (defined as a level of systolic pressure of at least 160 mm Hg and a diastolic pressure of at least 95 mm Hg) in the United States in white and black men and women is graphically displayed in Figure 2.

Pickering has decried efforts to establish a level of

**Table 1.** Causes of Diastolic Hypertension*

A. Primary (essential, idiopathic) hypertension, (80% to 90% of all patients)
B. Bilateral renal parenchymal disease, (5% to 15% of all patients)

*Incurable*

Chronic glomerulonephritis
Chronic pyelonephritis
Polycystic disease
Diabetic nephropathy
Systemic lupus erythematosus
Amyloidosis
Multiple myeloma
Scleroderma
Wegener's granulomatosis
Goodpasture's disease
Periarteritis nodosa
Balkan nephritis

*Sometimes Incurable*

Acute glomerulonephritis
Hypercalcemic nephropathy
Renal cortical necrosis
Renal involvement in gout
Toxic nephropathy

C. Other causes

*Incurable*

Cerebral ischemia (vertebrobasilar)†
Hyperdynamic $\beta$-adrenergic circulatory state†
Autonomic (diencephalic) seizure
Pseudohermaphroditism (↑ androgenic steroids)
Turner's syndrome (with or without coarctation)
Myxedema
Tabetic crisis†
Dysautonomia†
Abdominal angina
Inappropriate vasoconstriction
*Spinal cord lesion (noxious stimulus)*†
*Acute intermittent porphyria*†

*Sometimes Curable*

Unilateral renal parenchymal disease (including renal transplant rejection)
Occlusive renovascular disease
Thyrotoxicosis
Cushing's syndrome (hydrocortisone and corticosterone)
Primary aldosteronism (Conn's syndrome)
Acute coronary insufficiency†
Coarctation of aorta (above renal arteries)
Hypersensitivity reactions†
Encephalitis†
Acromegaly
Renal tumors or renin-secreting tumors (e.g., Wilms' tumor; juxtaglomerular cell tumor; renal carcinoma)
Excess desoxycorticosterone (or ? another mineralocorticoid); [enzyme defect (e.g., adrenogenital syndrome with 11$\beta$- and/or 17$\alpha$-hydroxylase deficiency)]
Ovarian tumors (sometimes ↑ steroids)
Hypercalcemia
Obesity
Excess ingestion of
  Licorice
  Carbenoxolone
  Sodium bicarbonate
Expansion of blood volume
Hypothalamic tumor† or dysregulation†
Poisoning with
  Thallium
  Carbon monoxide
Fibrosarcoma pulmonary artery†
Pork sensitivity†
Iatrogenic [birth control pills; corticosteroids; methylphenidate; desoxycorticosterone; vasopressor drugs (including *catecholamines*); monoamine oxidase inhibitors + tyramine or some *sympathomimetics*†]
*Pheochromocytoma*†
*Increased intracranial pressure*†
*Hypoglycemia*†
*Intracranial lesions*†
*Neuroblastoma,*† *ganglioneuroblastoma,*† *ganglioneuroma*
*Lead poisoning*†
*Acrodynia*
*Carcinoid*†
*Clonidine withdrawal*†
*Tetanus*†
*Factitious*†
*Toxemia of pregnancy*†
*Guillain-Barré syndrome*†

*Conditions in italics may have increased excretion of catecholamines and/or metabolites.
†May have paroxysmal hypertension.

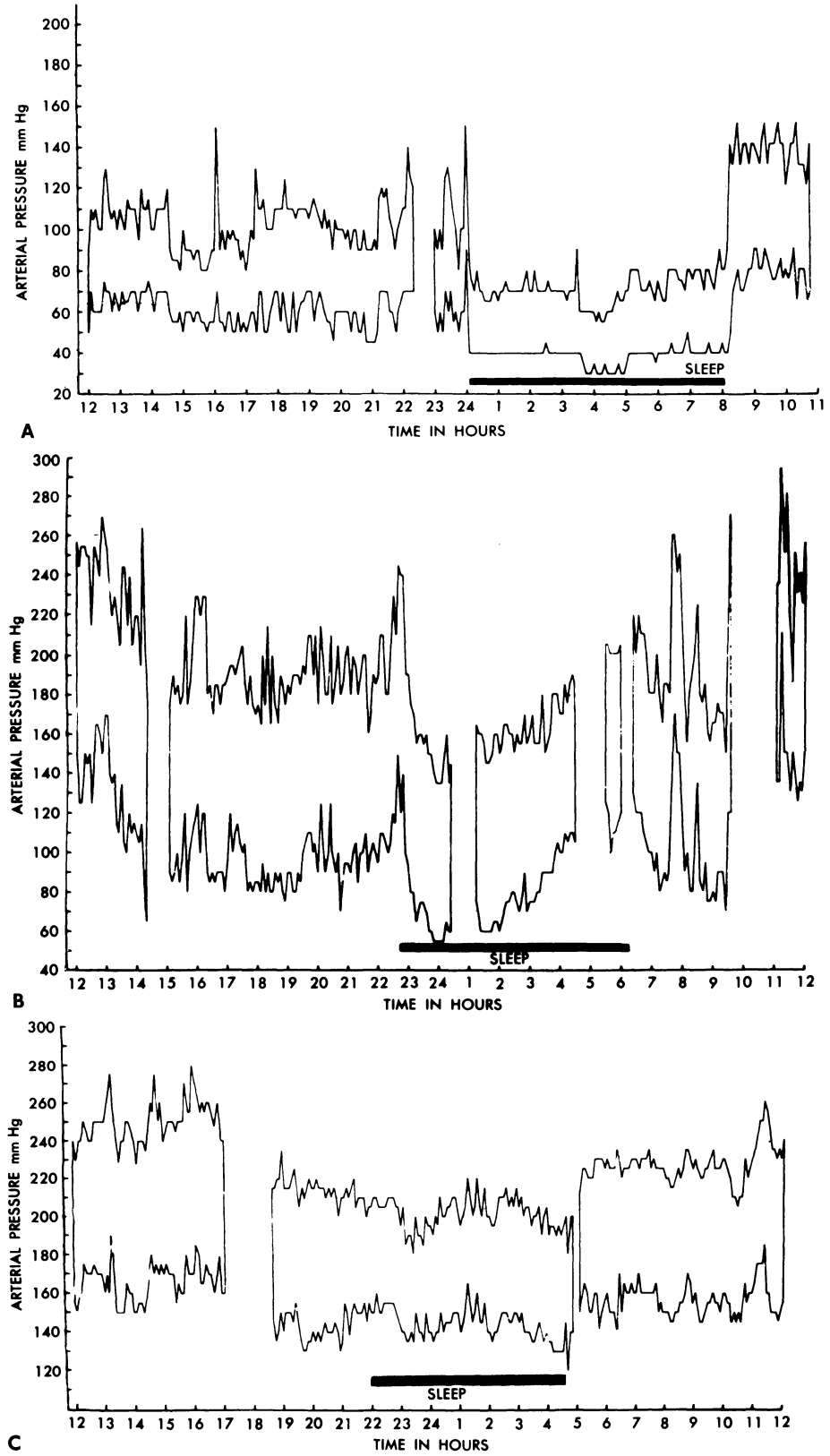


**Figure 1.** Arterial pressure plotted at 5-min intervals. Period of sleep is shown by horizontal bar. **A,** Normal subject. The high pressures shown at 16 and 24 h are due to a painful stimulus and coitus, respectively. **B,** Patient with essential hypertension in the benign phase. **C,** Patient with essential hypertension in the malignant phase. From Bevan AT et al., ref 20, p 329

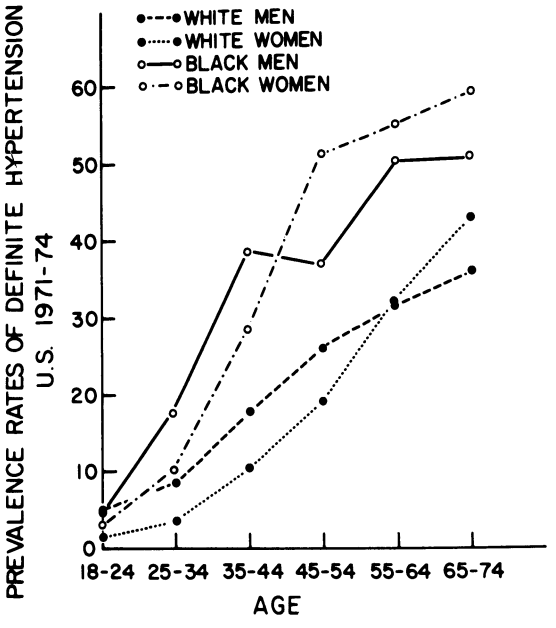


**Figure 2.** The prevalence of hypertension in the United States defined as a systolic blood pressure of at least 160 mm Hg or a diastolic blood pressure of at least 95 mm Hg. Data from the Health and Nutrition Examination Survey, 1971–1974. (Source: Advance data, vital and health statistics of the National Center for Health Statistics, No. 1, October 18, 1976.) From Kaplan NM ref 167, p 2

blood pressure which separates hypertensives from normotensives.[290] He points out that in frequency distribution curves of arterial blood pressure in populations, there is no dividing line which identifies a distinct hypertensive segment. Frequency distribution curves of arterial pressure are unimodal. Furthermore, he emphasizes that the relationship between arterial pressure and mortality is quantitative (i.e., the higher the pressure, the worse the prognosis). He views the deviation of blood pressure from the norm as quantitative rather than qualitative, and he claims that the attempt to divide pressures into normal and abnormal is artifactual. Nevertheless, there is great value in knowing what level of blood pressure is associated with a greater risk of cardiovascular complications and a reduced life expectancy.

From actuarial studies on men and women 15 to 69 years old (Table 2) it appears that diastolic blood pressures ranging even from 83 to 87 mm Hg and systolic pressures ranging from 128 to 137 mm Hg are correlated with increased mortality in men. On the other hand, this correlation is not apparent in women until the diastolic pressure ranges from 93 to 97 mm Hg or the systolic pressure reaches the 158 to 167 mm Hg range. With higher ranges of blood pressure and particularly when both systolic and diastolic pressures are progressively elevated, the reduced life expectancy for both sexes becomes increasingly more evident.

Because of these results, Kaplan has correctly pointed out that the criteria established by the World Health Organization for normotension (systolic less than 140 mm Hg and diastolic less than 90 mm Hg), hypertension (systolic greater than 160 mm Hg and/or diastolic greater than 95 mm Hg), and borderline levels (pressures between these limits) are not optimal; these criteria seem to be set too high and do not vary with age and sex.[167] Therefore, based on a 50% or greater increase in mortality in adults, he proposed the following criteria for hypertension:

**Table 2.** Ratio (Percent) of Actual to Expected Mortality

| | Diastolic BP | | | | | |
|---|---|---|---|---|---|---|
| Systolic BP | 48–67 | 68–82 | 83–87 | 88–92 | 93–97 | 98–102 |
| Men age 15 to 69 | | | | | | |
| 98–127 | 80 | 86 | 106 | 116 | 114 | — |
| 128–137 | 100 | 109 | 127 | 140 | 168 | 197 |
| 138–147 | 151 | 141 | 153 | 170 | 199 | 224 |
| 148–157 | — | 166 | 196 | 191 | 224 | 269 |
| 158–167 | — | 233 | 197 | 240 | 268 | 289 |
| Women age 15 to 69 | | | | | | |
| 98–127 | 57 | 56 | 55 | 58 | — | — |
| 128–137 | 62 | 60 | 64 | 74 | 65 | — |
| 138–147 | — | 71 | 73 | 72 | 117 | 132 |
| 148–157 | — | 61 | 83 | 96 | 98 | 139 |
| 158–167 | — | 97 | 150 | 125 | 172 | 205 |

Data from the 1959 Build and Blood Pressure Study of the Society of Actuaries.
From Kaplan NM, ref 167, p 2.

| | |
|---|---|
| Men under 45 years old | > 130/90 |
| Men over 45 years old | > 140/95 |
| Women any age | > 160/95 |

Table 3 reveals "normal" standards of blood pressure in children. The 50th and 95th percentiles for systolic and diastolic pressures of children and teenagers are tabulated according to age groups. Since the data represent a composite of several studies, it is felt that repeated blood pressure values above the 95th percentile should be considered abnormally elevated.[251]

Anxiety, fear, anger, pain, or discomfort (e.g., bladder distension), cold, exertion, recent smoking or eating, and certain drugs that have pressor effects can elevate blood pressure. The levels of blood pressure recorded by the patient or family member at home may be significantly lower than in the doctor's office.[11,157] More recently, de Simone and Baer found that roughly half of the patients they studied had significantly lower pressures when recorded by the patient than when recorded in a clinic office.[65] Because of the variability of an individual's blood pressure, one of us has expressed considerable concern over the physicians' reliance on blood pressures obtained in an office setting for optimal management of hypertensive patients with antihypertensive drugs.[281]

Accurate blood pressure determinations, which are representative of relatively basal levels and devoid of stress effects, are essential for optimal treatment. The important guidelines and pitfalls in taking blood pressure have been clearly outlined by Kaplan[167] and should be fully understood by those involved in the treatment of hypertension.

## Influence of Age, Sex, and Race on Blood Pressure and Its Complications

Prevalence of hypertension increases with age in practically all populations except for a few primitive unacculturated societies; furthermore, in the United States, hypertension develops earlier in blacks than in whites (Fig. 2). By the mid-30's, the prevalence of hypertension is significantly greater in both sexes of blacks as compared to whites. Some studies revealed that the rate of rise in pressure with aging was also partly related to the level of the pressure;[249] however, others have not found this relationship.[164]

The Framingham studies revealed that the risk of cerebrovascular accident of any type and also of other atherothrombotic brain infarction was greater in those under 50 years of age as compared to those 50 years of age or older (Fig. 3). These studies also clearly indicated that mortality rates in hypertensives (and in those with borderline hypertension) ranging in age from 45 to 74 years become greater with advancing age (Fig. 4) and with increasing levels of blood pressure (Fig. 5). Women tolerate hypertension better than men and mortality rates are higher in the latter at any level of hypertension; however, as blood pressure levels become elevated, the increase in cardiovascular disease and mortality rate becomes more pronounced in both sexes (Fig. 5).

**Table 3.** Percentile Values for Blood Pressure by Age

| | Systolic Pressure | | Diastolic Pressure | |
|---|---|---|---|---|
| Age | 50% | 95% | 50% | 95% |
| 0 to 6 mo | ≤ 80 | ≤110 | ≤45 | ≤60 |
| 3 yr | ≤ 95 | ≤112 | ≤64 | ≤80 |
| 5 yr | ≤ 97 | ≤115 | ≤65 | ≤84 |
| 10 yr | ≤110 | ≤130 | ≤70 | ≤92 |
| 15 yr | ≤116 | ≤138 | ≤70 | ≤95 |

From Mitchell SC et al., ref 251, p 3.

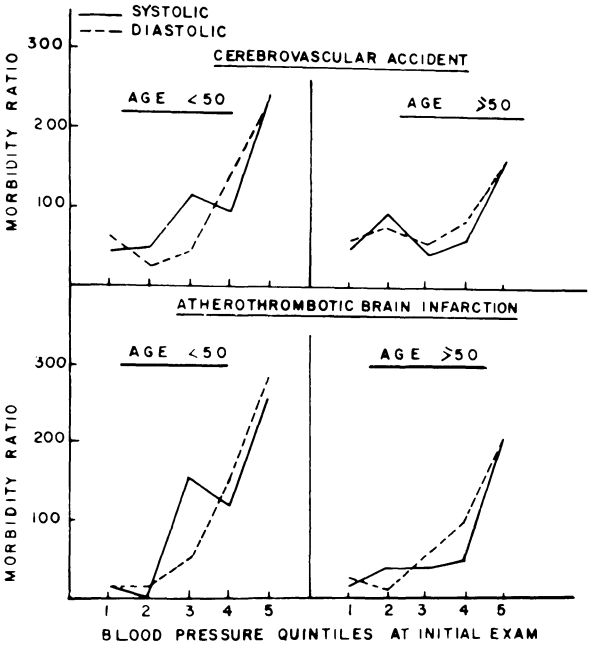


**Figure 3.** The risk (morbidity ratio) of having any type of cerebrovascular accident *(top)* or atherothrombotic brain infarction *(bottom)* over the 16 years of the Framingham Study, according to initial blood pressure level in men and women. The population is divided into those below and above age 50. The systolic and diastolic pressures are divided into fifths (increasing in severity on a 1 to 5 scale). From Kannel WB, ref 161, p 309. Reprinted by permission of the American Heart Association, Inc.

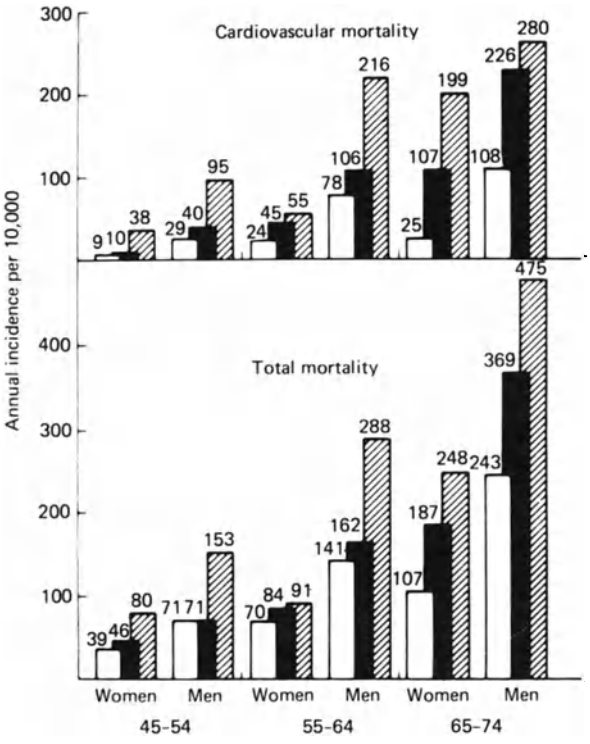


**Figure 4.** Cardiovascular *(top)* and total mortality *(bottom)* over 18 years' follow-up according to hypertensive status at the time of entry into the Framingham Study, for men and women ages 45–74. □ Normotensive (<140/90); ■ borderline; ▨ hypertension (≥160/95). From Kannel WB and Sorlie P, ref 162, p 555

Not only do blacks have a higher prevalence of hypertension (Fig. 2), but they also have blood pressures that are higher than whites at all ages after the mid-20's (Fig. 6); morbidity and mortality rates are also higher in blacks. It is noteworthy (Table 2 and Figs. 5 and 7) that elevated systolic pressure causes as much morbidity and mortality as elevated diastolic pressure. Systolic hypertension alone is an important risk factor for cardiovascular disease and an elevation of systolic rather than diastolic pressure may carry a greater risk for coronary heart disease.[165]

## Genetic Predisposition

Blood pressures of children frequently show a strong positive correlation with the parents' pressures.[138,202,366,367,369] The presence of essential hypertension in children is being recognized more frequently,[206,207] and in these children a family history of essential hypertension or its complications has been reported to be present in over 50%.[208] Genetic factors play an important role in the predisposition to hypertension, as has been known for many years.

The influence of environmental factors on blood pressures of families is difficult to assess; however, there is growing evidence for the importance of heredity on the level of blood pressure. For example, studies on blood pressure in a large series of male twins revealed that there was a two to three times greater probability of hypertension developing in both brothers if they were monozygotic than if they were dizygotic.[94] Others have reported a similar concurrence of hypertension in identical twins.[306] Furthermore, comparison of blood pressures of parents with those of true siblings and adopted siblings revealed a correlation of pressures only in the parents and true siblings.[26]

Available information indicates that essential hypertension appears between the ages of 20 and 45 years in perhaps 80% to 90% of the hypertensive population.[231,288,292] As has been known for many years, diastolic pressures usually plateau at ages 45 to 50 years, whereas systolic pressures continue to increase with aging because of the development of atherosclerosis.[30,167]

Recently Miall has stated that although the role of the genetic factor is now considered greater than previously, nevertheless evidence linking higher pressures with some factor or factors in the environment remains strong.[248] He further points out that studies of migrants show that no ethnic group is inherently immune to rises in pressure and that such studies have the best chance of identifying the environmental influences. The claim that genetic predisposition influences blood pressure levels in 60% of essential hypertensives whereas environmental factors are much less important[93] is very questionable, since it is difficult to establish accurately the incidence of hypertension in families.

## Environmental Factors

A number of environmental factors have been implicated in the genesis of essential hypertension; however, the evidence for this implication has often been circumstantial and the precise mechanisms whereby these factors may influence arterial blood pressure in the human have been difficult to decipher.

### Salt

A growing interest has centered around the relationship of dietary sodium chloride to both clinical and

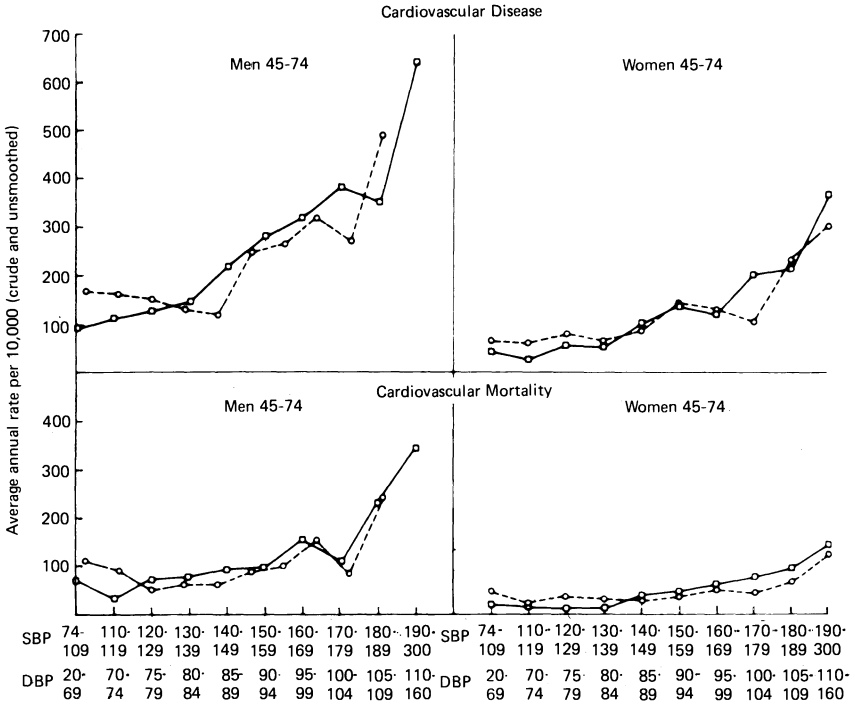


**Figure 5.** The incidence of cardiovascular morbidity *(top)* and mortality *(bottom)* during 18 years' follow-up of the Framingham study, plotted according to systolic and diastolic blood pressure at the time of entry for men and women ages 45–74. O—O Systolic; O---O diastolic. From Kannel WB, Sorlie P, ref 162, p 557

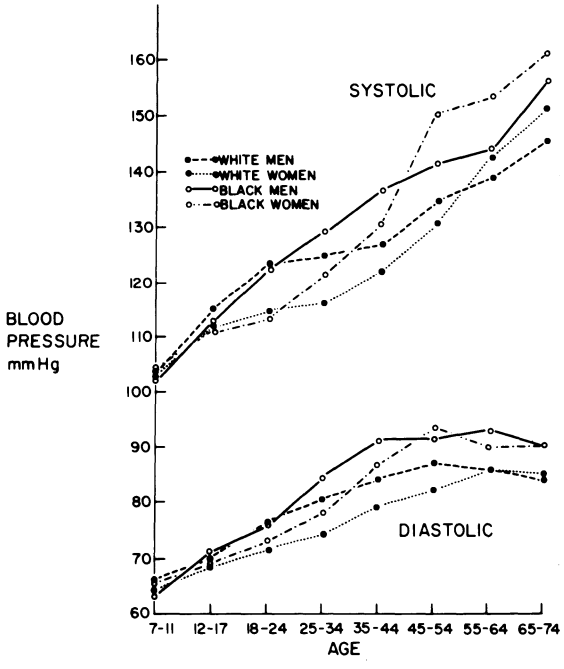


**Figure 6.** The mean systolic and diastolic blood pressures for white and black women in the United States. (Source: Advance data, vital and health statistics of the National Center for Health Statistics, No. 1, October 18, 1976.) From Kaplan NM, ref 167, p 10

experimental hypertension. It seems probable that a "salt appetite" is inherent and grows with repeated salt consumption. Primitive unacculturated tribes and societies throughout the world (e.g., Eskimos, Lapps, some American Indians, Australian Aborigines, and tribes in New Guinea, South America, and Africa) consume relatively small amounts of salt—i.e., several hundred milligrams to five grams of salt per day. On the other hand, some societies (e.g., the Japanese) may consume enormous quantities—up to 25 to 50 g/day![56] A good correlation between blood pressure and salt intake has been reported in persons living under similar conditions[56,57,212,284,293] (Fig. 7).

A 24-h urinary sodium is a fairly accurate index of sodium ingestion. Observations by Dahl indicate that under ordinary circumstances (i.e., without excess sweating) the daily salt requirement is probably well below 1 g—perhaps 0.1 g or less.[57] Evidence that salt is important in blood pressure control in humans is provided mainly by the effects of (1) dietary salt restriction, (2) increased sodium elimination (by diuretics), and by (3) the strong correlation between salt intake and the prevalence of human essential hypertension in different geographic areas and among different races.[57]

The effectiveness of rigid salt restriction (less

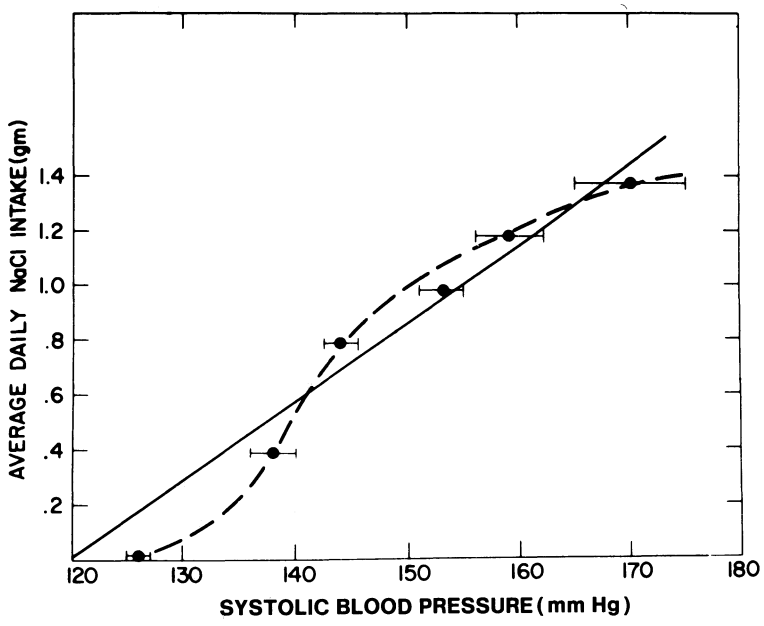


**Figure 7.** Correlation between average daily salt (NaCl) intake and mean (± S.E.) systolic blood pressures of rats after 12 months on various levels of salt intake. (*Note:* The sigmoidal curve represents the dose-response curve among six groups of rats, each on different NaCl intakes. The straight line indicates similarity of the data obtained in rats with those values which Dahl and associates obtained in humans.) From Dahl LK, ref 57, p 555

than 8 mEq of sodium per day) in the treatment of hypertension was clearly demonstrated by Allen and Sherrill[7] and later by Kempner[171,172] when he introduced the "fruit-rice" diet. Unfortunately, the degree of salt restriction necessary to produce a significant reduction of blood pressure is not known. Restriction of salt to 4 to 6 g/day may cause a moderate reduction of pressure;[37,286] however, for a marked lowering of pressure, the salt consumption must usually be less than 3 g/day.[353] Corcoran and co-workers[49] showed that a 200-mg sodium diet was necessary to obtain the maximum effect of sodium restriction. They also showed that the Kempner diet was in fact a practical low-salt diet.

The frequent effectiveness of diuretic drugs in lowering the blood pressure of hypertensive patients has further established the importance of natriuresis in the therapy of hypertension. It is virtually impossible to make an accurate estimate of daily salt consumption by questioning patients, since salt is added to almost all processed foods.

It is noteworthy that farmers in Akita, a northern province of Japan where large amounts of salt are used to preserve food, consume up to 35 g of salt daily. About 84% of these farmers have systolic pressures greater than 140 mm Hg and the most common cause of death is stroke.[334] In contrast, Yanomamo Indians in South America on a diet containing less than 300 mg of salt (i.e., less than 5 mEq of sodium per day) have virtually no hypertension—despite elevation of plasma renin activity to levels two to three times "normal" values.[273]

It is estimated that in the United States the average salt intake is approximately 10 to 14 g/day, with a daily range varying from 4 to 24 g.[57] Therefore, the daily salt requirement of less than 1 g is enormously exceeded in the United States as well as in other acculturated societies. Excessive salt consumption in "civilized" societies is all the more interesting if prehistoric man was, in fact, a herbivore who was perhaps deficient in sodium. Although there are now a number of epidemiologic studies which support Dahl's hypothesis that relates blood pressure levels to salt intake, some studies fail to substantiate the correlation.[57]

Hypertension can be induced in rats by chronically feeding salt, and the degree of systolic blood pressure elevation is correlated with the daily salt intake[244] (Fig. 7). Dahl and his associates demonstrated that, in unselected Sprague-Dawley rats, a very high salt diet caused no elevation of blood pressure in about one-quarter of the animals. The remaining rats developed hypertension of varying degrees—some dying in a few months with fulminating hypertension. They concluded that such disparate results were due to genetic variability in blood pressure responsiveness to salt.[151]

By repeated selective inbreeding of rats which demonstrate a hypertensive response to salt ingestion and also inbreeding those that failed to demonstrate this response, Dahl and co-workers ingeniously created a salt-sensitive (S) and salt-resistant (R) strain of rats. These experimental results clearly established that genetic influence was an important determinant of the blood pressure response induced by chronic salt ingestion in rats.[58,59]

Dahl has enumerated several factors which can modify the influence of salt consumption on the de-

velopment of hypertension in rats.[57] For example, the longer the period of salt ingestion, the more likely the development of hypertension. Also, as already mentioned, the level of mean arterial pressure is correlated with the daily amount of salt ingested. Furthermore, in hypertension-prone rats, it appears that the younger the animal when exposed to excess salt, the more susceptible is the animal to developing hypertension and the more severe is the hypertension. Louis and co-workers reported similar results.[209] (If this latter phenomenon applies to humans, it is another compelling argument against the use of baby food containing a high salt content.)

Increasing potassium intake will ameliorate the blood pressure elevation caused by salt consumption. Meneely observed that rats receiving salt plus extra potassium in their diet survived 7 or 8 months longer than those not given extra potassium, even though the blood pressures remained the same; he further emphasized that the Kempner diet was not only a low-sodium but a very high-potassium diet.[242,243] It is noteworthy that potassium is natriuretic whereas sodium is kaluretic.

The mechanism whereby sodium chloride can produce hypertension remains obscure. Tobian has reviewed some of the characteristics that appear in mammals susceptible to sodium chloride hypertension.[344] First, he pointed out the importance of the renal papilla and its possible relevance to hypertension because of its secretion of prostaglandins and Muirhead's antihypertensive neural lipid and also because of its possible role in the regulation of sodium excretion. It is noteworthy that, when the two strains of rats developed by Dahl were challenged with a high salt intake, renal papillary plasma flow increased significantly less in the salt-sensitive (S) strain (which became hypertensive) than in the salt-resistant (R) strain (which remained normotensive). It was concluded that the vascular resistance of vessels supplying the papilla in S rats was disproportionately greater than in R rats and that this difference in the two strains may be related to the rat's susceptibility to sodium chloride hypertension. Conceivably, a reduction in papillary plasma flow might limit the usual rapid excretion of an excessive salt load and thereby necessitate a rise in arterial pressure to induce a "pressure natriuresis." Tobian further speculated that, since a significantly reduced papillary flow occurs in Kyoto spontaneously hypertensive rats as well as in rats with "postsalt" hypertension, this flow reduction might be a hallmark for all types of experimental rat hypertension.[344]

According to Tobian, the hemodynamic responses to an expanded extracellular fluid volume and the increased cardiac output induced by excess salt intake in the S and R strains were quite different. Peripheral resistance rapidly increased in S rats whereas it decreased in the R strain; cardiac output in S rats eventually returned to control levels but the blood pressure and peripheral resistance remained elevated. In contrast, the cardiac output and peripheral resistance in the R strain returned toward control levels within 1 week and the blood pressure remained normal.

Some have claimed that there is hemodynamic and metabolic evidence that the spontaneously hypertensive rat (SHR) is hypersensitive to excess salt consumption.[54] However, we have found that on a high-salt diet blood pressures become significantly elevated in normotensive control rats as well as SHR.[348] The latter finding suggests that a genetic defect in sodium metabolism is not present in the SHR and is not responsible for the development of spontaneous hypertension in this model.

Most human beings with borderline hypertension who ingest excess salt seem to respond in a manner similar to S rats while normotensive subjects usually respond like the R strain.[228,229]

One currently accepted hypothesis whereby excess salt consumption induces early essential hypertension includes the following sequence of events: (1) renal salt and water retention, (2) increased plasma and extracellular fluid volume, (3) increased cardiac output, (4) autoregulation with an increased peripheral resistance, and (5) sustained hypertension.[47,344] Tobian demonstrated that hypertension-prone Dahl S rats have a lesser natriuretic capacity than R rats when the pressure and amount of blood flow through isolated S and R kidneys are kept the same. He further speculated that excess salt ingestion would raise extracellular fluid volume and thereby tend to elevate arterial blood pressure. If excess salt consumption continues, an elevated arterial pressure would be required to overcome the natriuretic limitation in S rats in order to maintain sodium balance. The hypothesis has been proposed that a defect in the natriuretic capacity of the kidney might exist in some patients with essential hypertension.[47,344]

Tobian and Binion found that the arterial wall of patients and animals with hypertension had increased amounts of sodium and water;[346] furthermore, there is evidence that vascular smooth muscle in hypertensive rats has an increased permeability.[107] These findings are particularly interesting since increasing the sodium content in isolated arteries increases their vasoconstrictor response to certain pressor agents.[134] Excess salt ingestion has been reported to enhance the response to angiotensin II in rats[326] and humans.[168] Some believe that the increased peripheral resistance occurring with excess salt ingestion may result from an enhanced ad-

renergic activity and the accompanying vasoconstriction.[135,295]

Blaustein proposed that sodium excess may alter the sodium-calcium exchange across smooth-muscle membranes such that there is a higher concentration of calcium within the cell, which in turn increases the degree of vasoconstriction and arterial wall tension.[27] Abboud has emphasized the neurohumoral interactions and hemodynamic adjustments which occur during chronic manipulation of sodium intake, and he points out that these interactions may mask direct effects of sodium on vasomotor control;[2] chronic sodium loading or restriction in normal subjects failed to produce any consistent change in arterial pressure or forearm vasculature conductance.

Finally, it should be mentioned that in several experimental types of hypertension Haddy and co-workers have found evidence for deficiency in ATPase activity;[128] the latter could result in an impaired efficiency of the sodium-potassium pump and an accumulation of intracellular sodium. There is now evidence that the sodium-potassium pump activity, including vascular smooth muscle, may be suppressed in animals with volume-expanded hypertension.[128,129] In addition, abnormalities of red blood cell sodium transport and diffusion have recently been reported in patients with essential hypertension;[36,110] whether similar abnormalities may exist in vascular smooth muscle and are somehow involved with excess vascular contraction and increased peripheral resistance remains to be determined.

Despite the attractive hypotheses which implicate sodium in the genesis of some forms of experimental and human hypertension, many studies of populations in Western countries fail to demonstrate a correlation between sodium consumption and hypertension.[192] Interpopulation studies are faced with the problem of the wide day-to-day variability in salt intake which makes interpretation of results particularly difficult.[283]

## Obesity

Obesity is defined as a weight-to-height relationship which exceeds the ideal value by 20% or more. A number of investigators have reported that there is a positive correlation between obesity and hypertension in children, adolescents, and adults.[44,50,152,163,196,203,208,255,329] This correlation is valid even when the blood pressure measurements are correct and do not merely reflect a fat arm. Furthermore, a strong correlation exists between the rate of blood pressure elevation and the rapidity of weight gain. There was also a greater incidence of hypertensive complications in obese than in nonobese adults.[343] Obese hypertensives have been reported to have twice the incidence of angina and sudden death as nonobese hypertensives.[9] Although hypertension alone may account for the increased incidence of coronary disease occurring in obese persons,[173] obesity per se may be an additional risk factor, particularly in men less than 40 years of age.[294]

The mechanism whereby obesity causes hypertension in a significant number of the population remains unclear. Some have suggested that increased consumption of sucrose may account for excess weight gain and hypertension.[3] Dahl has strongly argued that it is not weight reduction that lowers blood pressure in some obese patients, but rather the salt restriction that accompanied the caloric restriction.[57] Yeoman and co-workers also believe that excess salt consumption and the associated body fluid expansion can explain the hypertension occurring with obesity.[363]

In contrast, Reisin and associates demonstrated highly significant weight and blood pressure reductions which were directly associated and were present in both sexes and all ages.[298] Since weight and blood pressure reduction occurred in these latter patients without any salt restriction in the diet, it was concluded that weight reduction was in some way responsible for the reduction in blood pressure. It seems likely that the appearance of hypertension which accompanies the development of obesity may be related to the weight gain or an increased salt consumption or a combination of both. The fact that some markedly obese persons are normotensive further suggests that a genetic predisposition may exist in those who develop obesity and hypertension.

## Stress

The role of stress in the genesis and aggravation of hypertension is difficult to assess. It is well known that acute stress can significantly augment blood pressure. However, this rise in pressure is only transitory. Although the blood pressure elevation may be particularly striking in some, the same stimulus may cause a relatively mild elevation in others. It seems reasonable to conclude that activation of the adrenergic system or the responsiveness of the vascular system to the same stress varies considerably from one person to the next. Furthermore, there is evidence that a significant number of normotensive persons who have a "hyper-reactor" blood pressure response to the cold pressor test subsequently develop sustained hypertension.[143,144,300,342]

The question that remains unanswered is whether repeated and prolonged stress may result in

the establishment of permanent hypertension in human beings. The following have been cited as favoring the concept:[167]

1. Air traffic controllers, whose occupation causes severe psychologic stress, develop hypertension at a rate 5.6 times greater than nonprofessional pilots.[46]
2. Men exposed to the repeated stress of noise have higher blood pressures and a higher incidence of hypertension than those not so exposed.[154]
3. Nuns have lower blood pressures than women living in an unsheltered environment.[187]
4. Populations remaining in small, cohesive, and protected societies have lower blood pressures which do not increase with age, whereas those who move to less sheltered and more modern, disorganized, "pressurized," and urbanized societies have higher pressures which increase with aging.[40]

Some have linked the greater prevalence of hypertension in blacks than whites to a greater degree of stress[132] and discontent in blacks.[263] An inferior level of education[77] and low social class[333] may play a role in whites as well as blacks in causing hypertension and may account for a greater prevalence of hypertension in this segment of the population.

Certain personality traits, such as suppression of emotion,[291] and anxiety and depression,[35] are said to be more common in hypertensives than in normotensives. However, the implication that these traits may in some way be linked to hypertension has been questioned.[104,360]

Psychologic stress in mice may cause moderate hypertension which persists even after the stimulus is withdrawn;[141] furthermore, rats genetically predisposed to hypertension (e.g., Dahl's S rats) develop high blood pressure when exposed to food-shock conflict, whereas those not predisposed (the R strain) remain normotensive.[106] Monkeys exposed to stressful conditions requiring them to repeatedly press a lever to avoid a painful electric shock will develop hypertension;[99] however, the effect on the blood pressure of discontinuing the shock treatment was not reported.

It is noteworthy that the elevated blood pressures induced in animals by repeated stress will usually return to normal pressures after the stress is discontinued.[133] Friedman and Dahl suggested that a lag in return of the pressures to normal[105] was consistent with Lundgren's evidence that structural changes induced by hypertension reverse slowly.[215]

In their monograph, "Stress, Health, and Social Environment. A Sociobiologic Approach to Medicine," Henry and Stephens contend that there is a persuasive weight of human epidemiologic evidence connecting hypertension as well as coronary heart disease and even some types of cancer to problems of psychosocial adaptation.[140] These investigators reviewed the experimental findings which link psychosocial stimulation to functional and structural changes and the production of disease in animals. They also presented evidence for the role of the neocortex and the limbic system in social interaction, and they defined the neuroendocrine responses to this interaction.

From studies by Hallbäck and Folkow, it appears that activation of the adrenergic nervous system by social confrontation and arousal can alter the vascular structure of resistance arteries and thereby lead to or aggravate hypertension in the rat.[130] Adaptive changes in vascular smooth muscle result in a thickened wall-to-lumen ratio which increases vascular responsiveness to a given adrenergic stimulus.[97,98] Such structural alterations can disturb the function of resistance vessels. Increased resistance in systemic vessels would maintain hypertension whereas similar functional changes in the renal vasculature would cause the retention of salt and water.[16]

In experimental models of hypertension, increased vascular responsiveness can result from either vascular thickness or an increased vascular smooth-muscle sensitivity to norepinephrine or other pressor agonists.[28] Smooth-muscle hypersensitivity would aggravate the effects of repeated adrenergic activation; however, hypersensitivity of isolated human arteries to catecholamines, at least in one study, could not be demonstrated.[147]

It has further been speculated that vascular changes which result from repeated "defense" reactions to the daily environment may possibly disturb baroreceptor function.[140,327] Several investigators have demonstrated that in experimental and human hypertension there is an upward resetting of baroreceptors which then fail to buffer rises in pressure to the extent they normally should.[1,233,327] It should also be mentioned that stress may be accompanied by a diminished level of vagal inhibition.[159]

Therefore, theoretically, increased nervous stimulation might induce hypertrophic smooth-muscle changes with medial thickening. Such changes not only augment blood pressure responsiveness to adrenergic stimulation but may possibly diminish sensitivity of the baroreceptors and further interfere with blood pressure regulation and the maintenance of normotension.[140] Some recent experimental evidence indicates that baroreceptor activation may reduce reactivity to noxious stimulation through a baroreceptor-mediated reduction of cerebral arousal; therefore, the intriguing hypothesis has

been proposed that some hypertension may result from a learned blood pressure elevation response for which the reward is a baroreceptor-mediated reduction in anxiety or aversiveness to noxious stimuli.[76]

For completeness, other environmental factors with a potential to elevate blood pressure should be mentioned. *Cigarette smoking* may stimulate the adrenergic system[53] and elevate systolic and diastolic pressure.[8] *Alcohol* may also elevate blood pressure.[162,176,230] Of interest is evidence that ethanol can increase catecholamine synthesis and may thereby elevate blood pressure when large amounts are consumed.[117]

Certain *metals* have also been implicated in the genesis of hypertension. For example, some have claimed that excess amounts of cadmium in water may be a cause of elevated blood pressure;[22,118,319] yet the findings of others do not support this claim.[14,275] Low blood levels of zinc[341] and hypomagnesemia[167] have been detected in some hypertensives. Furthermore, elevated concentrations of lead have been found in some hypertensives.[15] It is of note that significantly elevated excretion of catecholamine metabolites may occur with increased lead absorption; apparently increased concentrations of lead in nonosseous tissues are associated with altered catecholamine metabolism.[325]

With regard to these latter environmental factors (cigarettes, alcohol, and trace metals), it must be concluded that there is no solid evidence that they play any significant role in causing essential hypertension.

## Theories Regarding the Nonenvironmental Genesis of Essential Hypertension

An enormous amount of clinical and basic research has been performed to elucidate the initial abnormality or abnormalities which lead to the development of essential hypertension. In addition to the environmental factors which may play a role in elevating blood pressure and also in aggravating hypertension, several major hypotheses have been proposed as the possible basic mechanism in the genesis of essential hypertension. These theories include the concept that one or a combination of the following may initiate hypertension:

1. An increased activity of the adrenergic system as reflected in cardiac augmentation and/or increased vasoconstrictor activity
2. An increased activity of the renin-angiotensin-aldosterone system as a result of altered regulation of renin secretion or secondary to a derangement of renal function
3. A decreased or defective activity of antihypertensive factor(s) in the renal medulla

The level of blood pressure is mainly a product of the cardiac output and peripheral resistance in the arterioles; however, aortic elasticity, blood volume, and blood viscosity can also influence hemodynamics and blood pressure.

Studies have shown that some essential hypertensives initially have an increased cardiac output; in time, the output returns to normal as the peripheral resistance is increased.[18,25,79,217]

An increased cardiac output has been noted particularly in adolescent, young, and borderline hypertensives; the plasma volume is usually normal but may be increased or decreased. Some of these hypertensives have a hyperdynamic ("hyperkinetic") circulatory state with hyperlability of the blood pressure, tachycardia, palpitations, and an increased responsiveness to beta-adrenergic stimulation.[100,108,120,149,155,156,314,357] Julius and Esler assessed the function of the autonomic nervous system in an attempt to define the initial cardiogenic abnormality in borderline hypertensives.[156,159] By pharmacologically blocking the autonomic influences on the heart, they determined that the increased heart rate in "hyperkinetic" borderline hypertension resulted solely from neurogenic influences. Similarly, the enhanced stroke volume response to venous filling, demonstrated previously,[82,338] was also found to stem from neurogenic influences on the heart.[156]

Most patients with established essential hypertension have a normal cardiac output and an increased peripheral vascular resistance, which accounts for the elevated blood pressure; yet in some hypertensives only the cardiac output appears elevated. The normal acute physiologic response to a high cardiac output is peripheral dilatation and a reduction in peripheral resistance, which results from a number of reflex mechanisms.[47,127] The concept of Guyton and co-workers that a chronically elevated cardiac output can trigger peripheral vasoconstriction through a process of autoregulation and thus induce persistent hypertension is intriguing. However, a review of major studies of this relationship in both humans and animals revealed no consistent evidence to support this concept.[178]

The explanation for an increased cardiac output, which occurs in some borderline hypertensives or patients during the early development of hypertension, remains undetermined. A primary increase in cardiac function could result from either an augmented activation of the adrenergic system or an increased responsiveness of the adrenergic receptors

in the heart, or both. A decreased vagal inhibition of the heart might also account for, or contribute to, an elevated cardiac output. Alternatively, the increased cardiac output in some of these patients might be a response to an increased blood volume brought about by salt and fluid retention by the kidney. Evidence against this latter hypothesis is the finding by Ibrahim and co-workers of a normal or reduced blood volume in borderline hypertensives.[148] They attributed the increased cardiac output in these patients to an elevated cardioadrenergic drive and an augmented cardiac contractility. The plasma volume in most hypertensives is normal or reduced.[74] Although a small number of hypertensive patients have an expanded plasma volume, Tarazi found that in these patients cardiac outputs were normal and almost identical to the outputs in patients with hypovolemia.[337] Peripheral resistance was increased in hypovolemic as well as in hypervolemic patients with essential hypertension and it is noteworthy that the resistance was, in fact, greater in the hypervolemic group. Some have reported a redistribution of blood volume in borderline hypertensives (i.e., a shift of blood to central or cardiopulmonary vessels), which they attributed to increased sympathetic activity accompanied by venous constriction.[310,311] However, most investigators have found no redistribution of blood in borderline hypertensives[82,363] or essential hypertensives.[246]

## The Adrenergic System in Essential Hypertension

### Plasma Catecholamines

Estimation of plasma catecholamines has proved valuable in assessing adrenergic activity under a variety of stressful conditions. However, it must be appreciated that plasma catecholamine concentrations depend not only on the degree of adrenergic activation and the amount of catecholamines released from the sympathoadrenal system but also on a number of other factors. These factors include the degree of diffusion from the synaptic cleft into the circulation, the extent of inactivation (i.e., by neuronal and extraneuronal uptake[150] and by enzymatic degradation via monoamine oxidase and catechol-*o*-methyltransferase[10]), the storage and binding capacity of intra-axonal granules for the catecholamines, and the renal clearance of circulating catecholamines. In addition, the rate of catecholamine turnover can be significantly altered not only by certain drugs but also by physical conditioning.[276] This latter point should be kept in mind, since the release of neurotransmitter and the physiologic response to a specific stimulus can be influenced by the metabolic turnover of norepinephrine—physical conditioning may be a determinant of plasma catecholamine levels.

Preliminary observations indicated that jogging of moderate intensity caused a much sharper rise of plasma catecholamines in sedentary young men than in those physically conditioned (Manger et al., unpublished). Others have also concluded that the concentrations of plasma norepinephrine depend on "interindividual differences in clearance and metabolism which may confound attempts to compare and characterize groups of patients with a single measurement."[297]

The importance of proper controls, especially when studying basal plasma catecholamine levels, has been emphasized. Sever pointed out that medical students, doctors, nurses, laboratory technicians, etc. should not be used as controls, since they are familiar with investigative procedures and are likely to be less stressed than others by the presence of their associates and the experimental procedures.[321]

In evaluating and interpreting studies of plasma catecholamine concentrations in human subjects, the possible influence of age, sex, race, emotional and physical stress, smoking, drugs, dietary sodium chloride, body posture, duration of rest, ambient temperature, method of sample collection, and delay of analysis and analytical procedure must be considered. As mentioned above, we also believe that physical fitness may be another determinant of plasma catecholamine levels. It is conceivable that decreased physical conditioning which usually occurs with aging may be accompanied by a greater norepinephrine turnover rate and, at least partly, account for the positive correlation between catecholamine concentrations and age.

In addition, several groups of investigators have demonstrated that dietary sodium intake can influence plasma norepinephrine levels. Both sodium restriction[214,267,301,305] and diuretics[339] can significantly elevate plasma catecholamines. Furthermore, a high sodium diet can elevate plasma catecholamine concentrations, and it has been speculated that this elevation might partly explain the rise in blood pressure observed when dietary sodium is increased in humans.[102,262] With regard to this latter finding, it is interesting that studies of hypertension induced experimentally by administrations of desoxycorticosterone and sodium chloride suggested that sodium excess decreased the capacity of sympathetic granules to bind and store norepinephrine, whereas sodium restriction had the reverse effect. Furthermore, there was a striking inverse relationship between blood pressure and storage capacity, sug-

gesting a role for the sympathetic nervous system in the regulation of blood pressure in this experimental model.[62]

Some types of physiologic stress may cause adrenergic activation without significant increases in plasma catecholamines. Therefore, one must recognize the inadequacy of plasma catecholamine concentrations as a totally reliable index of adrenergic activity.[220] A final point of note is that repeated determinations of plasma catecholamines over a prolonged period of time have not been performed to assess daily variability of catecholamine concentrations in normal or hypertensive subjects.

Borderline (or labile) hypertension presents an attractive condition to study since it is frequently an early predictor of established hypertension. The results of biochemical studies to assess the activity of the adrenergic system in borderline hypertensives have been inconclusive. Some investigators reported elevated urinary catecholamine excretion,[188,266] but this was not confirmed in a more recent study.[86] Plasma catecholamine concentrations were found to be normal[210] or elevated in only a minority of patients with borderline hypertension.[64] Although it has been reported that borderline hypertensives have a greater responsiveness and release of catecholamines to stimuli which activate the adrenergic system than normal subjects,[85,87,265] these findings require additional confirmation. The significance of hyperresponsiveness of the adrenergic system to various stimuli is uncertain; it is conceivable that repeated pressor responses may lead to sustained hypertension in some humans and animals that are genetically prone to develop hypertension.[130]

Of additional interest is the recent report by Oates and Robertson, who compared normal and borderline hypertensive subjects in the baseline state and following several stimuli.[271] No differences were noted in renin, noradrenergic, or hemodynamic responses when a sodium balance of 150 mEq was achieved in these subjects. With sodium restricted to 10 mEq, however, the same stimuli caused significantly greater increases in renin activity and plasma norepinephrine in borderline hypertensives.

Several groups of investigators have found significant elevations (> 2 standard deviations) of basal plasma catecholamines in a variable percentage (ranging from 19% to 75%) of patients with essential hypertension when compared with basal levels in normotensive subjects.[63,64,83,101,102,219,296,321,322]

In addition, some have reported a correlation between the diastolic blood pressure or mean arterial pressure and plasma norepinephrine concentrations in patients with essential hypertension.[64,112,145,210] Others found no significant differences in total plasma catecholamine concentrations[45] or in norepinephrine concentrations,[361] especially when age-controlled hypertensive and normotensive subjects were compared.[189,191] Still others have found normal plasma norepinephrine concentrations but elevated epinephrine levels in patients with benign essential hypertension.[101,102]

Lake and co-workers reported no difference between the concentrations of plasma norepinephrine in normotensive and hypertensive patients in the supine or standing position; however, they demonstrated a positive correlation between age and basal norepinephrine concentrations, and they emphasized the importance of age-matching patients and control groups.[190] Other investigators have reported similar results.[287,321,322] Yet, some have not discerned this relationship between plasma catecholamines and age.[61,63,64,145] It is noteworthy that by reanalysis of the data reported by Lake and co-workers, Sever indicated that age and norepinephrine values were related only in normotensive and not in hypertensive patients.[321] This latter observation was similar to the findings of Sever and co-workers in their own studies.[322]

Even if the adrenergic system does not release excessive amounts of catecholamines in patients with essential hypertension, defective inactivation might cause abnormally increased concentrations of neurotransmitter at receptor sites and thereby induce excessive vasoconstriction and hypertension.

## Vascular Reactivity

It has been suggested that increased vascular reactivity may be an early manifestation of essential hypertension; young, adult normotensive sons of hypertensive parents were found to have a significantly greater vascular response to norepinephrine infusions than those whose parents were normotensive.[70] Hyperresponsiveness to a variety of stimuli could result from hyperreactivity of vascular smooth muscle, i.e., an inherent abnormality in energetics of smooth-muscle contraction or relaxation, either genetically determined or possibly acquired. It has been suggested that an increased incidence of hyperresponsiveness to cold pressor stress in children of parents with essential hypertension, and the fact that these children not infrequently develop hypertension in adult life, favors a genetic role.[144,221,300,342] However, reliability of the cold pressor test for identifying those predisposed to developing hypertension has not been confirmed by many and its use has been abandoned.

Gitlow and co-workers presented evidence which they felt indicated a defective norepinephrine uptake mechanism in essential hypertensives.[115,116,241]

Such a defect could theoretically explain the greater pressor sensitivity to norepinephrine infusion observed in hypertensives when compared to normotensives.[69,71,119,221,238,240,364] However, as pointed out by Mendlowitz,[239] the neural uptake mechanism for the neural transmitter cannot be faulted as a cause of essential hypertension, since blockade of this uptake with amitriptyline (a tricyclic tranquilizer) has no effect on hypertension.[268]

Manger and associates infused norepinephrine into normal subjects and patients with essential or renal hypertension and observed that hyperresponsiveness of the blood pressure was not a constant finding in essential or renal hypertensives.[221] Hyperresponsiveness usually occurred in patients with the highest preinfusion pressures, and it could not be attributed to increased norepinephrine concentrations at receptor sites since the pressor response was not correlated with elevations of norepinephrine plasma concentrations (e.g., in some essential hypertensives, relatively small pressure increases occurred despite marked elevations of arterial plasma norepinephrine). A deficient clearance (or uptake) of norepinephrine was not demonstrated in the upper extremity of hypertensive patients, since A-V differences were even greater in hypertensives than in normotensives during high rates of norepinephrine infusion. They concluded that hyperresponsiveness may best be explained by vascular structure alterations, suggested by Folkow,[97] or by hyperreactivity of vascular smooth muscle, or by a combination of these factors.[221]

### Dopamine-β-Hydroxylase

Other biochemical determinants of sympathetic activity have also been studied in an effort to expose any abnormality of the adrenergic system underlying essential hypertension. For example, dopamine-β-hydroxylase (DBH) is released along with norepinephrine during sympathetic nerve activation, and some investigators have found elevated mean concentrations of DBH in patients with essential hypertension[112,359] or with borderline "hyperkinetic" hypertension.[6] Others have not confirmed these findings,[146,177,269] and it now appears that the serum levels of DBH are genetically determined and cannot be used as an index of sympathetic nerve activity for comparing hypertensive and normotensive subjects.[356]

### Cyclic AMP

Kuchel and co-workers have determined cyclic AMP (cAMP) concentrations in plasma and urine as a means of assessing beta-adrenergic activity.[185] It is known that cAMP, a "second messenger," increases in response to stimulation of beta-adrenergic receptors.[12,302] Further, it is believed that catecholamine stimulation of the beta-adrenergic system can induce hypertension by generating cAMP, which in the heart may increase cardiac contractility and heart rate and in the juxtaglomerular cells may increase renin release.[185,250] Kuchel and co-workers found that beta-adrenergic stimulation by isoproterenol resulted in a higher than normal plasma cAMP (in addition to an increased pulse rate and plasma renin activity) in some patients with borderline (labile) essential hypertension.[183,247] They defined this form of hypertension as "borderline beta-hyperadrenergic renin hyperresponsive," and they concluded that beta-adrenergic hyperresponsiveness was present in some patients with borderline essential hypertension. They were also able to define a group of patients with established essential hypertension as "stable beta-hypoadrenergic renin hyporesponsives;" these patients showed no increase of cAMP with beta-adrenergic stimulation.

Despite this intriguing biochemical dissection and identification of these forms of essential hypertension, described by Kuchel and his associates, the significance and interpretation of changes in cAMP remain to be determined.

### The Hyperkinetic "Beta-Adrenergic" Syndrome

The findings of an elevated cardiac output and increased heart rate[17,78,109,155,216,309,315] in a significant number of subjects with "hyperkinetic" borderline hypertension have further prompted the question of whether this augmented output leads to established hypertension by triggering an increased peripheral resistance via the mechanism of autoregulation.[126]

To test the hypothesis that an increased cardiac performance can lead to hypertension, Liard and co-workers studied the hemodynamic and humoral characteristics of acute hypertension induced by prolonged (7 days) stellate ganglion stimulation in conscious dogs.[205] An abrupt rise in mean arterial pressure occurred which was entirely due to increased cardiac output. However, following only 1 day of stimulation, the cardiac output had returned to control values and hypertension was sustained entirely by increased peripheral resistance. These hemodynamic effects were apparently mediated by increased activity of the sympathetic nervous system. When stimulation was discontinued, arterial pressure returned to control levels. Unfortunately, this model differed from what was anticipated; the increased cardiac output was very brief and the hy-

pertension was not accompanied by a hyperkinetic circulation with an increased heart rate. It was concluded that in this particular model hypertension may not have resulted from autoregulation but may have been caused by stimulation of a pressor reflex.

It has been suggested that in about 70% of borderline hypertensives with a normal cardiac output increased peripheral resistance could be attributed to nonneurogenic structural changes of the vessels which impede arterial blood flow; however, in approximately 30% of these patients, enhanced alpha-adrenergic vasomotor tone was evident.[48,88,156] An increased venous tone in borderline hypertension has also been reported but the mechanism for this latter abnormality is uncertain, since attempts to demonstrate an augmented alpha-adrenergic venomotor activity in this condition have failed.[156]

In borderline hypertension[88,254] and "hyperkinetic" borderline hypertension,[73,254] a substantial number of patients (30% in one series[88]) have elevated plasma renin levels at rest.

Some patients with borderline hypertension have a more pronounced increase in plasma renin than normal subjects with head-up tilting or standing.[85,183,253,360] Furthermore, in some patients, standing or tilting caused excessive excretion of urinary norepinephrine which was positively correlated with the increase in plasma renin.[85,183] Because of the importance of the renal sympathetic nerves and catecholamines on renin secretion,[349] the question has been raised as to whether a heightened sympathetic nerve activity is responsible for elevated plasma renin concentrations in borderline hypertension and in "hyperkinetic" borderline hypertension.[156]

Julius and co-workers concluded that in patients with borderline hypertension who have an increased adrenergic vasomotor tone and an elevated level of plasma renin, the hypertension results from increased adrenergic activity.[156] Their conclusion was based on the demonstration that beta-adrenergic blockade with propranolol caused a substantial fall in plasma renin without an appreciable effect on the blood pressure, whereas alpha-adrenergic blockade with phentolamine caused an abrupt decrease in blood pressure and no further reduction in plasma renin. These patients were also found to have an increased cardiac drive since propranolol administration caused a greater reduction of heart rate in borderline hypertensives than in normal subjects.[158]

It was postulated that in the majority of borderline hypertensives there is abnormal integration of autonomic nervous control, probably originating in the medulla oblongata.[159] The enhanced adrenergic activity is generalized and involves both alpha and beta receptors. In addition, evidence was presented of a diminished parasympathetic inhibition of the heart in patients with "hyperkinetic" borderline hypertension. As pointed out by these investigators, this reciprocal relationship of the autonomic nervous system (i.e., an increased sympathetic drive and a diminished parasympathetic inhibition) is characteristic of the functional organization in the higher integrative areas of autonomic control.[156]

## Baroreceptors

There is some evidence that a reduced arterial baroreceptor sensitivity to changes in blood pressure may exist in some patients with borderline hypertension.[24,121,335] However, this remains uncertain, if only because the methods used to measure baroreceptor sensitivity are not fully established.

## Concluding Remarks

In analyzing the evidence for the participation of the adrenergic system in essential hypertension, Kuchel indicated the unreliability of urinary measurements of catecholamines as an index of sympathetic nervous activity, particularly in hypertension where significant functional morphologic changes in the kidney may be present.[180] This conclusion was based mainly on concomitant measurements of plasma and urinary norepinephrine and calculation of the renal clearance of norepinephrine. It was shown that norepinephrine clearance is elevated in borderline (labile) but normal in stable hypertension, whereas the opposite was true for plasma levels of norepinephrine.[180,184] They also raised the interesting question of the possible importance of an interaction of several catecholamines on vascular receptor sites. For example, based on urinary catecholamine measurements, a dopamine deficiency relative to norepinephrine was postulated in some essential hypertensives.[55] Furthermore, a significantly elevated epinephrine excretion in low-renin hypertension (when compared with control subjects and patients without suppressed renin) was reported.[179,182] This latter observation, however, remains to be confirmed by others.

Kuchel suggested that this increased epinephrine (the endogenous catecholamine with the greatest beta-adrenergic receptor action) may result from a positive-feedback mechanism which could occur if beta-adrenergic receptors were hyporesponsive.[179] In keeping with this latter hypothesis, it is noteworthy that Lowder and co-workers contrasted the effects of hypoglycemia on plasma renin activity and cyclic AMP in low renin and normal renin essential hyper-

tension; they reported a blunted increase in plasma cyclic AMP during hypoglycemia in hypertensives with low renin and they concluded that a generalized beta-adrenergic hyporesponsiveness may exist in these latter patients.[211] Alternatively, Kuchel pointed out that hypersecretion of epinephrine may have been primary and may have induced a secondary subsensitivity of beta-adrenergic receptors.[179]

More recently, Eide and associates reported that the mean norepinephrine concentration in cerebrospinal fluid and plasma was significantly raised in patients with essential hypertension; the CSF norepinephrine concentration was positively correlated with the level of diastolic and systolic blood pressure when normotensives and hypertensives were analyzed together.[80] They reported an excellent correlation of plasma norepinephrine and CSF norepinephrine and, since there is a blood brain barrier for norepinephrine, these investigators suggested that the levels of peripheral sympathetic activity, plasma norepinephrine, and blood pressure reflect a major aspect of central norepinephrine tone. Although mean plasma renin activity was higher in hypertensives than in normotensives, the differences were not statistically significant in the small group of patients studied. However, from their results and previous studies they speculated that plasma renin activity may be a marker of sympathetic nerve tonicity.[80] Because of the small number of patients studied, it is premature to draw any conclusions regarding the results of Eide and co-workers.

As already mentioned, some investigators have found that high plasma catecholamines in hypertensives are more likely to be associated with an elevated plasma renin.[91,321] However, others have not been able to demonstrate any strong and consistent correlation between plasma renin activity and plasma catecholamine concentrations or urinary excretion of catecholamines in patients with essential hypertension.[102,139,145,339,355] Such correlation studies carry little weight because of the difficulty in adequately controlling the large number of variables (including protocols and methodology) that can significantly influence plasma catecholamines as well as plasma renin activity.

As can be gathered from the above discussion of the role of the adrenergic system in the genesis of borderline or essential hypertension, speculation and controversy abound. There is, as yet, no clear evidence which either establishes or exonerates the adrenergic system as playing a key part in the origin of hypertension in a large or even a small segment of hypertensive patients. From the available evidence, we believe that an overactive adrenergic system is probably only rarely the cause of essential hypertension.

## The Renin-Angiotensin-Aldosterone System in Essential Hypertension

Since the renin released from the kidney in some patients with renal artery stenosis or with renal parenchymal disease has been shown to be directly implicated in the production of hypertension, it was reasonable to suspect that renin might also be involved in the pathogenesis of essential hypertension. An additional suggestion for the latter is the finding that, when 24-h urinary sodium excretion is related to upright plasma renin concentrations, subgroups with low-, normal- and high-renin concentrations become identifiable.[194] (A similar classification has also been described in borderline hypertension.[89]) However, subgroups may or may not have a fixed identity, i.e., by remaining consistently in one category or another.

Renin reacts with renin substrate (a carrier protein which is an alpha globulin) in the circulation to liberate angiotensin I (a decapeptide), which is in turn converted by another enzyme to the powerful vasoconstrictor, angiotensin II (an octapeptide). This latter polypeptide is also capable of stimulating the adrenal cortex to secrete aldosterone, the most potent adrenal mineralocorticoid, which induces sodium reabsorption by the distal renal tubules. In addition, through its renal vasoconstrictive activity, angiotensin II at relatively low concentrations can increase salt retention; however, at high concentrations it can cause natriuresis.

Further, it should be mentioned that angiotensin II can stimulate the adrenergic system in several ways. It can act within the brain to cause a peripheral vasoconstriction via the sympathetic nerves,[21,95] it can augment the synthesis and release of norepinephrine in sympathetic nerve endings and inhibit norepinephrine uptake,[218,232,285,365] and it can induce secretion of catecholamines by the adrenal medulla.[31,299]

Several additional effects of angiotensin II have been reported. For example, angiotensin II can induce thirst (dipsogenesis) via a central action.[96,323] It can also sensitize vascular smooth muscle and adrenal cortical cells so that progressively lower concentrations of the hormone can produce hypertension;[51,66,234] prolonged low-dose angiotensin II infusion in normal humans is accompanied by an enhanced blood pressure response to this octapeptide.[272] Finally, it has been reported that angiotensin infusions may cause a greater vasoconstrictor response[111] and a greater rise in blood pressure[169] and plasma aldosterone concentrations[175] in patients with essential hypertension than in normal subjects; however, these findings require confirmation. Any of

these effects of angiotensin II may aggravate hypertension or play a role in its genesis.

A number of factors control renin secretion from the juxtaglomerular apparatus.[60] Five major factors are:[167]

1. A baroreceptor mechanism in the afferent arteriole. (A decrease or increase in pressure respectively stimulates or suppresses renin release.)
2. Sodium concentration in the macula densa. (A decrease of sodium delivery to this portion of the distal tubule stimulates renin release.)
3. Adrenergic system. (Stimulation of renal sympathetic nerves or infusion of catecholamines increases renin release via beta-adrenergic receptors; alpha-adrenergic receptor stimulation inhibits renin release.)
4. Circulating angiotensin II. (Intrarenal angiotensin II causes a direct feedback suppression of renin release. It is also noteworthy that angiotensin II can be cleaved to yield a heptapeptide, angiotensin III, which is as potent in suppressing renin release as angiotensin II[103]).
5. Plasma potassium concentration. (Increased plasma potassium inhibits renin secretion—apparently by diminishing tubular sodium reabsorption and thereby augmenting the delivery of sodium to the macula densa; hypokalemia increases renin secretion.)

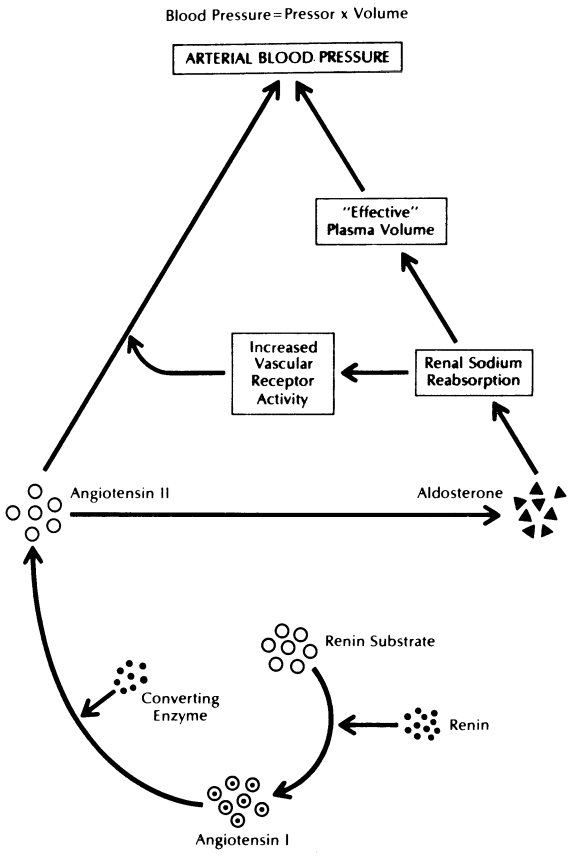


**Figure 8.** A dual mechanism regulating arterial blood pressure is postulated in the schematic above, in which renal and adrenal factors play major roles. Thus, renin release by the kidney results in production and activation of circulating angiotensin II, which not only has direct pressor effects but stimulates aldosterone release by the adrenals. In turn, aldosterone affects arterial pressure through induced changes in renal sodium reabsorption, which are important in maintaining plasma volume. Changes in sodium balance also appear to influence pressor effects of angiotensin by altering vascular receptors. Figure by Norman Blau, from Laragh JH, ref 194, p 2. Reproduced with permission

The proposed control of arterial blood pressure by the renin-angiotensin-aldosterone system is indicated in Figure 8. Laragh and co-workers have stressed the practical value of classifying essential hypertension on the basis of plasma renin activity (Table 4). They postulate that in a high proportion of patients with "benign" essential hypertension there is a subtle derangement of the renal-adrenal hormonal system normally operative in blood pressure control; in malignant hypertension the evidence is clear-cut that there is a marked elevation of renin which appears to evoke a pronounced hypersecretion of aldosterone.

Laragh and associates have proposed that essential hypertension in patients with high plasma renin activity results from excessive vasoconstriction.[194] In their experience, high-renin and some normal-renin hypertensives respond to antirenin therapy alone with drugs like propranolol. Further, they believe that the hypertension in patients with low renin is due to volume expansion because volume expansion lowers renin and because their blood pressures are often normalized by diuretics.

Laragh and associates further reported that studies with an inhibitor of the conversion of angiotensin I to angiotensin II identified the participation of a renin-angiotensin factor in all high-renin and 91% of normal-renin patients. On the other hand, this converting enzyme inhibitor was without effect in low-renin patients.[39,195] They concluded that the renin system significantly participates in sustaining the hypertension of all high-renin patients.

One of the most important developments that has come from the discovery of angiotensin and the angiotensin converting enzyme has been the synthesis by Ondetti and co-workers of the enzyme inhibitor captopril.[274] This was followed, as was to be expected, by a rush of papers, many of which bear the

**Table 4.** Characteristics of Renin Subgroups of 219 Hypertensive Patients

| Renin Activity | Prevalence in Essential Hypertension | Mean Age* (yr) | Diastolic Blood Pressure* (mm Hg) | Incidence of Heart Attack and Stroke† (%) |
|---|---|---|---|---|
| Low | 59 (27%) | 46.5 ± 11.3 | 104.9 ± 14.2 | 0 |
| Normal | 124 (57%) | 37.5 ± 12.0 | 103.5 ± 16.9 | 11 |
| High | 36 (16%) | 43.1 ± 9.8 | 124.0 ± 19.9 | 14 |

*Mean ± standard deviation.

†Based on a 7-year retrospective study.

From Albert Miller in Laragh JH, ref 194, p 11.

marks of undue haste. What follows can only be a rough appraisal of this data.

The main issue at this time is in what experimental models of hypertension, and in what classes of human hypertension is the inhibitor effective in lowering blood pressure. The mechanism by which it lowers pressure should give an important indication to what extent blockade of angiotensin is involved. Although enzyme inhibition may simultaneously increase bradykinin and thereby augment vasodilatation, the evidence regarding the potentiation of bradykinin is sharply contradictory and somewhat in favor of its being slight. Prostaglandins have not been demonstrated to be involved in the actions of captopril.

In contention is whether captopril lowers blood pressure effectively in low-renin hypertension relative to that in the high-renin variety. When captopril is given to hypertensives, plasma aldosterone is reduced and possibly a negative sodium balance is established. The rapidly accumulating evidence clearly indicates that most essential and renal hypertensives respond to captopril, but much remains to be determined as to how effective it is. Prompt remission of the hypertension in a malignant renin-producing tumor has been observed, an effect surely due to inhibition of angiotensin production.

In the two-kidney, one-clip models of experimental hypertension, the blood pressure seems to normalize according to Bengis and associates.[19] In one-kidney, one-clip hypertension, blood pressure does not return to normal. However, Bing and associates consider the role of angiotensin in two-kidney, one-clip hypertension controversial.[23] Experimental malignant hypertension in rats seems to be suppressed by captopril.

Captopril seems to be able to prevent the development of hypertension in SHR and abolish it if it has occurred. This has come as a surprise to many investigators who had confidently thought hyperactivity of the sympathetic nervous system was primarily involved. This has raised the question of whether captopril has a hypotensive action other than through its inhibition of angiotensin II generation.

Captopril does not lower pressure in ACTH-induced steroid hypertension in sheep. Based on the current evidence on captopril, it appears that angiotensin is more critically involved in human hypertension than had heretofore been expected.

Since an increased pressure in the afferent arteriole adjacent to the juxtaglomerular cells is known to suppress renin, the question has been asked why renin levels are not low in all patients with essential hypertension.[167] Since, in normotensives, plasma renin concentration is inversely related to blood pressure, it has been speculated that the negative feedback between blood pressure and renin release may be defective in many hypertensives and thus account for the inappropriately high renin-angiotensin concentrations.[213]

It is notable that, unlike the findings in normal subjects, an inverse relation between plasma renin activity and angiotensin II (i.e., a suppressed PRA in the presence of a relatively high angiotensin level) has been found in some patients with essential hypertension.[153,352] Consistent with these findings is the hypothesis of Sambhi and associates suggesting the presence of a circulating renin activator which accelerates the production of angiotensin I in some hypertensives.[313]

Controversy revolves around the significance of the levels of renin in patients with essential hypertension. Kaplan has listed the clinical conditions affecting renin levels (Table 5) and the mechanisms which may conceivably cause low-renin hypertension (Table 6). He has concisely presented the evidence which supports or refutes various mechanisms which might explain low-renin essential hypertension.[167] An elevated renal perfusion pressure is one plausible explanation for physiologic suppression of renin, and it is noteworthy that Schalekamp and associates found a low plasma renin concentration in those essential hypertensives with increased renal vascular resistance.[317,318] However, Case and associates found no differences in renal cortical blood flow

**Table 5.** Clinical Conditions Affecting Renin Levels

| Decreased PRA | Increased PRA |
|---|---|
| *Expanded fluid volume* | *Shrunken fluid volume* |
| Salt loads, oral or i.v. | Salt deprivation |
| Primary salt retention (Liddle's syndrome; Gordon's syndrome) | Fluid losses |
| Mineralocorticoid excess | Diuretic-induced |
| Primary aldosteronism | Gastrointestinal losses |
| Congenital adrenal hyperplasia | Hemorrhage |
| Cushing's syndrome | Salt-wasting renal disease |
| Licorice excess | Decreased effective plasma volume |
| Desoxycorticosterone (DOC), 18-hydroxy-DOC excess | Upright posture |
| *Catecholamine deficiency* | Adrenal insufficiency |
| Autonomic dysfunction | Cirrhosis with ascites |
| Therapy with adrenergic neuronal blockers | Nephrotic syndrome |
| Therapy with β-adrenergic blockers | *Decreased renal perfusion pressure* |
| *Hyperkalemia* | Therapy with peripheral vasodilators |
| *Decreased renin substrate (?)* | Renovascular hypertension |
| Androgen therapy | Accelerated-malignant hypertension |
| *Decrease of renal tissue* | Chronic renal disease (renin-dependent) |
| Hyporeninemic hypoaldosteronism | Juxtaglomerular hyperplasia (Bartter's syndrome) |
| Chronic renal disease (volume-dependent) | *Catecholamine excess* |
| Anephric | Pheochromocytoma |
| *Unknown* | Stress: hypoglycemia, trauma |
| Low-renin hypertension | Exercise |
| | Hyperthyroidism |
| | *Hypokalemia* |
| | *Increased renin substrate* |
| | Pregnancy |
| | Estrogen therapy |
| | *Autonomous renin hypersecretion* |
| | Renin-secreting tumors |
| | *Acute damage to J-G cells* |
| | Acute renal failure |
| | Acute glomerulonephritis |

From Kaplan NM, ref 167, p 191.

or angiographic vascular pattern between hypertensives with normal or low renin levels.[38] Low renin may reflect an impairment of basal renin secretion and responsiveness due to a reduction in renal arteriolar distensibility and in baroreceptor sensitivity of renal afferent arterioles. Such changes may possibly occur with increasing age and progressive nephrosclerosis; the latter may be more pronounced, of course, in the presence of hypertension.[277,332]

As Kaplan has stated, it might seem logical to explain suppressed renin in some patients with essential hypertension as being due to an expanded plasma volume. Despite this attractive hypothesis, which would also fit with the hypertension related to excess salt retention and overproduction of a mineralocorticoid, the majority of low-renin essential hypertensives do not have an increased fluid volume, and the evidence for a mechanism causing increased salt retention is only now under serious study. In reviewing the evidence for increased mineralocorticoid activity in low-renin essential hypertension, Kaplan has pointed out that there are as many or more reports showing normal levels of steroids when compared to those demonstrating elevated steroids.[167]

With regard to other mechanisms which might explain low renin levels in essential hypertension, some investigators have reported a decreased plasma catecholamine concentration at rest and in response to body tilting in low-renin hypertensives.[90] However, others found no differences in plasma norepinephrine concentrations under various conditions in low- and normal-renin essential hypertensives and normotensives.[252]

In analyzing the activity of the sympathetic nervous system in low-renin hypertension, Doyle and associates reported that despite a significant positive relationship between blood pressure and plasma catecholamines, renin levels were inversely related to blood pressures and catecholamine concentra-

**Table 6.** Possible Mechanisms for Low-Renin Hypertension

| Mechanisms | Clinical Expression |
|---|---|
| I. "Physiologic" inhibition of renin release | |
| A. Increased pressure at the juxtaglomerular apparatus and/or increased sodium load at macula densa | |
| 1. Elevated perfusion pressure | Essential hypertension |
| 2. Expanded effective plasma volume | |
| a. Renal sodium retention | |
| Primary | Liddle's syndrome |
| Secondary to increased mineralocorticoid activity | |
| Aldosterone | Primary aldosteronism |
| Desoxycorticosterone (DOC) | Congenital adrenal hyperplasia, adrenal tumors |
| 18-OH-DOC and other steroids | |
| Glycyrrhizic acid | Licorice, carbenoxolone |
| b. Prolonged excessive salt intake in genetically predisposed | |
| c. Decreased natriuretic hormone | |
| 3. Decreased capacity of vascular bed | |
| B. Decreased sympathetic nervous system activity | Diabetes mellitus, adrenergic blocking drugs |
| C. Increased potassium intake | |
| D. Increased systemic or intrarenal angiotensin II | |
| II. Derangement of juxtaglomerular apparatus | |
| A. Inability to produce or release renin | Chronic renal disease? essential hypertension |
| B. Defect in sensing mechanism | |
| III. Interference with generation of angiotensin II in vitro or enhanced generation of angiotensin II in vivo | |
| IV. Increased sensitivity to angiotensin II | |

From Kaplan NM, ref 167, p 293.

tions.[67] Their finding of an inverse correlation between blood pressure and renin level suggested that the effect of hypertension on the renal afferent arteriolar receptor might suppress renin release and overbalance the stimulatory action of norepinephrine to increase renin release.

As Kaplan has indicated,[167] *excessive potassium intake* is an unlikely explanation of the low renin levels since both intake and excretion of potassium have been reported to be lower in blacks despite their higher frequency of low-renin hypertension.[122]

Several concluding remarks are perhaps fitting with regard to therapeutic and prognostic implications based on plasma renin levels. Kaplan clearly argues that too much has been made of the probable enhanced response of low-renin patients to diuretics, and he correctly concludes that there has been an overinterpretation of the responses of these patients to various drugs.[167] Mineralocorticoid excess and volume expansion (with a lesser degree of vasoconstriction) have not been established as the cause of hypertension in low-renin essential hypertensives. Results of treatment with various diuretics or beta blockers have been inconsistent and have not clearly supported the hypothesis of the "low-renin volume expansion/high-renin vasoconstriction" model. In fact, a number of hemodynamic studies revealed that patients with low renin had *higher* peripheral resistance and were *more* constricted than those with high renin.[167]

With regard to prognosis, the original position taken by Brunner and Laragh and their associates[32-34,193]—namely, that low levels of renin protect against vascular disease—now appears untenable and unsupported by a number of other investigators.[68,72,114,125,256,330] Furthermore, the implications that drugs which raise renin levels are harmful and that therapy need not be so vigorously pursued in low-renin hypertensives seem invalid.[167]

As summarized by Kaplan,[166,167] sufficient evi-

dence has accumulated indicating that low- and normal-renin patients are equally susceptible to heart attacks and strokes. On the other hand, all agree that high-renin patients have more severe hypertension (as also occurred in the study by Brunner and associates[33]—see Table 4), and a higher incidence of vascular damage and complications. The degree of hypertension, and not the level of plasma renin or angiotensin, seems to be the critical determinant of vascular damage.

Kaplan appropriately concluded that "renin profiling remains an interesting investigational tool and offers little help to the patient or his physician. The diagnosis of low renin hypertension is usually irrelevant, its therapy remains empirical but effective and the prognosis depends largely upon the level of blood pressure and the ability to lower it."[167]

In a recent study on the relation between blood pressure and renin, renin substrate, angiotensin II, aldosterone, and urinary sodium and potassium in 575 ambulatory subjects (with blood pressures ranging from 94/58 to 250/145 mm Hg), Walker and associates reported a highly significant positive correlation between circulating renin substrate and blood pressure and a highly significant negative correlation between blood pressure and urinary potassium.[352] The renin substrate was the only component of the renin-angiotensin-aldosterone system for which a positive correlation with blood pressure was identified. The possibility that potassium may play a more important role in influencing the level of blood pressure of essential hypertensives than formerly appreciated is intriguing and merits further study.

Recently, Rosenthal and associates reported still another hormonal control mechanism which may possibly influence blood pressure via the renin-angiotensin system. These investigators demonstrated that somatostatin (growth hormone inhibiting factor) appeared to blunt the rise in blood pressure and plasma renin caused by beta-adrenergic stimulation.[307] Somatostatin significantly diminished plasma renin activity in all patients with high-renin essential hypertension; however, no change in blood pressure, stroke volume, or cardiac output was observed. The mechanism of action of somatostatin remains unclear.[308]

In discussing the basic mechanisms of essential hypertension, Genest has expressed the conviction (based on the findings of normal levels of plasma renin activity in the great majority of patients with essential hypertension plus the results of studies with angiotensin II antagonists) that the renal system is not involved in a causative way in the pathogenesis of essential hypertension.[113] It is too early to comment on the possible role of the tonin-angiotensin II system (identified by Boucher and coworkers[29]) and its relationship to blood pressure regulation and hypertension.

Investigations by Genest and his associates have revealed a significant increase in the concentration of aldosterone in groups of patients with mild essential hypertension; a significant increase or a normal or inappropriately high concentration was also seen in hypertensives with low and unresponsive renin.[113] They detected a decreased metabolic clearance of aldosterone and a blunted aldosterone responsiveness (except for ACTH stimulation) in patients with essential hypertension. In addition, they demonstrated a significant increase in the secretion rate and plasma concentration of another mineralocorticoid, 18-hydroxy-11-desoxycorticosterone, in two-thirds of patients with mild essential hypertension. Genest has proposed the scheme that in genetically predisposed subjects, various stimuli lead to the release of ACTH which induces excessive secretion of aldosterone and 18-hydroxy-11-desoxycorticosterone and thereby causes sodium retention—the latter leading to a higher peripheral resistance and an increased vascular reactivity to pressor agents.

The pathogenetic mechanisms involved in essential hypertension remain as confused in the minds of some and as unresolved with regard to the renin-angiotensin-aldosterone system as they do with regard to the adrenergic system.

## The Antihypertensive System in Essential Hypertension

Less is known about the mechanisms of a renal vasodepressor system. Our limited knowledge of the system has made it often impossible to define and assess in the human; therefore, studies have been performed almost exclusively on experimental animals.

Fasciolo proposed the concept that the normal kidney exerted a protective action against the development of hypertension.[92] Fifteen years later, both Grollman[123] and Muirhead and associates[260] hypothesized that renoprival hypertension resulted from a deficiency of a vasodepressor in normal kidney.

An expanded fluid volume appears to be the major cause of hypertension in anephric patients; however, the concept that renoprival hypertension may result partly from removal of the kidney's antihypertensive function gains some support clinically from the finding that bilateral nephrectomy may only reduce but not completely eliminate the hypertension of some patients, even in the absence of an overexpanded volume.[197]

The search for a vasodepressor substance of renal

origin continues but the identity of this substance remains uncertain. In 1940, Grollman and associates had reported a nonprotein, water-soluble renal extract which, when given orally, had the capacity of lowering blood pressure in rats and dogs with experimentally induced hypertension.[124] Page and co-workers also prepared kidney extracts which sharply lowered pressure in both experimental renal and human hypertension, including the malignant syndrome.[282] The extract was not dialyzable and in retrospect it probably contained prostaglandins and Muirhead's antihypertensive lipid. The study was abandoned because of febrile reactions induced by the extract. Subsequently, Hamilton and Grollman reported that this antihypertensive substance was thought to be a peptide.[131] In 1963 and 1964, Lee, Hickler, and co-workers discovered that extracts of renal medulla contained a lipid capable of causing an acute vasodepressor response.[142,201] Currently there is some evidence which suggests that deficiencies of prostaglandins[198,199,200,336] and kinins[225,226,227,368,370] may be implicated in essential hypertension. Furthermore, Muirhead and co-workers have identified two antihypertensive renomedullary lipids (one naturally occurring, the other semisynthetic) which are effective in lowering the blood pressure of rats with experimentally induced renal hypertension.[258,289]

Muirhead has over the years detailed imprecisely the evidence for a nonexcretory antihypertensive function of the kidney, which appears to reside in the renal medulla.[258,259] Confirmation of a renomedullary antihypertensive factor has been reported by other investigators using different experimental hypertensive animals.[222,223,331,345] Muirhead and associates clearly demonstrated that when renal medullary tissue was transplanted into the peritoneum or subcutaneous tissue, it prevented the development of renoprival hypertension in the dog and reversed the hypertension caused by renal artery clamping in the rat. Removal of the transplant (isograft) was accompanied by a return of the pressure to prior hypertensive levels (Fig. 9). Similarly, renomedullary transplants prevented the development of malignant renovascular hypertension in rabbits. On the other hand, transplants of renal cortex, liver, or spleen had no influence on blood pressure. Crude extracts of fresh renal medulla given intravenously caused a prompt vasodepressor effect and prevented or delayed the development of renoprival hypertension.

Muirhead also demonstrated that live renomedullary cells were required for the antihypertensive effect, since when these cells were lyophilized and transplanted into hypertensive animals there was no pressure change. The main cell type in the transplant was shown to be the renomedullary interstitial cell—a cell which was most concentrated in the renal medulla and which appeared to proliferate during the time the transplant exerted its antihypertensive function. The presence of lipid vesicles was identified in these cells and considered a possible source of their antihypertensive function.

Muehrcke and co-workers had previously found a reduced lipid content of renomedullary interstitial cells in patients with malignant hypertension and in rats with hypertension induced by mineralocorticoid administration;[257] this finding suggested that the lipid might exert an antihypertensive effect. Tobian and co-workers reported similar changes in the lipid

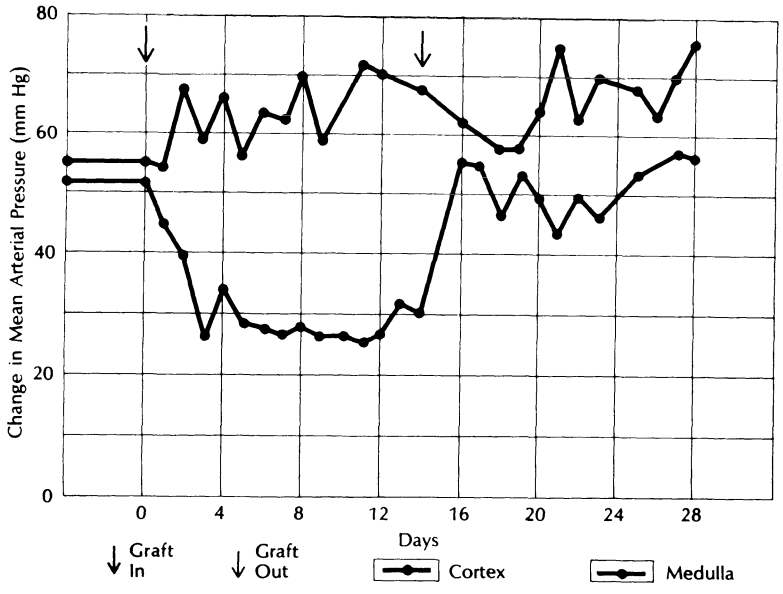


**Figure 9.** To ascertain whether renomedullary tissue could reverse established hypertension, inbred Wistar rats made hypertensive by renal artery clamping received either renocortical or medullary isografts. A blood pressure drop occurred only following medullary grafting; pressure stayed low until graft was removed and then returned to prior hypertensive level. Figure by Albert Miller, from Muirhead EE, ref 258, p 147. Reproduced with permission

content of renomedullary interstitial cells in experimental hypertension due to renovascular constriction or sodium loading.[345]

Muirhead and associates demonstrated that lipid-containing renal medullary interstitial cells were the main cell type within their transplants. Furthermore, they cultured these cells and found that subcutaneous injection of the cells exerted an antihypertensive effect; removal of the transplanted cells resulted in a return of the hypertension. Two distinct lipids with vasodepressor activity were identified and both prevented renoprival hypertension and reduced the blood pressure of animals with renal hypertension. One of these lipids proved to be a prostaglandin whereas the other did not appear to be a prostaglandin and was termed an antihypertensive neutral renomedullary lipid (ANRL). The latter is a naturally occurring substance which may prove to be a hormone. Neither of these could be derived from the renal cortex.[258]

More recently, Muirhead's group has described another biologically active lipid which has been characterized as an antihypertensive polar renomedullary lipid (APRL); however, the latter is a semisynthetic product and not a naturally occurring lipid. A bolus injection of APRL caused a rapid and pronounced depressor effect followed by a slow recovery; after ANRL injection there was a lag period followed by a slow and less pronounced decline in pressure and then a slow recovery.[289] Since ANRL is a naturally occurring lipid, it is interesting to speculate whether this depressor substance may be a hormone important in modulating blood pressure. There is conclusive evidence that renomedullary interstitial cells secrete three prostaglandins: $PGA_2$ and $PGE_2$, which are depressors, and $PGF_{2\alpha}$, which is a pressor.[260,261] However, as pointed out by Muirhead, there is no indication that release of prostaglandins from the renal medulla occurs as part of normal homeostasis.

It has been postulated that prostaglandins may exert an antihypertensive effect in several ways. Locally, in the kidney, they may oppose the effect of vasoconstrictor-antidiuretic agents and stimuli[5,41] (see also Chapter 13) and increase blood flow to the cortex while reducing flow to the renal medulla. Prostaglandins may also promote vasodilatation in peripheral arterioles. Vasodilating prostaglandins are synthesized not only in the kidney but also in arterial walls.[75,340] Prostacycline ($PGI_2$), which is synthesized by blood vessels, causes vasodilatation and inhibits platelet aggregation; synthesis of $PGE_2$, in vessel walls can inhibit release of norepinephrine from adrenergic nerves[136] and diminish vasoconstriction (see Chapter 13).

Angiotensin II may stimulate release of prostacycline from vessels and thereby attenuate the vasoconstrictor action of angiotensin.[4] While $PGE_2$ and $PGI_2$ cause vasodilatation and $PGI_2$ opposes platelet aggregation, it should be appreciated that $PGF_2$ and thromboxane $A_2$ (a product of prostaglandins in platelets which is released on aggregation) cause vasoconstriction.

Hence, a deficiency of vasodilator prostaglandins could result in both peripheral and renal vasoconstriction, and the latter could activate renal pressor mechanisms[258] (Fig. 10). In one study, administration of indomethacin (which blocks prostaglandin

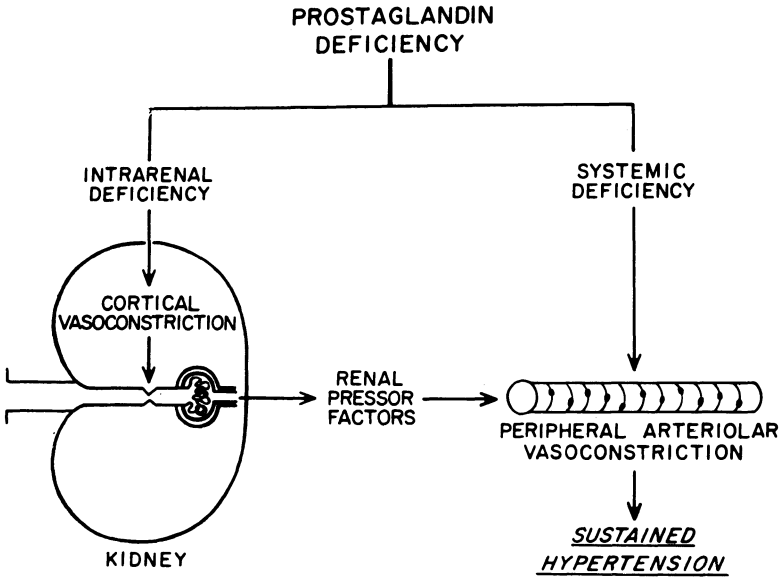


**Figure 10.** Schematic representation of a hypothetical role for a deficiency of intrarenal prostaglandins in the establishment of sustained hypertension. From Lee JB, ref 198, p 1078

synthesis) to patients with uncomplicated essential hypertension had little effect on blood pressure.[13] However, more recently Rodicio reported preliminary results indicating that renal synthesis of $PGE_2$ is increased in patients with essential hypertension; blockade with indomethacin induced a significant decrease in urine $PGE_2$ and in plasma renin activity which was accompanied by a significant increase in blood pressure. Aggravation of the hypertension was accompanied by sodium retention and a decrease in renal excretory function.[303] Rodicio's results are interesting but require confirmation.

It is pertinent that inhibition of prostaglandin synthesis adversely affects animals with hypertension due to renal ischemia.[304] Such inhibition also results in a greater reduction in renal blood flow and a greater renal vascular resistance during angiotensin infusion.[42,316] Intrarenal prostaglandins appear to play a role in modulating effects of some vasoconstrictors and in controlling renal blood flow and blood pressure.[137,237,347]

As stated by Muirhead, it is impossible to determine whether the antihypertensive function of the renal medulla depends on the lipids he has isolated or on the prostaglandins or both. It does appear that the kidney can exert an antihypertensive function through excretory control of sodium and volume excess and also through a nonexcretory function probably involving vasodepressor(s) elaborated by renomedullary cells. Muirhead has correctly indicated that removal of the renomedullary antihypertensive function through bilateral nephrectomy results in hypertension only when concomitant sodium volume loading occurs. However, it must be appreciated that bilateral nephrectomy also eliminates the prohypertensive potential of the kidney. Conceivably, the development of hypertension or protection against it may depend on the balance between prohypertensive and antihypertensive factors.[258]

A third vasodepressor mechanism to be considered is the kallikrein-kinin system. Kallikreins are enzymes which specifically act upon kininogen (an $\alpha_2$ globulin) to liberate kinins [kallidin (a decapeptide) and bradykinin (a nonpeptide)]. The kinins are ultimately degraded to inactive peptides by kininases. One kininase is identical to the enzyme which converts angiotensin I to angiotensin II.[84] This latter point should be recalled when considering antihypertensive action of drugs which inhibit this converting enzyme, since a decrease in generation of pressor substance (angiotensin II) would always be accompanied by an increase in vasodilators (kinins). Figure 11 shows similarities in peptide generation by renin and kallikrein enzymatic actions.[52] Kallikreins of organs and body fluids are chemically different proteins; furthermore, two kininogens and two kininases have been identified in plasma.[52] Kallikrein in plasma exists in an inactive prekallikrein form. On the other hand, kidney kallikrein is normally excreted in the urine; its excretion is augmented by sodium deprivation and diminished by increased sodium consumption. Plasma bradykinin and renin respond in a parallel manner to various stimuli,[245] including sodium depletion or loading,[362] but this is not true of urinary bradykinin.[351]

Evidence suggests that the kallikrein-kinin system may be significantly involved in sodium, potassium, and water excretion and in modulating intrarenal hemodynamics. Kallidin and bradykinin increase sodium, potassium, and water excretion[354] and, in addition, bradykinin is an arterial vasodilator in the kidney and elsewhere.

Significantly decreased urinary excretion of kallikrein has been reported in patients with essential

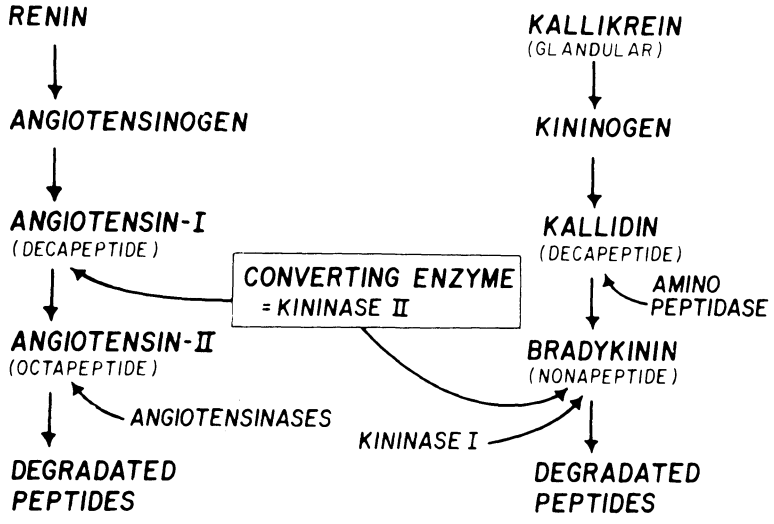


**Figure 11.** Diagram showing similarities of peptide generation by renin and kallikrein enzymatic actions. From Croxatto HR et al., ref 52, p 365

hypertension.[81,224] An inverse relationship between urinary kallikrein concentration and blood pressure was also found in 601 children. Also, black children excreted significantly less kallikrein than did white children.[170,204] Kallikrein excretion is decreased in children of hypertensive parents.[368] Kallikrein excretion was reported to be normal or increased in secondary types of hypertension.[224] However, some found that in renovascular hypertension with diminished function of the contralateral kidney, kallikrein excretion was decreased.[43]

It has been suggested that the neutral lipid and prostaglandins may act in concert with the kallikrein-kinin system to oppose those factors which elevated blood pressure.[52] As mentioned earlier, prostaglandins and the neutral lipid are synthesized in the renal medulla, whereas kallikrein is synthesized in the renal cortex.[270] Since bradykinin and prostaglandins (except for $PGA_2$) can be entirely inactivated during passage through the lungs, it seems unlikely that they can function as circulating hormones to buffer renin and angiotensin II or other pressor agents. However, kallikrein can cross the lung barrier and exert its effects on the arterial side.[52]

Vane and McGiff have proposed that prostaglandins interact with the principal blood-pressure–regulating systems to reinforce the kallikrein-kinin system and to buffer the adrenergic and renin-angiotensin systems.[350] The kallikrein-kinin and prostaglandin systems may be important in the maintenance of normal blood pressure.[235]

Since there is evidence linking basal release of renal prostaglandins to the activity of the renal kallikrein-kinin system,[264] and since prostaglandins oppose pressor hormone action[236] and adrenergic activity,[136] Sullivan and McGiff speculate that a deficiency of the renal kallikrein-kinin system may contribute to the development of hypertension by decreasing the production of one or more of the prostaglandins which have antihypertensive activity (see Chapter 13).

Finally, renin inhibitors[312,320,328] and dopamine[186] may contribute to the antihypertensive renal action. Kuchel has pointed out that dopamine can cause splanchnic and renal vasodilatation, natriuresis, and release of kallikrein from the kidney; furthermore, it can exert an inhibitory effect on presynaptic norepinephrine release and on secretion of renin and aldosterone.[181] Kuchel and associates have suggested that the kallikrein-bradykinin system may be under stimulatory dopaminergic control and involved intrarenally with some prostaglandins to form a natriuretic and antihypertensive system.[186]

Figure 12 reveals the formulation of a single hypothesis to explain the possible pathogenesis of essential hypertension. Admittedly, some of this formulation is speculative; however, Kaplan has reemphasized the important fact that more attention should be paid to reduction of salt intake for

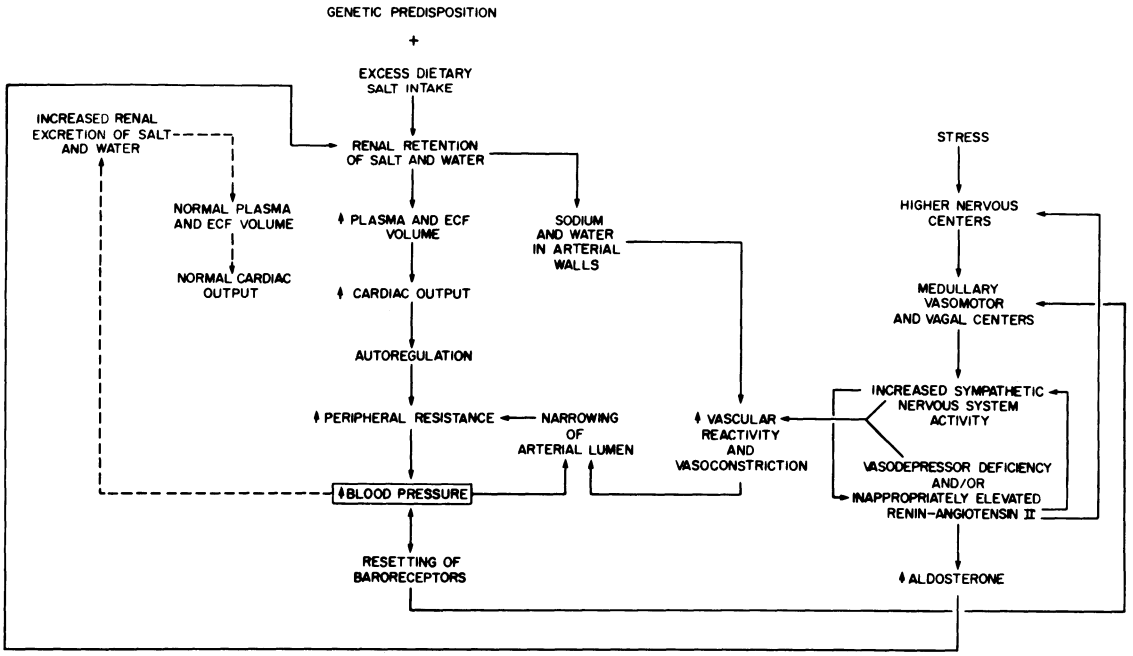


**Figure 12.** An overall scheme for the factors involved in the possible pathogenesis of essential hypertension. Modified from Kaplan NM, ref 167, p 63 and from Shepherd JT, Vanhoutte PM, ref 324, p 210

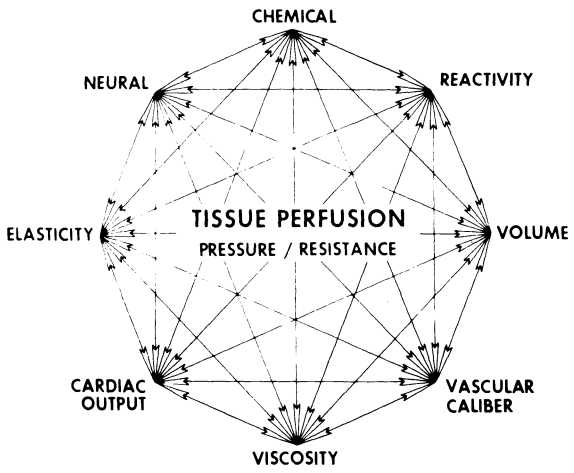


**Figure 13.** Page's mosaic theory of hypertension. From Khosla MC et al., ref 174, p 2867

treatment and especially for prevention of hypertension.

As proposed some 30 years ago by Page,[278] it seems most reasonable to view essential hypertension as a disease in which multiple regulatory mechanisms are constantly interacting to maintain the elevated blood pressure. This is "the mosaic theory." Although only one factor may be initially abnormal, its interrelation and influence on other factors will result in additional derangements. Page has emphasized that essential hypertension should be viewed as "a disease of regulation" and that one should attempt to define the predominant defects and alterations among the multiple regulatory mechanisms in order to provide the most rational treatment.[174,280] As Page correctly points out, there is nothing sacrosanct about his original concept of an octagon comprised of eight different regulatory facets which were interrelated and involved in the control of blood pressure and tissue perfusion (Fig. 13). Almost certainly, additional mechanisms and facets (e.g., prostaglandins, kallikrein-kinins, and hypertensive lipids) will emerge and have to be added to the expanded mosaic theory.

## Conclusions

Essential hypertension is a world health problem of enormous magnitude and its cause(s) remain an enigma. In the United States, hypertension, with its cardiovascular complications, is the nation's most common serious disease and the major cause of death. It is now recognized that a substantial number of children have hypertension. Why diastolic blood pressure increases with age, why essential hypertension is more prevalent and virulent in males than in females, and why blacks are particularly vulnerable to its complications remain unclear. Recent evidence indicates that the level of systolic pressure is a risk factor equally important as the diastolic pressure. The great challenge existing today is that a marked reduction in morbidity and mortality is achievable by adequate control of blood pressure with drugs.

While a predisposition to hypertension may be inherited in perhaps 50% of those afflicted, a genetic link is frequently absent. Although a number of environmental factors have been implicated in the genesis of essential hypertension, the evidence is often circumstantial. There is no question that excessive sodium ingestion can significantly elevate blood pressure in those genetically predisposed to hypertension. Increased potassium intake can ameliorate the hypertension caused by sodium excess. Whether sodium consumption is of central importance in the genesis of essential hypertension in the vast majority of those afflicted remains unknown. Although purely speculative, it has been proposed that excess salt consumption may cause the following sequence of events: (1) renal salt and water retention, (2) increased plasma volume, (3) increased cardiac output, (4) autoregulation with increased peripheral resistance, and (5) sustained hypertension.

The mechanism whereby obesity causes hypertension is unclear. Some believe excess salt intake accompanies weight gain and that sodium is the culprit; however, recent evidence indicates that weight gain per se can account for blood pressure elevation. Some predisposition to hypertension probably exists in these obese hypertensives since many obese persons are normotensive.

The role of stress in the genesis of hypertension is difficult to evaluate. Activation of the adrenergic nervous system can alter vascular structure in resistance vessels and thereby cause or aggravate hypertension. The evidence that prolonged stress in humans can cause sustained hypertension is suggestive but inconclusive.

In addition to the importance of genetic and environmental factors in causing and aggravating hypertension, several major hypothetical mechanisms have been proposed to explain the cause of essential hypertension—namely, an increased activity of the adrenergic system or the renin-angiotensin-aldosterone system or a deficiency of an antihypertensive factor in the kidney. A combination of these derangements could exist, as represented by the hypertensive mosaic proposed by Page.

Blood pressure elevation in the chronic phase of essential hypertension is due to increased peripheral resistance. In most hypertensives, plasma volume is normal or reduced, although a few have an expanded volume. In the great majority, cardiac output is normal; however, an increased output occurs in some borderline hypertensives during the early development of hypertension. The reasons for these hemodynamic abnormalities remain undetermined.

Some believe that hemodynamic and biochemical abnormalities in borderline hypertension result from neurogenic alterations in cardiovascular function; yet this remains circumstantial. A number of investigators have quantitated plasma catecholamines in an effort to assess the activity of the adrenergic system and its role in the causation of hypertension. Results of plasma catecholamine assay have been inconsistent. Since the plasma catecholamine concentration depends on so many variables (release, diffusion, uptake, metabolic degradation, storage, binding, turnover, renal clearance) even under "basal" conditions, the level of circulating catecholamines is not a satisfactory index of adrenergic activity. In addition, the importance of proper controls and the influence of age, sex, race, emotional and physical factors, etc. on the level of catecholamines have not been adequately considered in interpreting most studies on hypertensive patients. It appears that a small segment of the hypertensive population (including those with sustained essential hypertension as well as the borderline group) has elevated plasma catecholamines. Whether this finding results from an overactive adrenergic system which is responsible, even in part, for the hypertension is uncertain.

Probably most investigators believe that the precise role of the renin-angiotensin-aldosterone system in essential hypertension is as uncertain as that of the adrenergic system. This view is not shared by one of us (IHP), who believes the evidence now almost surely points to angiotensin as a core substance in most hypertensives and that essential hypertension may well be, in part, due to excessive vasoconstriction caused by angiotensin.

Not only is angiotensin II a very powerful vasoconstrictor (which can thereby influence peripheral resistance and kidney function), but it can also stimulate the adrenal cortex to secrete aldosterone and it can activate the adrenergic system in several ways (e.g., by acting within the brain, by increasing synthesis and release of norepinephrine from nerves, by inducing secretion of catecholamines from the adrenal medulla). In addition, angiotensin II can sensitize vasculature and adrenocortical cells so that their response to angiotensin II is augmented. Any of these effects may aggravate hypertension or play a role in its genesis.

Since angiotensin II generation depends on the amount of renin released from the juxtaglomerular apparatus, efforts have been made to define abnormalities of factors controlling renin release and to classify patients with essential hypertension on the basis of plasma renin activity. The claim that hypertension in the high-renin patients is due to excessive vasoconstriction (which responds best to antirenin therapy), whereas in low-renin patients the elevated pressure is due to volume expansion (which responds best to diuretics) is controversial. Furthermore, the claim that high- and normal-renin hypertension carries a much higher risk of cardiovascular complications than low-renin hypertension has not been proved. The degree of hypertension and not the plasma level of renin or angiotensin seems to be the critical determinant of cardiovascular damage.

The finding by some investigators of an increased plasma concentration of aldosterone and 18-hydroxy-11-desoxycorticosterone requires confirmation; the suggestion that these mineralocorticoids are increased by ACTH stimulation in subjects predisposed to essential hypertension is hypothetical.

Evidence is accumulating which supports the concept that the kidney can exert a nonexcretory (as well as excretory) "antihypertensive" function which may serve to counterbalance any "prohypertensive" activity. Several candidates—e.g., prostaglandins, kinins, and a renomedullary lipid identified by Muirhead—have emerged with the ability to exert a vasodilator and depressor function in experimental hypertension; however, their role in preventing clinical hypertension remains to be determined.

Prostaglandins synthesized in blood vessels can cause vasodilatation and inhibit norepinephrine release from adrenergic nerves.

Kallidin and bradykinin, which are generated by plasma or renal cortical kallikrein, may increase sodium, potassium, and water excretion and modulate intrarenal hemodynamics. Also, bradykinin is an arterial vasodilator in the kidney and elsewhere.

Therefore, the findings of a decreased urinary excretion of kallikrein in some essential hypertensives and an inverse relationship between urinary kallikrein and blood pressure in children (especially in black children and in children of hypertensive parents) merit additional confirmation and evaluation. The fact that bradykinin and renin respond in a parallel manner to various stimuli suggests that they may be interrelated in a counterbalancing manner, although the evidence so far is slight.

The possibility that prostaglandins and the kallikrein-kinin system and Muirhead's lipid interact to reinforce each other and buffer the adrenergic and renin-angiotensin-aldosterone-salt systems seems plausible.

It seems more apparent than ever that essential hypertension is a disease of regulation and that multiple regulatory mechanisms are interrelated and may be deranged. The challenge which persists is to decipher the initiating and predominant defect(s) and alteration(s) to permit the most rational and effective therapy.

### Acknowledgments

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# Pathogenesis of Hypertension

# The Risk of Hypertension: Genesis and Detection

# 2

U. Laaser

Epidemiology, a method of scientific investigation developed during the 19th century (by William Farr in 1839 and John Snow in 1849), contributed decisively after World War II to the study of noninfectious common diseases, especially cardiovascular disorders. The start of the Framingham Study in 1948 is an example. The classic definition of epidemiology was given by MacMahon and Pugh as the "investigation of the distribution of determinants of morbidity in man."[39] Further, the same authors went on to describe epidemiology according to its main concern: the identification of the components of the disease process that make possible the formulation of effective preventive measures.[40] In this way, the essential features of epidemiologic research (the population-related analysis of incidence, cause, and effects of the disease) were directed toward its final purpose: the interruption and therefore prevention of a disease process by intervention, i.e., the calculated interference with the genesis and course of the disease as early as possible.

Around 1970, at the start of the "post-Framingham era,"[21] the description of the cardiovascular risk profile was largely complete. From then on, the occurrence of heart attack and apoplexy—the most important specific causes of death and disability in our industrialized societies—could be predicted with notable accuracy on the basis of statistical relationships. But risk factors are only possibilities, not certainties, and so far only risk indicators of cardiovascular morbidity. It was not surprising, therefore, that epidemiologic research, turning in the post-Framingham era to intervention, its proper main concern in the spirit of MacMahon, could not attain any major breakthrough in this area. Among risk factors so far identified, only for nicotine abuse and to a limited degree for hypertension has it been established that "therapeutic" modification actually reduces cardiovascular morbidity.[4] On the other hand, the "diet heart hypothesis,"[30] which predicted a reduction of disease risk from the lowering of cholesterol levels, is increasingly under question.[41] This background helps clarify the attempts to break down further the complexity of the individual risk factors by the coordinated application of experimental, clinical, and epidemiologic methods, so as to find new and specific approaches for intervention.

In the case of hypertension, this means primarily the elucidation of its genesis, together with more intensive research into the hitherto neglected age groups of the elderly and, especially, adolescents and children. Most of the studies on cardiovascular epidemiology have been so far performed on a minority of the total population,[18] namely on middle-aged men—and to a smaller extent on middle-aged women—in industrialized countries.

Next to this historically misplaced emphasis in epidemiologic research stands a further, and in its effects perhaps worse, misorientation in the realm of classical, clinically oriented medicine: In the Western countries most of the human and financial resources have concentrated on the diagnosis and treatment of secondary forms of hypertension, although the proportion of secondary hypertension is steadily decreasing as studies on clinically selected patient groups are increasingly replaced by studies in representative populations. Only a few years ago we spoke of a 20% incidence of secondary hypertension;[3] the Göteborg Study[58] found only 5.7% such

cases in a representative group of 47- to 54-year-old males. Studies on the development of juvenile hypertension point in the same direction:[19] In 1968, Platt established the rule that hypertension in adolescents is mostly of a secondary nature; today we hold that hypertension of the adolescent is almost always a primary,[1] and that this primary blood pressure disorder of the young demands no less concern.[11]

## Factors that Play a Role in the Onset of Essential Hypertension

*Genetic factors* first gained prominence from the controversy between Platt and Pickering in the 1950s.[12] Today Page's mosaic theory,[45] imputing a multifactor origin, is widely accepted. The weight to be attributed to individual factors in the genesis of hypertension has been determined unequivocally in only a few cases. The importance of genetic factors has returned to the forefront in recent years, especially through twin research.

Familial aggregation of hypertension, in the sense that relatives of hypertensive patients display elevated blood pressure values more frequently than expected, has been known from clinical experience for a long time. Pickering found a regression coefficient of 0.2–0.3 between first-order relatives.[48] It remained unclear for a long time whether genetic mechanisms were responsible for these aggregations or whether they perhaps reflected only the social background common to one family. Thus, for example, Zinner concluded from his study of 721 children from 190 families that blood pressure variability within a family was conspicuously lower than between different families; he was, however, unable to reach any conclusions on the extent of a possible genetic influence.[60] Biron went a step further with his study of 274 families with adopted children, finding conspicuously higher correlations for the blood pressure values of natural children than for those of adopted children.[1] To be sure, it seems the influence of the common social background and environment cannot be completely excluded in this study, as only 78% of the adopted children were integrated into the new family before their first birthday; in others, the length of the adoption period was not taken into account.

The still insufficient evidence of appropriate correlations between newborn twins[28] seems also to warrant continued doubts about the dominance of genetic influences. The strongest argument for the heredity of hypertensive dysfunctions is probably derived from studies in twins. Though significant variations in the socialization process belie the assumption that the differences between mono- and heterozygotic twins (as well as those between twins and other siblings) are attributable only to genes held in common, the differences in the range of correlation coefficients argue against an exclusive explanation by common social components. According to a survey by Feinleib, the finding of correlation coefficients higher than 0.5 for systolic and diastolic blood pressure is twice as common in monozygotic twins as in heterozygotic twins, and three times as high as in simple siblings.[16] At any rate, according to Feinleib's calculations, the attempt to quantify the genetically dependent component of blood pressure variation finds it to be at least five times as dominant as the environmental influence. Admittedly, these calculations do not take into account the familial aggregation of weight and height indices, which are known to be related to blood pressure. Such additional computations, however, are unlikely to change the picture substantially.

Doyle provides a clue to the mechanism of chromosomal influence on the pathogenesis of hypertension with his finding that normotensive children of hypertensive parents display markedly high norepinephrine sensitivity.[13] Kass demonstrated recently that kallikrein elimination in the urine of children is inversely proportional to their blood pressure.[28]

To summarize, despite some persistent uncertainties, it may be assumed that the hereditary factor is a substantial codeterminant in the development of hypertension. It is still unclear how far this would be the case in a population free of other risk influences, such as excessive salt intake or hypercaloric nutrition. In other words, the genetic factor might perhaps become significant only under the influence of other risk factors.

It is medical common knowledge that reduction of the *salt intake* has a salutary effect on hypertension. It is interesting that salt intake in our customary range, namely 3–15 g/day, is biologically unnecessary, being rather a component of our cultural development. Evidently, evolution has equipped humans to survive salt deficiency rather than salt excess.[54] Figure 1 shows several populations in which prevalence of hypertension is closely correlated with salt intake. When these population groups are incorporated into the larger societies, their blood pressure values rise in clear correlation with increased salt intake. The rise in blood pressure with age observed generally in industrialized societies is almost completely absent in populations with a salt-poor diet. Dahl concludes from his findings in rats that the aging process may be accelerated or slowed down by the daily salt intake.[9] According to this, the age-dependent rise in blood pressure would be the re-

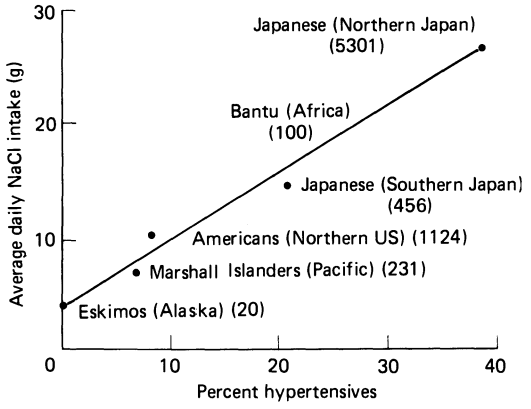


**Figure 1.** Connection between salt consumption and hypertension in different populations. From Weinsier RL (1976) Prev Med 5:7

sponse of the individual to environmental influences, determined by the duration of exposure. Dahl was also able to demonstrate that an excessive salt intake induces hypertension only in certain genetically determined animal strains, whereas other "hypertension-resistant" strains are not affected.[10] This, again, argues strongly for a chromosomally determined predisposition for development of hypertension.

If, however, a diuretic is administered along with the salt-rich diet to susceptible animals,[54] the expected rise in blood pressure fails to appear. These studies, together with research on hemodynamics,[7,8] suggest that excessive salt intake leads to hypertension through a chronic expansion of extracellular fluid volume. Following a complex mathematical analysis of diverse factors, Guyton ascribes a decisive influence on long-term blood pressure levels solely to the water-salt balance.[20] Under normal circumstances, salt metabolism in the healthy person is almost exclusively determined by salt intake.

Animal experiments offer a further essential insight, namely that the young rat is most sensitive to salt-induced hypertension and that in animals predisposed to the development of hypertension, exposure to salt need be only very short, provided they are young. It is well known that the salt content of commonly used baby food, as well as of cow's milk, is far in excess of the salt requirement. Dahl was able to induce hypertension in his hypertension-prone rats by feeding them commercially available baby food.

A further factor in the genesis of hypertension is *excessive weight*. It is also closely related to the genetic components discussed above, and possibly to salt intake as well, since high-calorie food contains higher amounts of salt. Three findings give evidence for the connection between overweight and hypertension:[42]

1. The hypertensive is more frequently overweight than the normotensive.
2. Overweight normotensives develop hypertension more frequently than persons of normal weight.
3. The hypertensive becomes overweight more frequently than the normotensive.

The quantitative relationship has been defined so precisely that a 10-kg weight variation is correlated to a 4-mm Hg change in diastolic blood pressure.

The Evans County Study conducted an open trial of intervention therapy by weight and salt intake reduction.[24,55] Over a 1-year period, this resulted in a pronounced lowering of blood pressure with additional weight loss and, accordingly, a substantially reduced need for hypertensive medication. It was not established whether the weight reduction was connected with increased nicotine abuse, which in turn correlates negatively with blood pressure and weight. To be sure, increased nicotine abuse would, as mentioned above, lower the blood pressure further, but at the cost of augmenting the true final risk, namely that of cardiac infarction. Paraphrasing and modifying Heyden's statement,[21] the slimmest smoker still runs a higher risk of infarct than the overweight nonsmoker. Excessive weight plays a role not only at the extreme range of a weight-height index; the dynamics of weight changes are apparently also important, so that Heyden was able to show that weight gain in the third decade of life has a particular risk connotation.[23]

The relationship between the presence of *trace elements, water hardness,* and *cardiocirculatory disorders* has been under repeated investigation since 1957, when Kobayashi reported correlations between the composition of river water and apoplexy rates in Japan.[31] The statistical connection between cardiovascular mortality and the mineral content of drinking water is clear and undisputed: the softer the water the higher the mortality rate.[50] Furthermore, a 12-city study in England and Wales indicates that hypertension may be the mediating factor in a higher incidence of cardiocirculatory diseases, especially apoplexy, although sufficient extensive, prospective investigations have not yet been carried out. From the actual investigations on trace elements, results are available only on cadmium, and they suggest a connection with the incidence of hypertension.[46] Cadmium content in particular could explain the difference in cardiovascular mortality between regions with hard and with soft drinking water, as the bone cadmium concentration of endangered populations in soft water areas is

about double that of control populations in areas with hard drinking water. Furthermore, it seems to be established that renal cadmium content is higher in hypertensives than in normotensives. It is also known from animal experiments that cadmium intake in food can induce hypertension in rats; on the other hand, this hypertension can be controlled by a cadmium-binding chelate.

The so-called *psychosocial factors,* such as occupation, income, and sedentary habits, did not yield any clear-cut correlations. In general, hard work, with the emphasis on "hard," seems to lower the incidence of cardiac infarcts, according to a study by Paffenbarger,[44a] who also notes that the number of workers classified as engaged in "very strenuous" labor has decreased from 40% to 5% during the 22-year observation period. The extent of the role played by hypertension as a risk factor remains to be seen. It is known from the Evans County Study that the occupational group of farmhands with the hardest physical activity demonstrated the lowest coronary morbidity together with comparatively lower blood pressure readings, as compared with nonagricultural occupational groups.[6] Stress research seems to offer a very promising starting point for an understanding of the genesis of hypertension. Folkow and Neil advanced a neurogenic hypothesis, according to which a corticothalamic mechanism could induce structural adaptations in the peripheral vascular system if it were stimulated frequently enough over prolonged periods of time.[17] This may correspond to data in the Cologne Study[34] showing that, even in adolescents with elevated blood pressure, a correlation can be found between systolic blood pressure and norepinephrine production. That transient blood pressure variations may be influenced by emotional stress has been corroborated by Sokolow, for example, in a study of 50 hypertensive patients in whom blood pressure levels correlated with the frequency rate of positive and negative events as recorded in diaries.[52] Male office workers showed blood pressure fluctuations up to 80/50 mm Hg at a mean level of 130/76 mm Hg. Besides this, almost all investigators described consistently a hypertensive personality profile marked by suppressed aggression. Nevertheless, these investigations are not sufficient to answer the question of the long-term effect of such stress stimuli. Long-term and extensive studies failed repeatedly because of the difficulty in defining stress and dealing with it by biochemical parameters or questionnaires.

In summary, it may be said that from an epidemiologic point of view the following factors seem to be widely accepted as conducive to the development of hypertension: a hereditary component, salt intake, and weight gain with resulting obesity. Not conclusive but very promising are the findings of stress research. Figure 2 presents a tentative simplified diagram of the various concepts and results of investigations on the genesis of hypertension. It is based on the hypothesis that stress factors induce by way of sympathetic stimulation an increase in catecholamine elimination, leading thereby to a hyperkinetic, cardiac-output–dependent hypertension. Under the influence of other factors (salt intake, weight gain), this results in the development of components of vascular resistance, devolving into manifest hypertension, which in turn would lead, in combination with other risk factors of the cardiovascular system (hypercholesterolemia, nicotine abuse, diabetes mellitus), to the well-known cardiovascular complications.

The beginnings of this development are to be sought in childhood and adolescence. Increasingly, therefore, epidemiologic research has turned its attention to younger age groups, although the lessened severity of risk factors renders their recognition difficult. The need for such studies has been underscored by findings such as "fatty streaks" in the aortic wall of young children.[43] One apprehension that would have stood strongly in the way of epidemiologic studies was, at least with respect to blood pressure, not confirmed: Blood pressure values, especially elevated ones, are indeed sufficiently reproducible in childhood as well as in adolescence. Thus, Zinner was able to show for the first time that children with blood pressure in the high-normal range for their age group show a clear tendency to

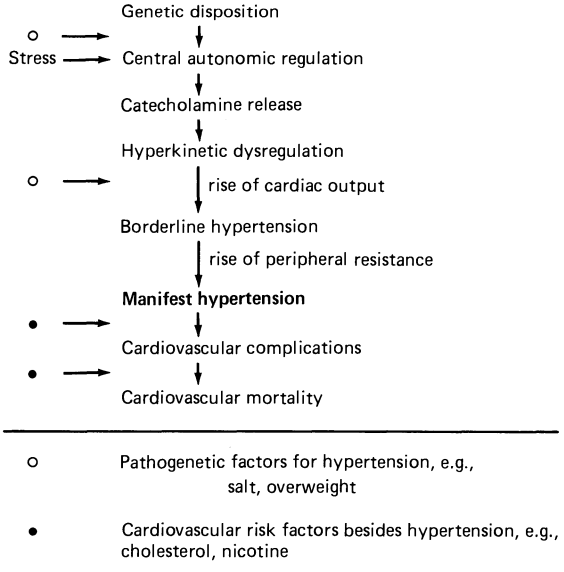


**Figure 2.** Genesis of hypertension in youth (hypothetical).

maintain their relative position over several years.[61] There is evidence that other risk factors are demonstrable very early and in many cases remain demonstrable for some years. This risk factor persistence is the basic prerequisite for early preventive measures. If one presumption for early intervention is the constant demonstrability of increased risk parameters, another is proof of their long-term and sufficiently high predictive value for the later development of cardiocirculatory disease. This was investigated as early as 1940 for juvenile hypertension.[25] In cases of clearly elevated blood pressure, there is little doubt about the worth of risk indicators: Heyden, for example, reported that only 12 of 30 hypertensive adolescents in the Evans County Study had normal blood pressure after 7 years.[22] Two had already died at that time from the effects of their disease.

Primary hypertension in adolescence and childhood is seldom characterized by extreme values. Hull, for example, believes that rising blood pressure levels are accompanied by a higher incidence of secondary causes for hypertension.[26] Essential hypertension in adolescence and childhood is characterized rather by borderline blood pressure values which, depending on age, may be below the lower limit of 140/90 mm Hg set by the World Health Organization from adult studies.

In these age groups blood pressure is very sensitive to external and internal stimuli. This led to attempts to apply Smirk's basic blood pressure concept[51] to the growing years, although its application is disputed even for adults.[32] While it is possible that the above-mentioned stability of blood pressure measurements as shown by their reproducibility may depend on the experimental situation, it is equally possible, and even probable, that a so-called "autonomic" or "nervous" elevation of blood pressure is indicative of an increased long-term risk. Thus, a controlled stress during blood pressure screening might even be useful for the detection of persons at long-term risk for high blood pressure. Identification of long-term risk would therefore be expected less from basal or resting measurements than from the further analysis of hyper- or normokinetic disturbances of blood pressure regulation in adolescence.[49]

Though several extensive epidemiologic studies on the cardiovascular risk profile of adolescents have been initiated since the mid-1970s,[33,57,44] present knowledge does not allow a sufficiently sensitive or specific identification of adolescents and children who, in all probability, will be found, upon reaching middle age, to be in the upper range of distribution with regard to blood pressure, cholesterol, and other risk factors.[15] The final answer to this question will

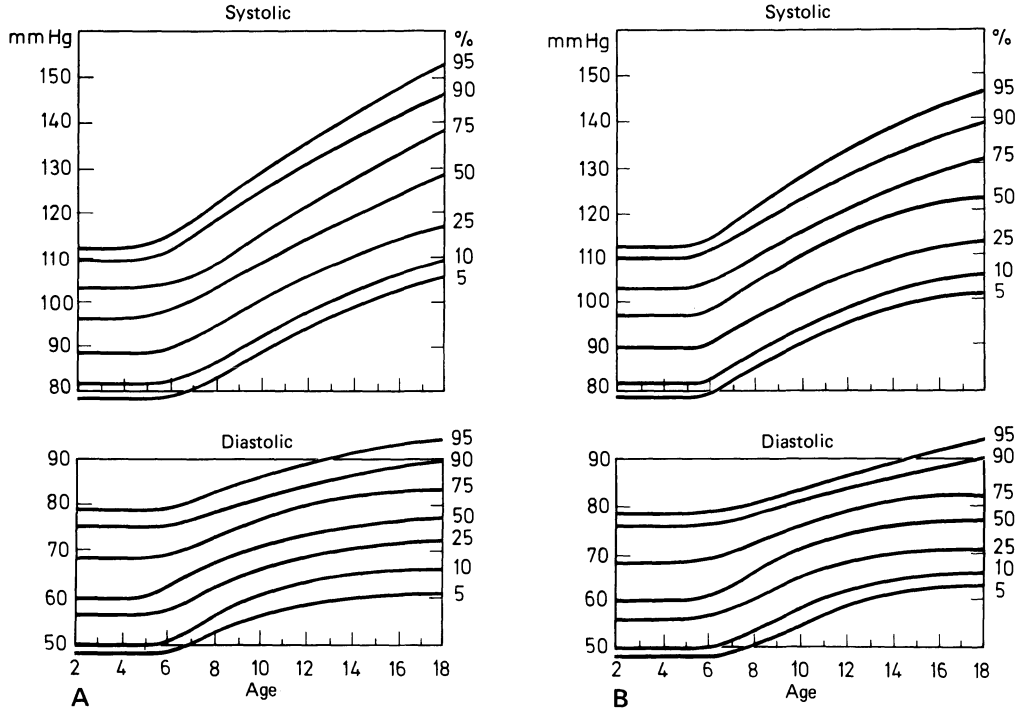


**Figure 3.** Blood pressure percentiles during growth. **A**, in boys (right arm, seated); **B**, in girls (right arm, seated). Modified from Blumenthal S, ref 2

remain open for a few more years. Nonetheless, the above-mentioned reproducibility of blood pressure measurements in childhood and adolescence makes it possible to depict blood pressure readings according to age- and sex-dependent percentiles (Fig. 3),[2] thus making it easier to exert long-term control. In this way, not only would the absolute blood pressure value be replaced by the much more differentiated percentile concept but an essential dynamic element would be introduced: that not only is the one-reading relative percentile position fundamental for evaluation but also the changes in percentile positions observed over the years, such as departures from the 25–75 percentile range.

## Recognition of Hypertension in the Population

Within the cardiovascular risk profile, hypertension not only plays a particularly prominent role but is also relatively easy to assess methodologically. The efficacy of intervention in cases of moderately to seriously elevated blood pressure appears to be well established.[27,56] For the Federal Republic of Germany, about 6 million hypertensives have been estimated so far, some of whom require treatment, others of whom are treatable. Many authors make much lower estimates of at least the number of hypertensives in need of treatment.[47] Unfortunately, there is still no reliable evidence establishing with sufficient authority the prevalence of elevated blood pressure values in the Federal Republic of Germany. While boundary values[59] and survey methods[12] have been internationally established to a large extent, there is not the least agreement on matters such as how many measurements are necessary, in which body position they should be taken, or how far the situation should be taken into account. The indication for treatment is also often disputed, especially in elderly patients.[37] These questions, as well as the establishment of end values for hypertensive treatment, are being answered on the basis of individual medical experience, simply because of the lack of more advanced data.

In recent years, the "incidental screening" approach has been employed to take maximum advantage of unused capacities for the early diagnosis of hypertension. Three problems arise from this approach:

1. Early recognition without adequate early treatment is useless. Several papers of recent years have shown that only one-fourth to one-third of known hypertensives are treated effectively.[5,14] Furthermore, while about half of all hypertensives are unaware of their disease, not all of those undergoing treatment for hypertension actually need it.[47]
2. Inadequate definition of the underlying criteria combined with faulty use of measurement tools leads to a heavy burden of so-called false positive results; i.e., subjects classified mistakenly as suspected hypertensives must be reevaluated by additional costly diagnostic means.
3. The insights gained thus far from legally required medical checkups demonstrate the need to carefully analyze the efficacy and efficiency of early diagnostic examinations before further such programs are instituted.[29]

Such an analysis must be preceded by consideration of the context in which the early diagnostic examinations should be carried out. A study carried out by the Panel Doctors' Association of Nordrhein-Westfalia seems to imply that the capacity for blood pressure screening as a part of established programs for the early detection of cancer could be considerably expanded.[36] But as long as there is controversy concerning the indications for treatment and there is no guarantee of long-term supervision with active follow-up of treated hypertensive patients, the wide-scale introduction of screening measures can hardly be advocated.

*The present state of knowledge on the risk of hypertension can be summarized as follows:* The estimation of hypertension as a cardiovascular risk factor is hardly in dispute. The pathogenetic mechanisms for primary hypertension are still only partly understood. The efficacy of intervention is sufficiently established only for chemotherapy, and only for certain population groups. Intervention by the recognition and effective treatment of all hypertensive individuals has not yet been achieved, at least in the Federal Republic of Germany. However, a nationwide hypertension education program is currently being organized by the German Institute for High Blood Pressure Research.[12]

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# Behavioral Patterns as They Relate to Hypertension

3

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For a long time, accumulated evidence has suggested that emotion, life situations and stress, and other behavioral and environmental variables may play a significant role in the development, maintenance, treatment, and prevention of hypertension. The evidence is both of a direct and indirect nature: anecdotal reports of physicians, assessments of psychological characteristics of hypertensive patients, epidemiologic and sociological studies, and a large psychophysiologic literature demonstrating various influences of behavior on blood pressure changes and other responses of the cardiovascular system. For general reviews, see Cohen and Obrist,[15] Eyer,[27] Gutmann and Benson,[42] Harris and Forsyth,[48] Heine,[49] and A. Shapiro et al.[88,89] One striking example derives from the data showing that blood pressure does not rise with age in some black societies, whereas in others one finds more typical increases.[4] Such conflicting data have prompted the conclusion that hypertension, though an exceedingly complex disorder, is closely related to environmental and behavioral processes, and that the disorder is initiated only under conditions of the stress of living in modern societies. Community disruption and increased work pressure are often cited to be among the most important ingredients of this process.[27] Although many investigators agree that behavioral and social factors are associated with variability of blood pressure and with the incidence of hypertension, the causative role of such factors is not accepted by everyone nor is it well understood. Such factors probably do not act in isolation and undoubtedly interact with various other possible determinants of the disease, such as obesity, genetic susceptibility, smoking, salt and cholesterol intake, other dietary factors, and various physical features of the environment such as air and water pollutants.

If behavior has an influence on blood pressure and hypertension, the disease process must be mediated by central and autonomic nervous system mechanisms involved in the regulation of the cardiovascular system.[14,26,32,78] Humoral and biochemical processes are also associated with the neural and cardiovascular changes related to elevated levels of blood pressure. It is not our intention here to examine or to try to account for the sequence of steps leading from behavior on the one hand to essential hypertension on the other. Little is known about this transformation, although researchers have investigated and speculated about the role of excessive sympathetic nervous system activity,[26] idiopathic high cardiac output states,[22,39,43] and generally about neurogenic factors, particularly in essential hypertension. It seems likely that neurogenic hypertension represents only a part of the total population of individuals with abnormal elevations of blood pressure. It is not clear whether the behavioral and environmental correlates found so far to be associated with hypertension, as reported in the literature, apply both to neurogenic hypertension and to hypertension related to other than neural influences. Some instances of hypertension secondary to kidney or endocrine malfunction may also have a neurogenic component in their etiology.

In an attempt to differentiate neurogenic from nonneurogenic hypertension, Esler et al. distin-

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guished two groups of patients with mild essential hypertension: those patients who had relatively elevated levels of plasma renin activity and those with normal levels.[26] The high-renin subgroup also had a higher heart rate and an elevated plasma norepinephrine concentration. Through the use of autonomic blocking agents, these investigators were able to establish that the high-renin group sustained their increased blood pressure by means of overactivity of the sympathetic nervous system. Through psychological test methods, it could also be established that patients with mild high-renin essential hypertension as a group were controlled, guilt-prone, and submissive, with a high level of unexpressed anger, and sustained their blood pressure by means of overactivity of the sympathetic nervous system. Normal-renin patients were not different from normal control subjects in these psychological characteristics. Esler et al. state that the pathogenesis of elevated blood pressure in the high-renin mild hypertensive group may involve a behavioral pattern (primarily suppression of anger) which is related to increased sympathetic nervous system activity, but they also suggest that the behavior pattern could actually follow from increased sympathetic nervous tone, rather than the other way around.[26] Their research does not make clear why increased blood pressure is the major outcome in this group of patients (high-renin) rather than some other symptom, inasmuch as excessive sympathetic nervous system activity has been believed to be a causal factor in other psychophysiologic disorders as well. Moreover, it is not known whether the heightened sympathetic nervous tone represents a constitutional predisposition in these patients, or whether the sustained and heightened sympathetic nervous tone results from repeated elicitations of behaviorally induced patterns of nervous reaction. Is the excessive sympathetic tone acquired through some process of conditioning and learning? The possibility that any or all of these explanations apply is suggested by the various areas of research reviewed below.

Aside from the many unresolved questions of neurogenic versus nonneurogenic hypertension, we should also point out at the outset that the literature to be discussed is uneven in many respects. The populations studied vary considerably in their composition, according to age, sex, severity and duration of hypertension, presence of other illnesses, sociocultural factors, and so on. The variable quality of the behavioral data, the incompleteness of experimental designs, and the inadequacy of comparison or control groups make interpretations of the significance of the studies difficult. Granted these limitations, our purpose in this paper is to give an overview of behavioral, social, and psychological factors in hypertension. The particular studies and findings mentioned were selected out of a much larger body of literature as a means of illustrating the role of emotional factors, stress, experimentally induced stress, and behavioral modifications of blood pressure in hypertension. The latter field has attracted renewed interest in recent years with the discovery of biofeedback and the resurgence of other psychological methods of achieving some degree of voluntary control over visceral, covert somatomotor, and central nervous system processes in normal and patient populations.[91,95] Clinical research on biofeedback, relaxation, and other methods of lowering blood pressure in patients with essential hypertension will be reviewed with the aim of stimulating further interest on the part of clinicians and researchers in these nonpharmacologic approaches to treatment and prevention.

## Personality Variables

### Clinical Studies

For at least four decades an attempt has been made to link certain personality characteristics with a tendency to respond to emotionally arousing events with greater than normal increases in blood pressure. One of the earliest descriptions of such a "hypertensive personality" comes from observations made by Alexander in his clinical practice.[1] He described the psychodynamic structure of the hypertensive patient in terms of a conflict between intense, aggressive, hostile impulses and equally strong passive-dependent tendencies. Over a period of time, the continued inhibition of hostile tendencies leads to permanent histologic changes and a chronic elevation of blood pressure.

The presence of such a conflict has been observed by many investigators, who have also emphasized other kinds of specific behavior patterns in hypertensives. Binger felt that the sudden loss of security was a key to the development of hypertension,[9] while Dunbar observed signs of passivity and a high incidence of emotional instability in her own hypertensive patients.[20] On the basis of ratings made during a series of interviews, Gressel et al. described hypertensive behavior in terms of obsessive-compulsiveness and subnormal assertiveness.[41] Other investigators have related measurable pressor responses to specific traumatic events in the life of the hypertensive patient.[79,104]

In spite of the consistent findings of many early investigations, the studies share a common lack of

objectivity. Furthermore, most of the hypertensive patients were under treatment for psychiatric problems and as such displayed neurotic behavior patterns that may not be characteristic of all hypertensive patients.

### Psychological Test Inventories

Psychological tests have also been utilized in an attempt to determine if there are certain characteristics which define the hypertensive's personality. A recent review of the literature[38] has indicated that neither projective techniques nor rating scales have been able to discriminate between the behavior patterns of hypertensive and nonhypertensive patients. More current research conducted with paper and pencil inventories shows that these tests present more promise of yielding fruitful results. From paper and pencil inventories there is some evidence that hypertensives tend to exhibit poor adjustment or low ego strength, a common characteristic of neurotic behavior.[46,58,77] In addition, these tests point to the hypertensive as a basically submissive individual.[44,46,77]

An interesting finding by Naditch, using a modification of Rotter's Internal-External Scale, is the indication that hypertension in black males is related to the degree of discontent they express about their social situation and a feeling of being powerless to do anything about that situation.[70] Shekelle et al. found that hypertensive women between the ages of 45 and 64 years show a type A coronary-prone behavior pattern, characterized by haste, aggressiveness, and excessive drive (according to the Jenkins Activity Survey).[96] There is also evidence that a widely varying or labile blood pressure, rather than a high level of pressure, is related to a particular personality pattern. Ostfeld and Lebovits indicated that the highly labile individual was impulsive, hypochondriacal, and hysterical according to the Minnesota Multiphasic Personality Inventory.[71]

Studies using paper and pencil inventories have been more objective and have utilized more careful control groups than the early clinical evaluations. They have tended to substantiate some of the clinical descriptions of the hypertensive person, particularly with regard to the concepts of poor adjustment and submissiveness. It has not been proved, however, if these characteristics are unique to hypertension or if they tend to accompany other disorders as well. Furthermore, they may merely be a product of the patient's reaction to being "ill." At any rate, research on paper and pencil inventories has opened other possible avenues of investigation that might be explored in future studies.

## Stress and Sociocultural Variables

According to Glock and Lennard, stress "refers to an event or experience in the life of an individual which has specific physiologic consequences."[36] These result in "disturbance in the equilibrium of the organism." While there is no evidence that stress is specific to hypertension, it has been noted that traumatic events can play a part in causing hypertension in an individual with a certain genetic predisposition and can exacerbate hypertension which already exists.[34]

### Natural Disasters

Certain life-threatening events have been observed and the effects on blood pressure noted. Soldiers who spent at least a year in desert warfare were reported to have unexpectedly high blood pressures from 4 to 8 weeks after retiring to a noncombat area.[40] Similar rises in blood pressure were noted during a long siege and bombardment of the city of Leningrad.[65] When a ship loaded with explosive chemicals blew up and set off an explosion in a chemical plant in Texas, significant elevations in blood pressure were found in the majority of victims. After 10 to 14 days, however, blood pressures returned to normal.[81]

### Culture and Urbanization

While there are exceptions, urban living has been associated with a variety of stressors which pose a constant threat and challenge to existence. Individuals living in high-stress areas of Detroit (defined by low socioeconomic status, high population density, high residential morbidity, and high rates of marital breakup) were found by Harburg et al. to have much higher blood pressure levels than their counterparts in lower-stress areas.[45] This was particularly true for black males, whom Harburg et al. felt were continually forced to restrain their hostile feelings. Investigating crowding, one aspect of urban living, D'Atri and Ostfeld found a relationship between degree of crowding, blood pressure, and pulse rate.[18]

In a comparison of rural and urban Zulus, Scotch showed that the latter group had a higher frequency of hypertension for all ages and for both sexes.[85] Maddocks surveyed the inhabitants of two relatively isolated Pacific Islands and concluded that hypertension was virtually nonexistent among them.[62] Similarly, Lowenstein found blood pressures of two Indian tribes in Brazil to be low relative to other populations.[61] These investigations and the work of

Page et al.[72] suggest that the frequent rise in blood pressure with age which is observed in many societies is a consequence of civilization and acculturation.

Cruz-Coke et al. introduced the concept of "ecological niche" in order to explain the low blood pressure among groups living in relatively isolated regions where traditions remain constant.[16] When these people migrate to urban centers, their blood pressures rise. Both environmental changes and racial susceptibility are believed to explain the difference between many of these groups. The influence of racial susceptibility may explain why Beiser et al. revealed no evidence of an age-related rise in blood pressure for either rural or urban groups among the Serer of Senegal.[4] Henry and Cassell analyzed data from 18 different epidemiologic investigations done in various parts of the world.[51] They reasoned that a failure to show a blood pressure rise with age was associated with a stable culture where tradition, rather than change, was important.

### Occupational Stress

Constant exposure to job stresses has been a factor frequently associated with heightened blood pressure (see ref 69 for an extensive review). Cobb and Rose found the incidence of hypertension in a stressful occupation—that of air traffic controllers—was four times greater than in second-class airmen, who are subjected to less stress.[13] Furthermore, those air traffic controllers who worked in high-traffic-density centers exhibited more cases of hypertension than individuals in centers of low traffic density. In summarizing various Russian studies, Miasnikov found hypertension associated with what he calls "work under nervous stress."[65]

Not only are there stresses associated with various occupations, but the loss of one's job can be perceived as very traumatic. In a longitudinal study of men undergoing job loss due to permanent plant shutdown, Kasl and Cobb found that blood pressure levels were higher during the anticipation of job loss and unemployment than during periods of stabilization on new jobs.[58] Individuals with the most severe unemployment experience had elevated blood pressure for the longest time periods.

### Prolonged Illness

While there is no direct proof that prolonged emotional states lead to hypertension, one finds that blood pressure is temporarily raised by affective illnesses. Heine and Sainsbury provided some evidence that prolonged depressive states were related to raised levels of blood pressure during illness.[50] Blood pressure during illness tended to be correlated with anxiety and agitation, which characterized the depression. Friedman and Bennet found the diagnosis of anxiety to be significantly associated with both depression and hypertension.[33]

It is apparent that people are subjected to many kinds of stressors in their daily living. Naturally occurring disasters, urbanization, occupational stresses, and prolonged illnesses all play a role in the elevation of blood pressure. The effects of stress, however, are not specific to hypertension and often are associated with more generalized physiologic responses. In fact, traumatic events may exacerbate a number of psychosomatic disorders,[36] a fact which leads one to arrive at a multifactorial hypothesis in the causation of hypertension.

## Experimentally Induced Stress

### Human Studies

By means of experimental stimuli, it has been possible to manipulate blood pressure levels in human beings and to show how hypertensives differ physiologically from normotensives. Ayman and Goldshine were able to demonstrate that a breath-holding test could cause blood pressure rises from two to four times greater in hypertensive patients than in normotensives.[2] In response to a cold pressor stimulus, normotensive subjects reached a maximum increase in blood pressure sooner than high and low blood pressure groups, but the hypertensives responded with far greater blood pressure increases.[102] During mental arithmetic performed under duress, hypertensives exhibited hemodynamic changes and blood pressure elevations that persisted longer than in a comparison group.[12] A delayed recovery of blood pressure to normal levels was also found by Baumann et al. in response to an arithmetic task.[3]

A variety of stimuli have been utilized in human studies and have yielded relatively consistent results. Jost et al. subjected hypertensive patients and normotensives to many different stimuli presented in sequence—a buzzer, a bright light, emotionally disturbing questions, and memory tests of rapidly increasing difficulty.[57] In all parts of the experiment, hypertensives had longer-lasting blood pressure changes, which were generally in an upward direction. Cold pressor, injection of normal saline, a frustrating task, threat of electric shock, and frustration by an irritating technician all produced greater blood pressure rises in hypertensives than in control

groups.[82,86] Engel and Bickford found that hypertensives would react to any stressor with a maximal blood pressure response, regardless of the stimulus.[25]

Interview techniques have also been utilized as a means of stimulating pressor responses in human beings. Wolff and Wolf have found that all individuals respond to topics of conflict with rises in blood pressure, but hypertensives show much greater increases.[104] The amount of blood pressure change depends on the meaning of the stimulus to the subject. Innes et al. noted that no specific topics were associated with blood pressure increases, but blood pressure levels took longer to return to normal in hypertensives and neurotics than in controls with low blood pressure.[54] Apparently the critical factor in distinguishing hypertensives from normotensives is not just the level of response but the prolonged reaction which hypertensives have to stressful stimuli.

### Animal Studies

***Noxious Stimuli.*** By utilizing animals in a laboratory situation, it is possible to reproduce many environmental stressors and to manipulate the level and duration of the stimuli more precisely than is possible with human subjects. For example, it has been demonstrated that rats exposed to loud noises over long periods of time will develop signs of hypertension.[28,64,105] Chronic intermittent exposure to auditory, visual, and motion stimuli[99] as well as chronic sound withdrawal[63] induced hypertension and even produced histologic changes in rats. Rats exposed to crowded cages for short periods of time experienced blood pressure elevations which reverted to normal levels in a few days. Exposures of 6 months or more were associated with more permanent blood pressure effects and with increased mortality, frequently due to cerebral vascular lesions.[52]

***Classical Conditioning.*** Using Pavlovian techniques of conditioning, Russian researchers have been able to produce hypertension in animals experimentally.[98] A condition called "experimental neurosis" was induced by simultaneously presenting conflicting excitatory and inhibitory stimuli. While experimental neurosis was accompanied by the onset of hypertension, this condition usually ceased when the conflict-producing situation changed. After inducing experimental neurosis in cats, A. Shapiro and Horn were unable to obtain signs of hypertension in these animals, although a condition of acute anxiety resulted.[87] Gutmann and Benson feel that this may be due to the fact that the stimulus conditions were not sufficiently stressful.[42] In a study by Dykman and Gantt, however, a conditioned hypertensive response in dogs was found to persist for over a year without further conditioning.[21]

***Operant Conditioning.*** Operant conditioning techniques have enabled researchers to reinforce specific changes or patterns of change and have led to greater blood pressure increases and more lasting effects than Pavlovian conditioning. Pressing levers for 15 days under various shock-avoidance schedules resulted in the elevation of blood pressure in experimental monkeys. Forsyth found that the more difficult or demanding the schedule, the higher was the initial pressure and the longer it persisted at heightened levels.[30] It has been suggested that the actual time course for the elevation of blood pressure may take several months before there are significantly high blood pressure levels, which then become fixed at higher levels.[31] With direct reinforcement of increases in blood pressure, Harris and Brady demonstrated elevations of as much as 50–60 mm Hg in diastolic pressure produced on an acute basis in baboons.[47] With 12-h conditioning schedules, more chronic effects of 30–40 mm Hg were maintained over the course of the conditioning sessions.

Herd et al. are of the opinion that the presence of a noxious stimulus in itself is not enough to cause arterial pressure to increase.[53] Operant conditioning with squirrel monkeys has led to the finding that schedules that exert strong control over an animal's behavior bring about the highest and most persistent blood pressure elevations. Friedman and Dahl's work with rats substantiates this finding, for merely shocking rats or exposing them to food deprivation failed to result in a rise in blood pressure.[34,35] They feel that exposure to conflict, especially in a strain of hypertension-susceptible rats, brings about long-lasting blood pressure increases.

Experimental evidence with human beings, as well as with lower animals, has provided sufficient evidence that stress can produce acute pressor responses. The reactions of hypertensives are generally more elevated and of a longer duration than those of normotensives. Investigations of animals have resulted in even greater blood pressure changes. Apparently the presence of a noxious stimulus has not been as effective in producing hypertension in experimental animals as the utilization of complex operant schedules, where the animal is exposed to relatively long periods of conflict and continuous behavioral adjustments are required.

## Behavioral Methods of Treatment

In view of the assumed and documented social and psychological components of essential hypertension,

behavioral methods have been proposed for the treatment and prevention of the disorder. Such methods offer nonpharmacologic means of lowering pressure. As such, they can be adjunctive to standard medical approaches to treatment and can be used to enhance the effectiveness of antihypertensive drugs, to reinforce compliance with drug regimes, to reduce drug dosage in some cases, or to substitute for drug treatment that is not effective or results in intolerable side effects. The choice of any one of the particular behavioral methods of treatment described below will probably depend on many considerations, including those of background, training, and experience of the clinician. The methods each have different rationales, although they may all achieve some common final effect. A. Shapiro et al. reviewed the behavioral literature, including the use of biofeedback techniques, relaxation techniques, psychotherapy, environmental modification, and suggestion and placebo effect.[89] The conclusion was that all methods seem to produce modest decreases in blood pressure, but that clinical data were lacking on persistence of the effects, comparative effectiveness of the different methods, mechanisms and outcomes, and interaction of methods with drug treatment. In the opinion of A. Shapiro et al., the major difference among the methods is the ease with which they can be applied clinically.[89]

## Biofeedback

Biofeedback may be defined as "a method of achieving voluntary control or self-regulation of specific physiological responses or patterns of responses (e.g., visceral, electrocortical, and covert somatomotor). The method involves presentation to the individual of a sensory display of his ongoing physiological activity as it is occurring in time."[90] Rewards for the appropriate responses, various incentives, or other means of motivating the subject to concentrate on the task and produce the desired changes are usually part of the method.

Much of the basic human research on the voluntary control of blood pressure by means of biofeedback techniques follows the procedures first described by D. Shapiro et al.[92] Using a newly devised constant cuff pressure technique, relative information is provided about changes in blood pressure on each beat of the heart, and median systolic or diastolic blood pressure is tracked continuously.[103] In a number of studies, it was shown that normal human subjects were able to modify their systolic or diastolic blood pressure by small but significant amounts with relatively brief periods of training.[92,93,94] Further research indicated that the biofeedback control of cardiovascular parameters could be quite specific, in that various patterns of change in systolic blood pressure and heart rate could be modified by human subjects. Thus, subjects could make systolic pressure and heart rate increase or decrease together and to some extent could make them change in opposite directions, i.e., heart rate increase and blood pressure decrease or vice versa.[83] This research on the voluntary control of patterns of cardiovascular responses indicates the clinical potential of selecting biofeedback treatments aimed toward alteration of specific cardiovascular responses or combinations of responses, in the same way that different drugs are directed to the control of different functions mediating the regulation of blood pressure. The limitations of this conception would largely depend upon existing capabilities for simple, noninvasive recording of the relevant responses. Further support for the usefulness of biofeedback in the control of blood pressure in normal subjects was obtained by Brener,[10] Brener and Kleinman,[11] and Fey and Lindholm.[29]

Clinical data on the usefulness of blood pressure biofeedback have been reviewed extensively by A. Shapiro et al.[89] and D. Shapiro et al.[95] For example, Benson et al. obtained data on five patients with essential hypertension who were studied in 12 to 34 sessions of training.[8] Reductions of 17 to 34 mm Hg systolic pressure were shown. Similar techniques were used by Goldman et al., who reported average reductions of 4% systolic and 13% diastolic in seven patients with essential hypertension.[37] The reductions in pressure were also correlated with improvements on a test of cognitive function (category test of Halstead-Reitan Neuropsychological Test Battery for Adults). Kristt and Engel also employed the constant cuff method and a similar training procedure in five patients with essential hypertension having a variety of cardiovascular and other complications.[60] Reductions of 10% to 15% were observed in both systolic and diastolic pressure. Medication was reduced in some patients, and beneficial effects were also observed in nonlaboratory settings by the use of home recordings and home training procedures. Another innovation of the Kristt and Engel research involved the method of training patients both to increase and decrease blood pressure as a means of enhancing self-control. Using biofeedback and verbal praise for reduced pressure, Elder et al. reported decreases of about 20% on the average in diastolic pressure in six patients.[24] These results were replicated by Elder and Eustis in a sample of 22 patients, but the reductions were much smaller.[23] In one of the few comparative studies so far reported, Surwit et al. compared blood pressure–heart rate biofeedback, electromyographic biofeedback, and relaxation-meditation with eight patients in

each condition, over eight training sessions, including a 6-week and 1-year follow-up.[101] All patients showed average reductions in pressure of about 17/9 mm Hg during the initial baseline sessions. Further reductions occurring as a result of training were very small or nonexistent. By and large, follow-up values were still much lower than original values in the patients' medical histories, but about the same as final pretreatment values occurring after the baseline sessions. The study points up some of the complications of establishing appropriate baselines and evaluating variability of blood pressure in assessing behavioral (or other) treatments for essential hypertension.

Further discussions of the problems of patient motivation, compliance with biofeedback (and other related) treatments, medical and physiologic complications, experimental design and problems of clinical research in this area, and practical clinical issues are discussed by Miller,[66] Miller and Dworkin,[67] Schwartz and D. Shapiro,[84] D. Shapiro et al.,[95] and A. Shapiro et al.[89]

Finally, mention should be made of the work of Patel,[73–76] involving the combined use of electromyographic feedback, electrodermal feedback, stress management, and yoga relaxation exercises. This research on an extensive number of subjects has also effectively employed cross-over designs, follow-up studies, and stress testing (cold pressor, treadmill) as a means of assessing the value of the combined behavioral treatment approaches. By and large, the results were positive in indicating clinically significant reductions in blood pressure and also reductions or complete discontinuation of medication in many patients.

The rationale for using biofeedback for reductions in physiologic functions other than blood pressure depends on the assumption that blood pressure can be lowered through reductions in sympathetic nervous system activity or total muscular activation. Basic research using biofeedback methods in normal and patient subjects provides ample evidence that other cardiovascular responses (e.g., skin temperature, peripheral blood flow, arterial pulse wave velocity, or pulse propagation time) may be brought under some degree of voluntary control. Their potential usefulness in the treatment of essential hypertension, according to differences in stage and severity of the illness, needs to be considered by physicians and researchers.

## Relaxation

Relaxation and meditation have been proposed as treatments for hypertension for various reasons. If excessive reactions to the stresses of everyday life are presumed to play a role in the disease, then relaxation may help the patient reduce physiologic or psychological states associated with increases in blood pressure, e.g., muscle activity, autonomic nervous system activation, anxiety, depression.

Relaxation may be achieved in any number of different ways. One method is "progressive relaxation," based on the early work of Jacobson.[55,56] The practice involves exercises in tensing and relaxing various muscles and muscle groups to achieve greater recognition of one's own muscle tension and to bring about complete muscular relaxation. Support for the value of this technique for hypertension was reported by Shoemaker and Tasto.[97]

A second systematic approach to relaxation has been developed by Benson, using a procedure derived from transcendental meditation, but without the spiritual features associated with that practice. Benson gives the following rationale for the "relaxation response": "The pathogenesis of several major diseases such as hypertension is associated with an integrated hypothalamic response triggered by situations requiring continuous behavioral adjustments."[5] This response is comparable to the emergency reaction, defense reaction, or fight-flight response—patterns of behavior and physiologic response described by many investigators. According to Benson, this hypothalamic response is mediated by increased sympathetic nervous system activity and is associated with increases in catecholamine production, oxygen consumption, heart rate, respiratory rate, arterial blood lactate, and increased muscle blood flow; and hypertension may result from frequent elicitation of this reaction.

The effects of the relaxation response are completely opposite to the emergency reaction and can be achieved by a variety of relaxation methods. The basic elements common to such relaxation are: a mental device or mantra, a passive attitude, decreased muscle tonus, and a quiet environment. A number of clinical studies have been carried out by Benson and associates which suggest a positive benefit for patients with essential hypertension and for other disorders. For example, Benson et al. reported decreases of 11/5 mm Hg in 14 patients who were maintained on constant antihypertensive medication.[6] Similar reductions were obtained in a study of unmedicated borderline hypertensives,[7] with additional benefits resulting from continued practice in subsequent months. This relaxation procedure is very simple to explain, easy to practice, and economical.

Aside from progressive relaxation, transcendental meditation, and the relaxation response, several other relaxation procedures have been employed. Some derive primarily from Eastern cultures and involve methods that have been around for centuries,

such as various forms of yoga and Zen meditation practice.[17,100] Other procedures involve the use of hypnosis, involving suggestions to facilitate mental and bodily relaxation.[19] Autogenic training methods, which are closely related to hypnosis, involve self-suggestions for inducing relaxation and control of physiologic states.[59]

### Psychotherapy

Various psychotherapeutic approaches have been applied to the treatment of essential hypertension, such approaches being the primary psychological methods in existence long before biofeedback and relaxation approaches came into vogue. As A. Shapiro pointed out in 1960 in reviewing the prior literature on psychotherapy for hypertension, inasmuch as data on the placebo effect suggest that the relationship between doctor and patient can exert a hypotensive effect, "proper and rational use of the doctor-patient relationship has a potent ameliorative effect in hypertensive vascular disease. . . ." The major early studies in this area include Reiser et al.[79] and Moses et al.[68] No comprehensive or large-scale studies involving psychotherapy have been reported in recent years. Psychotherapy traditionally involves various methods such as reassurance and the discussion of personal problems to promote insight into the basis for anxiety and other emotional reactions to life situations and stress. In current thinking, alternative methods involving more direct modifications of maladaptive behavior or the methods of relaxation or biofeedback described above would be a substitute for the less well-defined procedures of psychotherapy.

## Summary and Conclusion

The purpose of this chapter is to give an overview of the role of behavior in hypertension. As is apparent from the diverse facts and observations summarized, there are numerous associations between hypertension and various behavioral, social, and environmental conditions. The evidence as a whole supports the position that behavior can influence variability of blood pressure and incidence of hypertension.

We have described a number of illustrative studies concerning the role of personality variables (clinical studies, psychological test inventories), stress and sociocultural variables (natural disasters, culture and urbanization, occupational stress, prolonged illness), experimentally induced stress (human studies, animal studies including studies of noxious stimuli, classical conditioning, operant conditioning), and behavioral methods of treatment (biofeedback, relaxation, psychotherapy). At the sociocultural level, the critical variables related to high blood pressure and incidence of hypertension seem to involve work pressure, community disruption, social and natural threats, and rapid social change. At the level of individual personality, hypertensives may be characterized as poorly adjusted, submissive, anxious, and unable to express anger. At the behavioral level, demanding situations requiring continuous behavioral adjustments or other anxious physical stresses (such as in certain occupations) may precipitate increases in blood pressure and lead to hypertension. The quality of the studies supporting generalizations is quite uneven. Commonalities among the findings at the various levels of discourse (social to individual) need to be examined more closely.

The causal nature of the association between behavior and hypertension is not well understood or agreed upon yet. Behavioral influences may operate in interaction with other factors, e.g., diet, genetic susceptibility. More research is needed to examine these interactions more closely. Research on the differentiation of neurogenic and nonneurogenic mild essential hypertension, in terms of plasma renin activity, promises to be productive, particularly in showing psychological factors to be associated with the neurogenic subclass of hypertension. Additional research is needed to substantiate and extend these findings. Most useful is the strategy of gathering simultaneous data on cardiovascular, hormonal, psychological, and behavioral functions in patients with essential hypertension, and of attempting categorization of hypertensive patients according to the various measures.

Finally, the recent interest in and development of behavioral methods of treatment suggests that nonpharmacologic approaches to the control of hypertension may be useful in clinical medicine as an adjunctive method to drug treatment, and possibly as a means of reducing drug dosage or of providing an alternative means of reducing pressure in patients for whom drug treatment is not adequate or for whom drug treatment produces intolerable side effects. The data to date are encouraging, and further progress will be made in collaborative efforts of clinicians, physiologists, and behavioral scientists.

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# Hypertension and Obesity

# 4

J. G. Wechsler, H. Ditschuneit

According to the 1976 nutrition report by the German Association for Nutrition,[29] 56% of the male and 47% of the female population in the Federal Republic of Germany are at least 15% overweight by the Broca scale.* While it is almost unanimously accepted today that excess weight is the consequence of a positive caloric balance,[18,63] the causes leading to this disturbance of the caloric balance in the obese but not in the normal-weight person are unknown.[19] There are no doubts on the correlation of an increased morbidity and mortality rate with excess weight.[44,70] S. von Basch pointed out the frequent coincidence of overweight and elevated blood pressure as early as 1893.[7] Numerous epidemiologic studies show hypertension to be one of the first-order risk factors for atherosclerotic diseases.[100a]

The following survey will demonstrate correlations between hypertension and excess weight. Connections between weight reduction and blood pressure lowering will be discussed on the basis of the authors' own studies, as well as the potential for the prevention of atherosclerosis suggested by their results.

## Epidemiology and Incidence of Overweight

Economic and social variables exert a direct influence on mean weight and morbidity due to obesity. In a retrospective study of the years 1933–1951 in Bonn, the incidence of obesity correlated closely (Fig. 1) with the average amount of available calories.[41] This investigation showed that the percentage of overweight patients exceeding 10% on the Broca scale was about 9% in 1933, about 2% in 1946, and about 11% in 1951.

In 1976, a study of eight population groups in the state of Hesse in the Federal Republic of Germany showed that 47% of the women and 56% of the men were overweight. Persons with excess weight of more than 15% by the Broca scale were considered overweight.[29] Ries gave an overweight rate of 50% in 1970 for the urban population of Leipzig.[94] An investigation by Müller in 1970 of about 80,000 persons in the German Democratic Republic showed one-third (19% men and 42% women) to be 20% overweight according to Broca.[75] Excessive weight seems to be more prevalent in the countryside than in the cities of the Federal Republic of Germany.

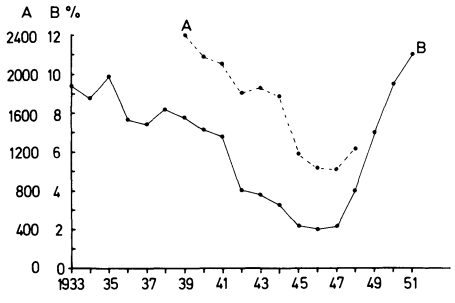



**Figure 1.** Incidence rate of obesity and caloric intake. ●—● Percentage of the obese patients in 34,468 men and women of the Medical University Hospital, Bonn, in the years 1933–1951 (B). ●--● Available number of calories in the years 1939–1948 at the time of food rationing (A). From Grosse-Brockhoff F, ref 40

*Broca scale $= \frac{\text{body weight (kg)}}{\text{normal weight (kg)}}$

Normal weight = body height (cm) − 100 (kg)

Von Knorre described 27% of the men and 52% of the women in rural areas as overweight in 1971.[57] A 1968 mass study in Yugoslavia found 29% of the men and 42% of the women heavier than their ideal weight,[89] whereas in Great Britain excess weight was computed in the total population as 48% for the men and 46% for the women in 1971.[72] In Spain, only 7% of the men and 23% of the women were classified as overweight in 1959.[28] In Sweden, on the other hand, 50% of the over-40 population was overweight.[100]

Obesity is more common in women than in men. The incidence of obesity increases with age, although beyond age 60 the proportion of obese persons relative to the overall population decreases again.[13] In the USA and Canada, overweight men and women are found with equal frequency.[23] The literature indicates an incidence between 20% and 30% for obesity in the USA.[64,96,101]

According to the literature, the incidence of obesity in childhood is between 1% and 20%.[40] Measurements of 7000 school children of the Ulm area revealed that 8.3% of the boys and 11.3% of the girls were more than 20% overweight.[33] According to Broca, normal weight is calculated as weight in kilograms equal to height in centimeters minus 100. Statistics compiled by American life insurance companies define ideal weight as the weight with the highest life expectancy.[70] Apart from the tabulated consideration of age and sex, a classification according to body build into three different orders has also been made.

## Epidemiology and Incidence of Hypertension

Most investigators[65,73,111,113] cite an incidence of 25% for hypertension as a first-order risk factor for atherosclerotic diseases.[100a] The incidence of hypertension in factory workers of a large Swiss concern was slightly higher at 28%.[45] Other studies give a somewhat lower incidence for hypertension: 15% to 20%.[62,86,104,106] In the USA, blood pressure values over 160 mm Hg systolic or 95 mm Hg diastolic were found in 17% to 27% of the black population but in only 10% to 14% of whites.[77,103] The incidence of hypertension in the overall population is reported at 12% to 26%. An increasing incidence of hypertension occurs with advancing age. Up to age 50, men have higher blood pressure values than women, whereas women display higher values after age 50.[76] The World Health Organization (WHO) has defined three ranges of blood pressure.[116] According to this definition, a blood pressure reading of 140/90 mm Hg is regarded as high-normal for all age groups. Readings over 160/95 mm Hg are judged pathologic in all cases. Values between 140 and 160 mm Hg systolic and 90 to 95 mm Hg diastolic are considered borderline.

## Artifactual Errors of Blood Pressure Measurement in Obese Patients

Direct intra-arterial blood pressure measurements yield similar readings in both the brachial and the femoral arteries.[81] Using the method of Riva-Rocci-Korotkow, however, a higher value is measured on the thigh (with the same cuff) than on the upper arm.[81] The cause of this discrepancy is thought to be the greater soft-tissue thickness of the thigh. Accordingly, some investigators believe that there is danger of obtaining false blood pressure readings in obese patients.[12] Ragan and Bordley,[90] Pickering et al.,[88] Bjerkedahl,[14] and Loewe[60] found good correlation between measured blood pressure and upper-arm circumference. After correction tables were compiled for different upper-arm circumferences, correction tapes were developed which could be attached directly to the blood pressure cuff.[84,87] Other investigators, however, were not able to demonstrate a direct correlation between degree and direction of the measurement error and the limb circumference.[37,53,78,91] Even with small arm circumferences, the blood pressure reading by indirect measurement was too high or too low in half the subjects examined. Thus, it appears that correction formulas and correction tapes are based upon false premises in assuming accurate measurements for small limb circumferences, as well as in attributing a linear correlation between measurement error and upper-arm thickness. In each individual case, the fat-pad thickness, muscle tone, vascular elasticity, tissue water content, and bone–to–soft-tissue ratio seem to exert an indeterminate effect on the blood pressure value measured indirectly.[2,4,10,37a,56] The length and width of the cuff (Fig. 2) also have a decisive influence on the accuracy of the measurement.[37a,55] The broader the cuff, the closer the correspondences between indirect and direct measurement of arterial blood pressure. The Committee for Cardiovascular Diseases of the World Health Organization recommends a cuff 14 cm wide;[116] the German Association for Circulatory Research prefers one 13–14 cm wide and 50 cm long.[30] Cuffs 18 cm wide should be used for indirect blood pressure measurements on thick upper arms in obesity,[30,37a] or else the blood pressure should be measured directly intra-arterially.[78] Nevertheless, numerous studies suggest that the elevated blood pressure often found in the overweight patient cannot be attributed entirely to artifactual errors of measurement in obese patients with thick upper arms.

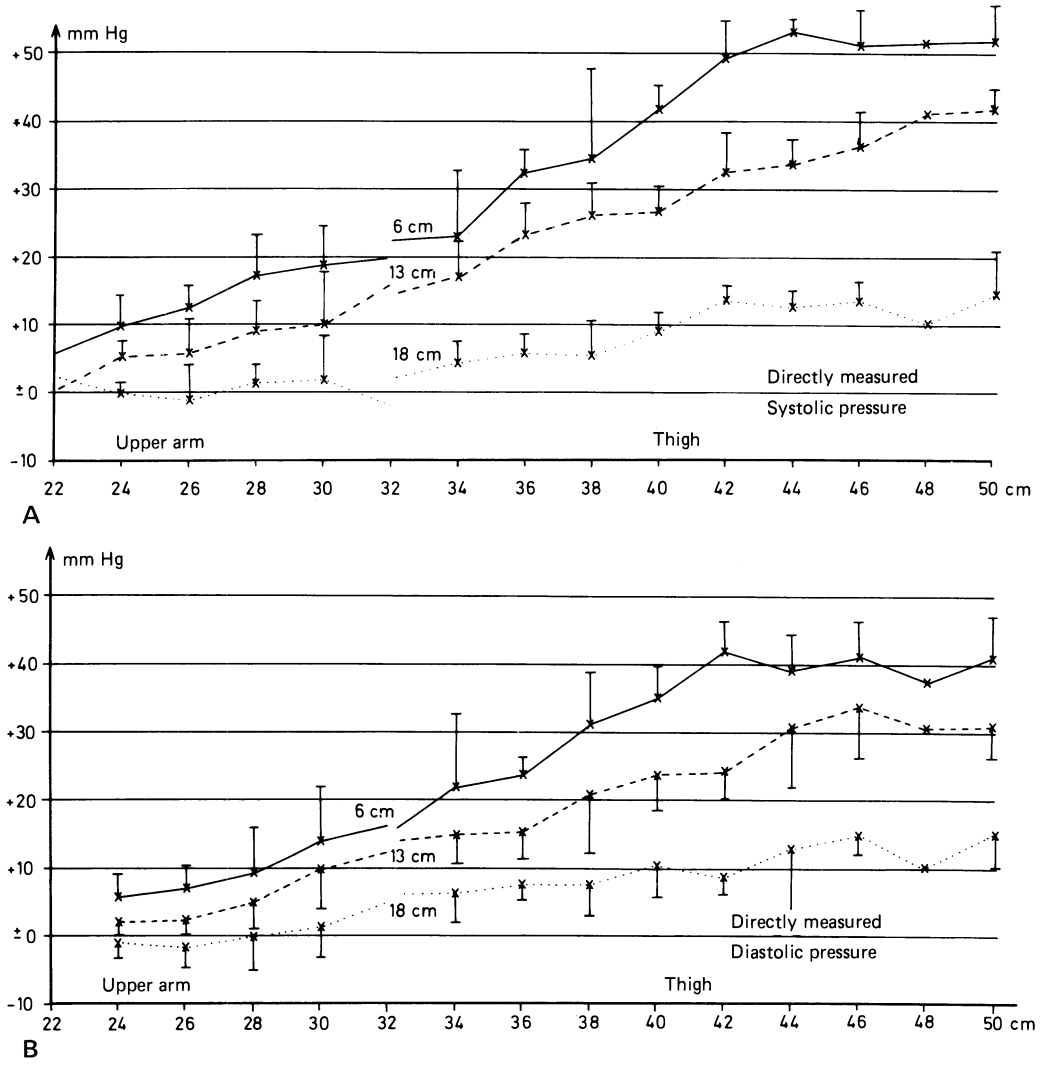



**Figure 2.** Accuracy of indirect blood pressure measurements (**A**, systolic; **B**, diastolic) in relation to cuff width and arm or leg circumference. From Gillmann H et al., ref 37

## Correlations between Body Weight and Blood Pressure in Children and Adolescents

A better correlation of systolic blood pressure with weight and size has been described in adolescents;[93] it was highest between 9 and 14 years of age. In 1975, Stine and co-workers[105] found in 920 children the highest correlation between weight and skin-fold thickness, and a more clearly positive correlation between weight and systolic blood pressure than between skin-fold thickness and systolic pressure. The diastolic blood pressure values correlated in a similar way. On the average, black children had lower correlation coefficients than white children.

Londe found in apparently healthy children a significantly higher incidence of obesity in hypertensive children than in the control groups.[61] Contrary to findings in white children, Boyle was unable to find a correlation between excess weight and hypertension in black children.[16] In 15- to 19-year-old high school students, 9.3% showed positive correlation of hypertension with excess weight, with hypertension occurring more frequently in blacks.[27] Court and coworkers examined 209 obese children (87 boys and 122 girls) and found a good correlation between excess weight, skin-fold thickness, and blood pressure.[22] Figure 3 shows the relationship between fat, as a calculated percentage of body weight, and systolic and diastolic blood pressure. A correlation be-

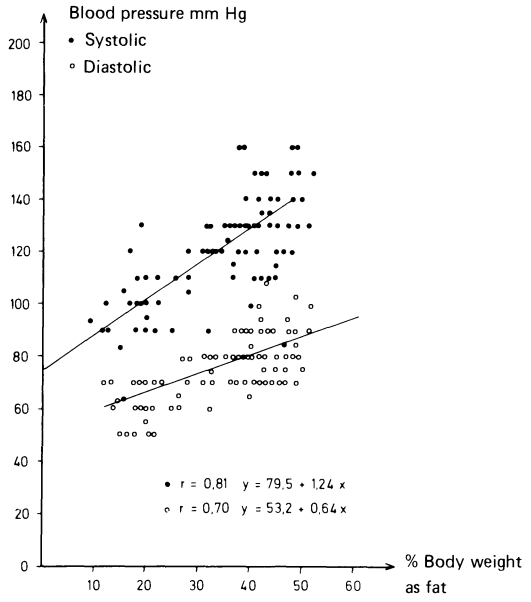



**Figure 3.** Correlation between fat percentage of body weight and blood pressure. From Court JM et al., ref 23

tween the degree of overweight and sex, age, or duration of obesity could not be found. Numerous other investigators arrived at similar results, finding a close association between body weight and blood pressure.[49,52,58]

## Correlation between Body Weight and Blood Pressure in Adults

Clinical and epidemiologic investigations and studies of the relation between body weight and blood pressure from different continents are summarized in Table 1. Most of the authors found a close correlation between blood pressure and body weight, i.e., between hypertension and obesity. In light of the Framingham Study, Kannel and co-workers were also able to demonstrate the existence of a direct correlation between overweight and incidence of hypertension (Fig. 4).[53] The risk of developing hypertension was reported at 320% (normal, 100%) in the presence of excess weight above 20%. In the same

**Table 1.** Correlations between Body Weight and Blood Pressure

| Author | Country | Study Population | Findings |
|---|---|---|---|
| Master and Oppenheimer, 1929[66] | USA (New York) | 91 obese women and 8 obese men | Hypertension in 67% of the cases. The greater the overweight, the higher the blood pressure. Dependence of blood pressure on age and duration of obesity also found. |
| Hartmann and Christ, 1929[42] | USA | 1083 women over 15 years and 959 men (patients of the Mayo Clinic) | Good correlation between increase in weight and systolic blood pressure in men and women as well as between weight and diastolic blood pressure in women. |
| Robinson et al., 1939[96] | USA | 7478 men, 3405 women | Clear rise of blood pressure with overweight. Hypertension 6 times more frequent in obese women, 1–2 times more frequent in obese men. |
| Levy et al., 1946[59] | USA | 22,741 members of the Armed Forces | Probability of developing hypertension increased in overweight individuals. |
| Boynton and Todd, 1948[17] | USA | 75,058 students of the University of Minnesota, 43,800 men, 31,258 women | Clear correlation between systolic and diastolic rise of blood pressure and body weight in all age groups. |
| Bjerkedahl, 1957[14] | Norway | 14,784 persons, 11,063 men, 3721 women | Increase of systolic and diastolic blood pressure with body weight. |

(*Continued*)

**Table 1.** Correlations between Body Weight and Blood Pressure (*Continued*)

| Author | Country | Study Population | Findings |
|---|---|---|---|
| Boe et al., 1957[15] | Norway (Bergen) | 22,718 men and 40,258 women | Weak correlation between overweight and hypertension: 3 mm Hg systolic and 2 mm Hg diastolic rise of blood pressure per 10 kg increase of body weight. |
| Master and Lasser, 1958[67] | USA | 5612 healthy persons over 65 years. 2922 men, 2690 women | In both sexes, increase of blood pressure with increase of weight. No correlation of blood pressure with absolute body weight, but clear correlation with relative weight. |
| Whyte, 1959[115] | Australia (Sydney) | 100 men, 20–40 years old | Positive correlation between blood pressure and body weight as well as body fat. |
| Build and Blood Pressure Study, 1959[100a] | USA | 4.9 million members of a life insurance company | Increased mortality in overweight and hypertension. |
| Nutrition Survey of the Armed Forces, 1960[79] | USA (Philippines) | 1333 members of the Armed Forces (20–49 years old) | Significant positive correlation between blood pressure and overweight. |
| Pflanz, 1961[86] | FRG (Gießen) | 9456 patients of an outpatient department | Hypertension in 18.9% of all subjects, on the average clearly higher blood pressure values in obesity (Fig. 6). |
| Pflanz, 1964[85] | FRG (Hannover) | 594 men, 834 women | Two-thirds of study population were overweight; obese men and women had 3 times higher incidence of hypertension than normal-weight persons. |
| Stamler et al., 1961[102] | USA (Chicago) | 1329 factory workers 40–49 years of age | Hypertension rate doubled in obese persons. |
| Alexander et al., 1962[3] | USA (Texas) | 50 patients, extremely obese | Hypertension in 58%, but no correlation between blood pressure level and degree of overweight. |
| Epstein et al., 1965[34] | USA (Tecumseh, Michigan) | 8641 men and women between 20 and 79 years | Significant correlation between blood pressure, body weight, and skin-fold thickness. |
| Tibblin, 1967[108] | Sweden | 855 men with hypertension (50 years) | Good correlation of blood pressure and overweight. In obese hypertensive patients, left cardiac hypertrophy 3 times more frequent than in normal-weight hypertensives. |
| Kannel et al., 1967[53] | USA | 5127 men and women (30–62 years) (Framingham Study) | Good correlation of blood pressure with weight in all age groups. Higher hypertension rate in obese men and women than in normal-weight persons. Risk of developing hypertension increases with body weight. |

(*Continued*)

**Table 1.** Correlations between Body Weight and Blood Pressure (*Continued*)

| Author | Country | Study Population | Findings |
|---|---|---|---|
| McDonough et al., 1967[68] | USA (Evans County) | 3102 persons (15–74 years) | Hypertension more frequent in blacks than in whites. Higher body weight and higher blood pressure values in black women, not in men. |
| Aleksandrow, 1967[1] | Poland | 10% of adult population | Clear rise of blood pressure with increased weight, more frequent occurrence of hypertension in obesity. |
| Chiang et al., 1967[21] | Taiwan | 1822 men (40–59 years) | Significantly thicker skin folds in hypertension. On the average, 5 kg more weight in hypertensives than in patients with normal blood pressure. |
| Patzold, 1969[83], 1972[82] | FRG (Norden) | 2461 patients | Hypertension in 50% of the obese patients; clear correlation between hypertension and Ponderal index. |
| Harty and Beaven, 1972[43] | New Zealand | 61 obese women | Significant increase of hypertension with rising body weight ($p < 0.0005$). |
| Keys et al., 1972[54] | USA, Northern and Southern Europe | USA: 2442 railway employees; Finland and Netherlands: 2439 men; Italy, Greece, and Yugoslavia: 6519 men | Significant correlation between blood pressure and relative weight and fat mass. Frequent occurrence of CHD with overweight and obesity in USA and Northern Europe, not in Southern Europe. |
| Huneke et al., 1972[50] | GDR (Leipzig) | 1000 obese patients | Of 1000 essentially obese patients, 524 had coronary insufficiency and 173 had hypertension. In obese hypertensive patients the incidence of coronary insufficiency was 71.1%. |
| Tran et al., 1973[109] | France | 8660 men (20–55 years old) | Close correlation between blood pressure and body weight, build index, subscapular skin-fold thickness and lipoid mass. |
| Tsomondo, 1973[110] | Rhodesia (Salisbury) | 283 white men | Significant ($p < 0.01$) correlation between blood pressure and obesity. Rise of systolic and diastolic blood pressure by 0.3 mm Hg per 1 kg excess body weight. |
| Escher et al., 1974[35] | Switzerland (Eastern) | 1400 factory workers | Incidence of hypertension: 16%, incidence of overweight: 20%, significant positive correlation between increase of blood pressure and overweight. |

(*Continued*)

**Table 1.** Correlations between Body Weight and Blood Pressure (*Continued*)

| Author | Country | Study Population | Findings |
|---|---|---|---|
| Tanaka et al., 1974[107] | Japan | Case control in two different populations (5829 and 5440 persons) | Incidence of cerebrovascular insults significantly increased in hypertension (systolic and diastolic). Not increased in overweight and hyperlipemia. |
| Seedat, 1974[99] | South Africa | 500 Africans and 500 Indians (male and female) | Overweight in 34% of the Africans and 24% of the Indians, more frequently in women. Hypertension in 7% of the Africans and 5% of the Indians. Hypertension and obesity more frequent in women than in men. |
| Lovell, 1974[62a] | Australia (Melbourne) | 866 persons, 25% of Italian descent | Untreated patients (men and women) showed significant correlation between systolic and diastolic blood pressure values and overweight, independent of their descent. |
| Rimm et al., 1975[95] | USA | 73,532 women (Tops members) | Close correlation between overweight and blood pressure, even in 20–30-year-olds. |
| Johnson et al., 1975[52] | USA | 546 young persons (black and white) 15–29 years old, case control over a maximum of 9 years | Clear correlation between weight and blood pressure at the first and second date of examination, weak correlation in black men and young white women. |
| Hohlweg-Majert et al., 1975[48] | FRG (Mannheim) | 4749 pregnant women | Obese women had 5 times higher incidence of hypertension than normal-weight women. The higher the weight, the more frequent the complications of pregnancy. |
| Morton and Knudsen, 1975[74] | USA (Oregon) | 15,887 young men (age 16–30 years) | Clear correlation between hypertension (in 3.8% of total study population) and overweight. |
| Weinsier et al., 1976[114] | USA (Texas) | 1483 members of the US Air Force, males | Weak positive correlation between blood pressure and total body fat mass. |
| Berglund et al., 1976[11] | Sweden (Göteborg) | 106 men with hypertension (age 47–54 years) | Higher incidence of overweight in hypertensive patients than in the control group. |
| Glocker et al., 1977[38] | FRG (Ulm) | 357 patients after stroke | Hypertension and overweight 3 times more frequent than in healthy control group. |

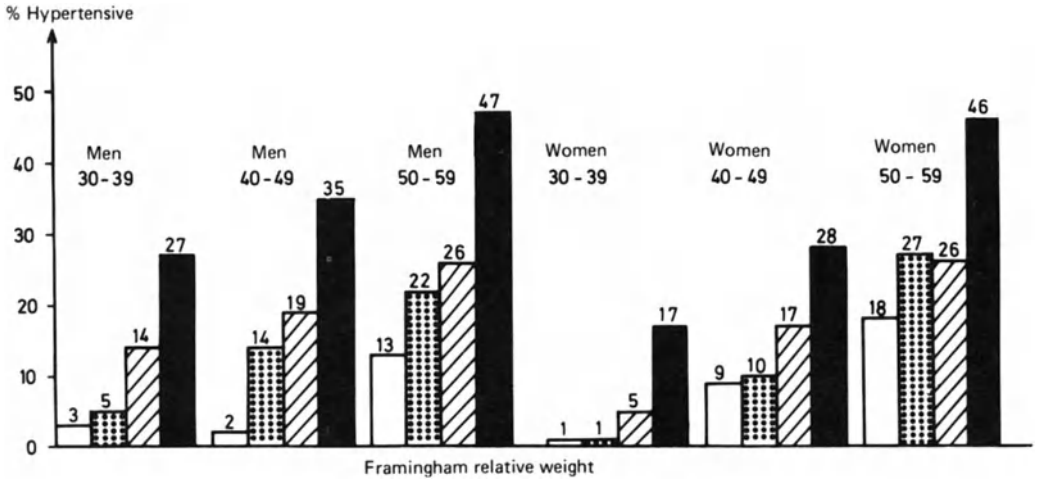



**Figure 4.** Correlation between overweight and hypertension in the Framingham study. ☐ Under 85, ▦ 85–99, ▨ 100–114, ■ over 114. From Kannel WB et al., ref 53

way, Levy and co-workers were able to establish, in a study of 22,741 members of the American Armed Forces, a greater probability for the development of hypertension in previously overweight persons.[59]

The correlation coefficients of systolic blood pressure and overweight are 0.3 in both men and women.[53] In their Tecumseh Study in Michigan, Epstein and co-workers found the highest correlation coefficients between systolic blood pressure and relative body weight: 0.33 for the 30–39 age group.[34] The lowest correlation coefficients were found between 60 and 79 years of age. Similar relations were found for diastolic blood pressure. Tsomondo described a significant ($p < 0.01$) correlation between blood pressure and overweight, as well as a mean increase in systolic and diastolic pressure of 0.3 mm Hg per kg of body weight gain.[110] A larger study in 67,976 adults by Boe in Norway placed the increase in blood pressure at 3 mm Hg systolic and 2 mm Hg diastolic per 10 kg of weight gain.[15] Master demonstrated a clear correlation between excess weight and blood pressure on the one hand, and hypertension and duration of obesity on the other hand.[66]

Tran described a positive correlation between blood pressure and body weight, build index, subscapular skin-fold thickness, and lipoid mass (Fig. 5).[109] A positive correlation between hypertension and Ponderal index** was found by Patzold.[82,83] Epstein[34] and Chiang[21] were likewise able to establish significant correlations for blood pressure, excess weight, and skin-fold thickness. Numerous investigators have found a tendency for rising blood pressure with increasing age.[66,86,115] Figure 6 shows this correlation for obese and normal-weight persons. The relation between blood pressure and body weight appears to be clearer in women than in

$$**\text{Ponderal index (PI)} = \frac{\sqrt[3]{\text{body weight (kg)}}}{\text{body height (cm)}}$$

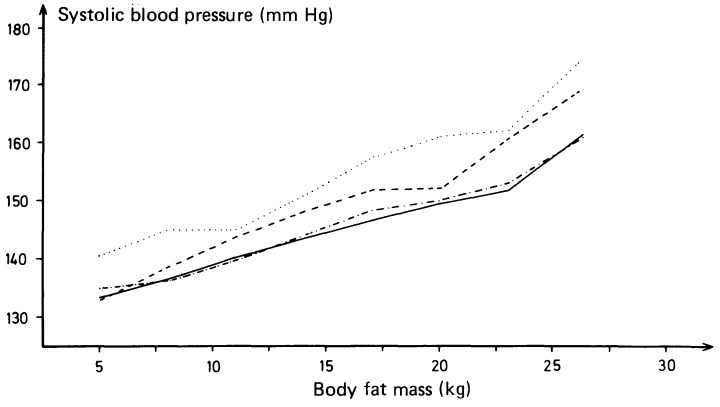



**Figure 5.** Variation of systolic blood pressure as a function of body fat mass. —— Less than 30 years, ·-·-· 30–39 years, ---- 40–49 years, ···· more than 50 years. From Tran MG et al., ref 109

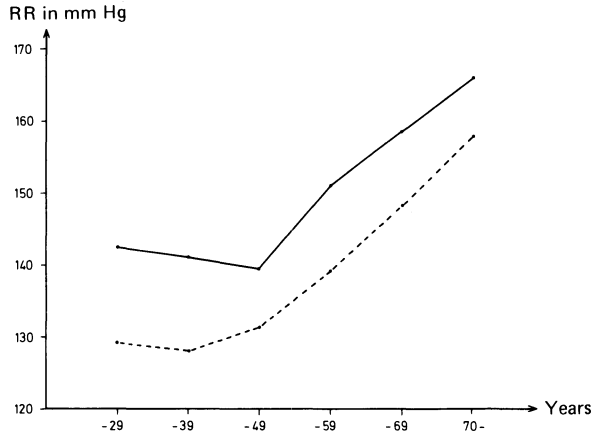



**Figure 6.** Dependence of systolic blood pressure on age in obese (●—●) and normal-weight (●--●) subjects. From Pflanz M, ref 86

men.[34,96] Palmai described a positive correlation between change in skin-fold thickness and change in blood pressure.[80] Johnson reported a weak correlation between blood pressure and body weight for young white women and black men.[52] McDonough found no relation between body weight and blood pressure in black males.[68] Alexander could not find a positive correlation between the two parameters, blood pressure and body weight, in obese patients.[3]

Increased morbidity and mortality rates have been reported where obesity and hypertension coincide.[53,100a] Tibblin found left cardiac hypertrophy three times more frequently in obese than in normal-weight hypertensives.[108] In a study of 4749 pregnant women, Hohlweg-Majert reported hypertension five times more frequently in obese than in normal-weight women.[48] Complications of pregnancy were more frequent as body weight increased.

Hypertension has been confirmed as a risk factor for cerebrovascular accident.[38,107] Tanaka could not confirm that overweight in itself increases the risk of cerebrovascular accident.[107] Huneke[50] and Keys[54] reported an increased incidence of coronary diseases in obesity and hypertension for Middle and Northern Europe, as well as in the USA, but not for Southern Europe. Thus, obese and hypertensive patients are at considerably greater risk for coronary heart disease and cerebrovascular accident than persons with obesity or hypertension alone.

Positive correlations between body weight and blood pressure as well as increased mortality and morbidity in the presence of obesity and hypertension have been corroborated by the overwhelming majority of investigations. Further studies are nevertheless needed to clarify the interplay between hypertension and overweight with respect to cause and effect.

## Blood Pressure and Weight Reduction

As early as 1918, Benedict reported a lowering of blood pressure in 25 men under a regimen of caloric reduction.[9] In 1928 Baumann found a significant fall of blood pressure in most of 183 obese patients with a reducing diet and salt restriction.[8] Evans discovered hypertension in 61 of 100 obese patients, and 75% of those found to be hypertensive reacted to weight loss with a distinct fall of blood pressure.[36] No effect of weight reduction could be detected in patients with severe hypertension.

Dahl made a study of overweight patients with hypertension.[26] Caloric reduction (to 600–800 cal/day) and salt restriction induced a fall of blood pressure more frequently than caloric reduction alone. Salt restriction alone, however, led to a fall of blood pressure in all patients. The correlation between salt intake and blood pressure had already been pointed out by Dahl in earlier studies.[24,25]

Salzano reported a significant reduction of systolic blood pressure in 81% and of diastolic blood pressure in 65% of obese subjects.[98] Further investigations on the interrelationship between blood pressure and weight reduction have been compiled by Chiang.[20]

The Evans County Study achieved greater lowering of blood pressure in a group of 63 obese and hypertensive patients under dietary treatment (700 kcal/day) and salt restriction (about 1 g/day) than in a control group of 64 hypertensive patients.[46,47,69] Both groups received antihypertensive medication. The systolic pressure fell 18 mm Hg in the dietary treatment group and 12 mm Hg in the control group. The average lowering of diastolic blood pressure was 13 mm Hg with a diet, 8 mm Hg without a diet. Miall and co-workers found in younger adults a better correlation than in older people between body weight and blood pressure, as well as between weight change and blood pressure.[71] Bartels and associates conducted a comparative study with a low-calorie mixed diet, a low-calorie formula diet, and total fasting.[6] In all three regimens a distinct fall in blood pressure could be detected along with the weight loss, although the fall in blood pressure was statistically significant only in the group with the reducing diet. In a comparative study by Reisin and co-workers a significant lowering of blood pressure was also achieved by a significant weight reduction without restriction of salt intake.[92] The reported

therapeutic effect was equal for young and old patients of both sexes, for all degrees of hypertension, and for both moderate and extreme obesity.

## Our Results

In our study of 189 overweight patients (108 men; 81 women; average age 35 years; average weight 176%, where 100% = ideal weight according to Metropolitan Life Insurance Company), we found hypertension in 50.9% in accordance with WHO criteria. Of the obese patients, 27.2% were found to have borderline hypertension, while 21.9% were normotensive. We consider these results to be of particular importance, as most of the patients were young adults ranging in age from 15 to 35. Calculating the partial correlation (age factor eliminated) between systolic blood pressure and percentage overweight (Fig. 7), we found significant relationships ($r = +0.372$, $p < 0.01$) in 73 obese males. In 96 women (Fig. 8) we also found significant correlations ($p < 0.001$), with a correlation coefficient of 0.451. The relations between diastolic blood pressure and overweight are also shown in Figures 7 and 8. With correlation coefficients (partial correlation) of +0.414 for men and +0.472 for women, the results were also statistically significant ($p < 0.001$).

The results for diastolic blood pressure and age, excluding weight (partial correlation), were not significant. Among 73 males, the correlation coefficient was +0.106; among 96 females, +0.123. However, the correlations between systolic blood pressure and age among males were significant ($r = 0.231$) with a 5% probability of error; for females the correlation coefficient was 0.301 with an error probability of 1%.

## Discussion

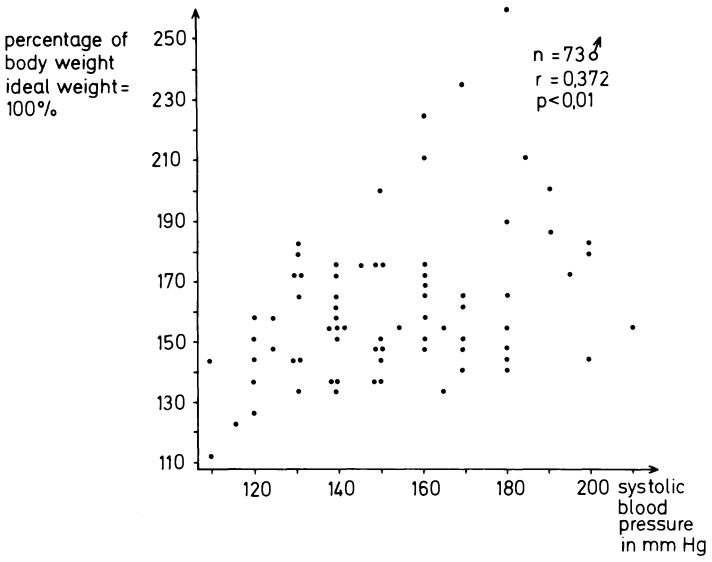
The correlation between overweight and hypertension is well-documented.[15,34,49,52,53,58,59,61,66,80,82,83,96,105,109] Most investigators have found higher morbidity and mortality rates when obesity and hypertension are combined than when obesity or hypertension occurs alone.[48,50,53,54,100a,108]

Elevated blood pressure readings in the obese are frequently attributed to errors of measurement due to increased fat mass in the upper arm, and are thus regarded as artifactual.[14,60,88,90] Most investigators, however, find no direct correlation between degree and direction of the error in indirect blood pressure measurement and upper-arm circumference.[2,4,10,14,37a,53,56,60,78,88,90,91] Numerous direct intra-arterial measurements of blood pressure confirm the positive correlation between overweight and high blood pressure. Comparisons between direct and indirect blood pressure readings in normal and overweight subjects show the error in measurement to be within acceptable limits. The international recommendations for the indirect measurement of blood pressure should be followed, especially in extreme obesity.[30,37a,100a]

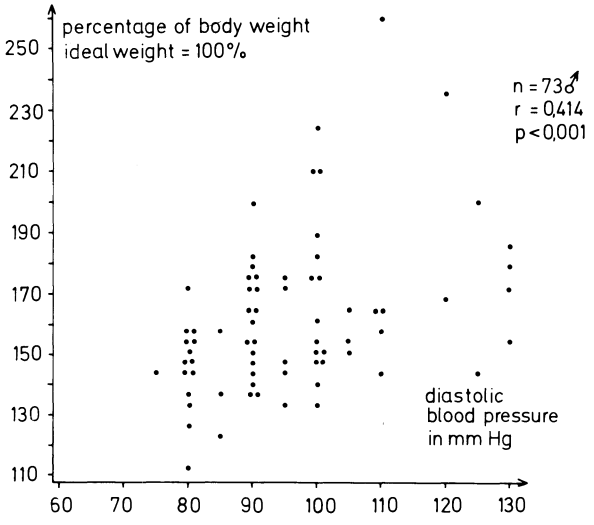
Caloric reduction with weight loss results in a lowering or normalization of blood pressure in almost all cases of essential hypertension with essential obesity[8,9,21,31,32,36,45,46,71,92,98,112] (Fig. 9). Alexander and co-workers found an increase of stroke volume and cardiac output with normal peripheral resistance in obese hypertensives;[4,19] they considered the enlarged vascular system with increased blood and plasma volumes to be the cause. Oxygen consumption and cardiac diameter increase with excess weight. Alexander described the opposite after weight loss: Statistically significant drops in oxygen consumption, blood volume, cardiac output, and arteriovenous oxygen differences were observed in nine extremely obese patients after drastic weight loss (39–84 kg).[5] Blood pressure values dropped as well, while the peripheral vascular resistance remained unchanged. It can thus be seen that hemodynamic factors play an important role in the genesis of hypertension in overweight individuals and in the lowering of blood pressure with weight loss. Dahl and Love[24,25] and Isaacson[51] found a direct connection between high salt intake and the incidence of hypertension. Simply by reducing the salt intake, elevated blood pressure values could be lowered.[26] Medicinal therapy and salt restriction lead to better results in the long-term treatment of hypertension than does treatment with tablets alone.[46]

Pathogenically, hypertension from high salt intake or delayed salt excretion, e. g., sodium retention due to hyperinsulinemia, is attributed to an increase in the extracellular volume, which in turn causes a rise of cardiac output due to the expanded plasma volume. The total peripheral resistance remains unchanged initially. "Cardiac output" hypertension progresses to "resistance" hypertension only when peripheral autoregulatory mechanisms produce vasoconstriction in an attempt to counter the elevated perfusion pressure and increased blood flow.

Simple obesity and essential hypertension often go hand-in-hand. Both obesity and hypertension are amenable to dietetic therapy through caloric reduction and sodium restriction. More aggressive public education and the promotion of good general health

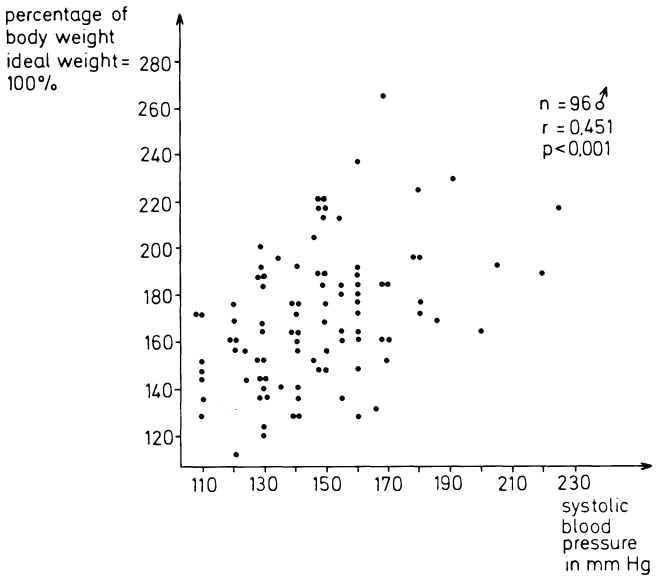



A

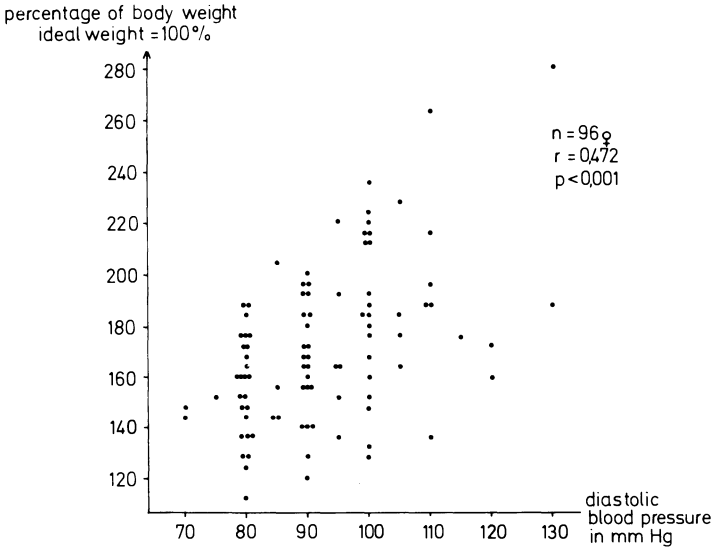



B

**Figure 7.** Correlation between body weight and systolic (**A**) and diastolic (**B**) blood pressure in 189 obese patients. The ideal percentage body weight according to the Metropolitan Life Insurance Company is 100%.




A




B

**Figure 8.** Correlation between age and systolic (**A**) and diastolic (**B**) blood pressure in 189 obese patients.

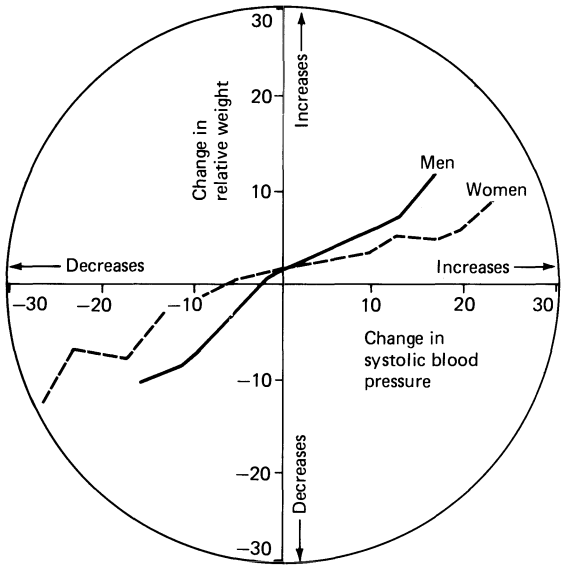



**Figure 9.** Changes in systolic blood pressure level with changes in relative weight, Framingham study. From Gordon T, Kannel WB (1973) Geriatrics 28:80

measures could significantly reduce the prevalence of obesity and hypertension, and thereby lower the high morbidity and mortality rates.

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# Hypertension and Arteriosclerosis

# 5

G. Schettler, H. U. Comberg

## Pathogenesis

According to Doerr,[10–12] arteriosclerosis develops only when suitable conditions exist. These are defined first by a vascular wall factor; second, by a so-called general factor, meaning the hemodynamic and humoral load on the vascular wall; and third, by a barrier factor. The latter is responsible for plasma infiltration and leads to further transformation of the vascular wall. Doerr is of the opinion that fat accumulation in the plasma, as in nutrition atheroma, leads in humans to the so-called storage xanthomatosis, but not to atherosclerosis. Furthermore, according to Doerr, a simple elevation of blood pressure without any general metabolic disorder does not cause arteriosclerosis. A slight relaxation of the internal stability of the arteries would have to be present. More intense forms of sclerosis ensue only if several factors coexist.

There is no doubt that arteriosclerotic changes of the vascular wall are greatly accelerated and intensified by hypertension. There is a hardening of structures, especially in the media, even in the absence of accompanying hyperlipemia. But even normal concentrations of blood lipids are sufficient for additional fats to infiltrate the vascular wall. The changes grow more pronounced with advancing hypertension. Thus, the filtration pressure shares to a large extent the responsibility for the so-called combined lesions of arteriosclerosis. This is also indicated by the existence of specific sites of predilection. Thus, we know that lipid deposits, especially low-density-lipoprotein (LDL) infiltration, are pronounced in the area of the mitral and aortic valves, which must withstand a higher arterial pressure, while the tricuspid and pulmonary valves, which are subjected to venous pressure conditions, show no lipid deposits.[54] Atherosclerosis of the pulmonary arteries develops only in the presence of pulmonary hypertension.[27]

If we view the processes individually, we can reduce the complex pathogenesis to a primary disturbance of the interfacial conditions between the plasma and vascular wall. Certain plasmatic disorders, such as homocysteinemia, hypercholesterolemia, and particularly LDL hyperlipoproteinemia, damage and detach arterial endothelial cells. Evidently the platelets are of particular importance here. According to Ross et al.,[40] the platelets produce a hormone-like factor which, when released, stimulates the proliferation of vascular smooth-muscle cells.

Endothelial cells of different origins appear to have different properties.[4] An essential property of vascular endothelial cells is their ability to produce substances that stabilize the inner surface of the vessels, such as plasminogen activator, prostaglandin, and heparin. Endothelial cells also possess receptors for vasoactive substances such as angiotensin II, for other hormones and neurotransmitters, for lipoproteins and other blood components. The selective transport and metabolism of substances can be demonstrated experimentally as well as in tissue culture. It has also been shown that high-density lipoproteins (HDL; alpha-lipoproteins) and low-density lipoproteins (LDL; beta-lipoproteins) are taken up competitively, and that the endothelial cell can bind, transport, and metabolize large quantities of lipoproteins. In the human endothelium, about 10–11 g of LDL are metabolized. All lipoproteins present in the blood are catabolized in this way. It is clear that disturbances of this endothelial

function must induce changes in the plasma components. As regeneration of normal endothelium is very slow, initial and progressing lesions may have serious consequences through a persistent possibility of damage. Vascular ramifications are particularly susceptible, as endothelial ablations can apparently be caused there by incoming pressure waves. In cases of massive desquamation, endothelial cells can be found circulating in the blood.

Defects in the endothelial cell layer are sealed within a very short time, in seconds to minutes, by thrombocytes. The platelets adhere to the subendothelial connective tissue and then spread out,[4,35-37] triggering complicated chemical processes such as the release of adenosine diphosphate, serotonin, prostaglandin, endoperoxide, thromboxane, and other enzymes. These substances cause the adherence of more blood platelets, making possible the formation of mural thrombi. It is likely that the substances mentioned above also exert an effect on the vascular wall itself or the interior of the vessel. Smooth-muscle cells in the subintima and media contract, and their growth is stimulated. Haust et al.,[25,26] Wissler,[55] and others have dealt with the pathogenetic significance of these smooth-muscle cells. A sequence of events is involved in these combined, complex lesions. Local proliferation of cells, new formation of interstitial substance and fibers, storage of plasma components (especially lipoproteins), cellular decay, hemorrhages, and intramural thromboses form the substrate for the developed atherosclerotic lesion. The focal changes typically seen in humans are probably determined not just by plasma conditions but primarily by hemodynamic factors. The initially significant intramural fibrin release and clot formation, postulated repeatedly since Rokitansky[38,39] and corroborated by many studies,[4,13-15,35-37] are also initiated and accelerated by local elevations in pressure. Time and again we see that the causal sequence for the genesis of atherosclerosis is determined on the one hand by plasmatic factors and on the other by mural factors.

Tissue cultures of smooth-muscle cells have proved important as models. Ross et al.[40] demonstrated that cultures of such cells survive in serum obtained from plasma, but do not proliferate. Only when plasma was made to coagulate in the presence of washed platelets did the platelet-plasma serum prove to be as growth-stimulating as serum extracted from whole blood. The process of characterizing this proliferation-stimulating substance is still going on. It is presumed to be a strongly alkaline, heat-resistant glycoprotein with a molecular weight of about 13,000 daltons. Insulin works in a way similar to this factor. It is noteworthy that the diabetic patient with hypertension and hyperlipoproteinemia is at particular risk for developing arteriosclerosis. The specific role played here by insulin has not yet been determined. The pattern of insulin distribution, in particular, must still be investigated. Tissue cultures may again be of help in this regard.

The proliferation of smooth-muscle cells may induce a healing process in defective endothelial areas; on the other hand, a further transformation of smooth-muscle cells may take place, resulting in the development of xanthoma cells with newly formed elastin and collagen. Today this is regarded as a necessary step in the formation of a fibrous plaque. If local nutritional disturbances cause the plaque to soften, thrombi form in these ulcerated areas. They may be located on the intima or intramurally. The presence of free fatty acids promotes calcium salt deposition, and then the actual process of vascular "calcification" begins. All the processes mentioned above lead to the so-called combined or complicated lesion of arteriosclerosis, which is irreversible and results in extensive loss of arterial function. Thus, narrowing of the lumen, loss of elasticity, and hardening also determine the clinical process of arteriosclerosis. Apparently the fibrous plaque is a precursor of the complicated lesion, whereas this cannot be assumed for the very first lesion, the so-called fatty streaks, which generally are reversible. If an injurious stimulus persists, such as long-term hyperlipoproteinemia, the fatty streaks may undergo further alterations.

All this means that the simple lipoid theory of human arteriosclerosis as advanced by Anitschkow[2,3] and other authors must be modified. There is no doubt, however, that changes in plasma lipoproteins are extremely important in the initial phase as well as in the development of combined lesions. Now, it has been observed that some forms of hyperlipemia scarcely aggravate atherosclerosis in humans, while other very aggressive lipoprotein complexes can have devastating consequences even in adolescents and middle-aged persons. It is now known that these differences are not due to the total concentration of individual plasma lipids such as triglycerides and cholesterol, but that the protein-containing lipid complexes can exert very different effects. Genetic and biochemical studies have helped in understanding the causal interrelationships.

On the basis of investigations in the 1930's by Macheboeuf,[34] Bennhold,[5] and others, Gofman et al.[17-19] have found an atherogenic effect in certain cholesterol-containing plasma lipoproteins. They isolated these substances by ultracentrifuge and found certain pathogenic complexes that can also be demonstrated in humans. According to Bennhold,[5] protein bodies may be the transfer vehicles, and certain apoprotein classes have now been isolated. In

1953 we were able to demonstrate with refined techniques and combined procedures that certain forms of hypercholesterolemia, either inherited or acquired, have a lasting influence on the atherosclerotic process. Some forms of familial hypercholesterolemia, hypothyroidism, certain nephrotic syndromes, diabetic hyperlipoproteinemias, and paraproteinemias were found to be particularly aggressive.[41–44]

Great progress has been made in recent years in the classification of pathogenic hyperlipoproteinemias.[23] Lipoprotein electrophoresis in agarosis has made it possible to separate different lipoprotein classes. Using the analytic ultracentrifuge, Seidel[45] identified distinct concentration minima in the density ranges $d = 1.006$ and $d = 1.063$ g/ml. This led to the fractionation of plasma proteins into three main density classes: the very-low density lipoproteins (VLDL, $d < 1.006$ g/ml), the low-density lipoproteins (LDL, $d = 1.006$–$1.063$ g/ml), and the high-density lipoproteins (HDL, $d = 1.063$–$1.21$ g/ml). Later, this spectrum was subdivided further. The density range 0.90–1006 was subdivided into chylomicrons and true VLDL (boundary density, $d = 0.95$ g/ml); the LDL fraction was subdivided into LDL-1 and LDL-2 at $d = 1.019$ g/ml, and the HDL fraction into the subclasses HDL-2 and HDL-3 at $d = 1.125$ g/ml. Electron microscopy shows all lipoprotein fractions as round particles varying greatly in size from 10,000 Å (chylomicrons) to 75 Å (HDL). Although all lipoprotein fractions contain the three main lipid classes (phospholipids, triglycerides, and cholesterol), they differ markedly in their relative lipid composition as well as in their protein/lipid ratios, which may range between 1:99 (chylomicrons) and 50:50 (HDL). Of greater importance than these differences, however, is their apoprotein composition, which is of major biological significance as will be shown later.

So far, three main families have been differentiated on the basis of apoprotein identification. These can be divided into subgroups further:

1. Lipoprotein A (LP-A), found mainly in the HDL fraction and $\alpha$-lipoprotein band
2. Lipoprotein B (LP-B), the main component of the LDL class with $\beta$ mobility
3. Lipoprotein C (LP-C), probably found as a "pure" family only in the HDL fraction

Apoproteins D and E can be found throughout the density range, i.e., in the VLDL, LDL, and HDL fractions. In terms of their apoprotein composition, the VLDL and chylomicrons represent heterogeneous macrocomplexes with molecular weights up to several million daltons. Undoubtedly one of the most notable achievements of lipoprotein research in recent years has been the success in isolating these apoproteins in their pure form by a combination of laborious physicochemical processes, making them accessible to further biochemical and physiochemical analysis. We now know the amino acid composition and carboyhydrates for all apoproteins (Apo-A I, Apo-A II, Apo-B, Apo-C I, Apo-C II, Apo-C III, Apo-D, and Apo-E) and the primary structure for some of them. These apoproteins range from 7 to 30,000 daltons in molecular weight.

Goldstein and Brown[21] were able to demonstrate in fibroblast cultures that cellular cholesterol synthesis is regulated under normal conditions by so-called receptors. Apo-B–containing lipoproteins, primarily LDL and VLDL, are bound to a specific receptor by their protein component and are incorporated into the cell in the form of endocytotic vesicles. Lysosomal enzymes break down the apoprotein component into amino acids that are released within the cells. Cholesterol esters released from lipoproteins are split, enabling the free cholesterol to reach the microsomes where it inhibits the cellular synthesis of cholesterol. The free cholesterol activates an acetyl-CoA cholesteryl-acyltransferase, so that it can be esterified and stored in the cell. Prostaglandin $E_2$ inhibits the intracellular esterification of cholesterol. The activity of the Apo-B receptor is self-regulated by a feedback mechanism: more Apo-B receptor is formed at the cell surface upon depletion of cellular cholesterol and, conversely, cholesterol enrichment leads to a decrease of receptors; in this way the cell protects itself against being flooded with plasma cholesterol. These feedback mechanisms are also influenced by hypertension, as has been shown both experimentally and in tissue cultures under pressure. Carbon monoxide affects these control mechanisms as well, especially at the most important production site of the vascular wall, the smooth-muscle cell. It accelerates the binding and uptake of LDL and at the same time inhibits its intracellular breakdown. These changes deserve particular attention with regard to the arteriosclerosis-promoting role of cigarette smoking.

Goldstein et al.[22] have done studies on type-II familial hyperlipoproteinemia. In heterozygotes, the number of LDL receptors is reduced by one-half; in homozygotes, they are completely absent. This explains why such persons are so severely threatened by early arteriosclerosis, which is often fatal even in childhood. A rise of blood pressure is not necessary in such states, but it increases the risk, especially in heterozygous hypercholesterolemias. In this hereditary form of hypercholesterolemia, the patients apparently lack the gene necessary for Apo-B receptor synthesis. In view of the doubtlessly genetically de-

termined hypertension, these perhaps double familial afflictions are of great importance in understanding the pathogenesis not only of atherosclerosis in general but also of specific cases. The apparent protective effect of high HDL classes in the arteriosclerotic process remains to be clarified. The HDL classes are not only genetically determined but may also be influenced physically. Distinctly high HDL classes are found in the plasma of athletes under constant physical training, such as long-distance runners. Apparently there are direct correlations between the onset and extent of arteriosclerosis on the one hand, and the concentration of HDL classes on the other. The higher the HDL class (which incidentally is also high in the arteriosclerosis-protected normally menstruating woman), the less danger of arteriosclerosis for the patient. Remarkably, additional pressure rises do not cause increased susceptibility in such cases. The protective role of these lipoprotein classes needs further detailed clarification. It is noteworthy that the resistance to arteriosclerosis observed decades ago by Russian authors in patients with cirrhosis of the liver or chronic hepatic disease has again become of topical interest, as these patients manifest high HDL classes.

In summary, it may be concluded that the components of the pathogenetic risk triad of hypertension, hyperlipoproteinemia, and heavy cigarette smoking influence one another to a significant degree. Thus, the disproportionate increase in risk in the presence of these three factors is relevant from a biochemical, pathologicoanatomical as well as a clinical point of view. As a result, a change in any one of these risk factors, but particularly in all three, must be of protective significance in the arteriosclerotic process. Second-order risk factors such as diabetes mellitus, lack of exercise, and psychic and socioeconomic stress may also exert effects through the same mechanisms. It follows from these discussions that hypertension performs a key function through its increase of the filtration pressure. All prophylactic and therapeutic measures must be based on these interrelations. They will be discussed in the chapters that follow, after a review of epidemiologic results.

## Prognostic Aspects of Hypertension

Hypertension is one of the most important risk factors in the development of arteriosclerosis. Cardiovascular diseases are responsible for nearly half (47%) of all mortalities, about two-thirds of which (25%) are caused by coronary artery sclerosis, and of the remaining third (15%) by cerebral artery sclerosis. According to Heyden,[28] hypertension ranks third among the risk factors for myocardial infarction and first for stroke (Table 1).

**Table 1.** Gradation of Risk Factors

| |
|---|
| For myocardial infarction |
| 1. Hypercholesterolemia |
| 2. Inhalation of cigarette smoke |
| 3. Hypertension |
| 4. Hyperglycemia/diabetes mellitus |
| 5. Hyperuricemia/gout |
| 6. Obesity (indirect) |
| For stroke |
| 1. Hypertension |
| 2. Ischemic heart disease |
| 3. Diabetes mellitus |
| 4. Obesity |

From Heyden S, ref 28.

Before examining in detail the correlation between hypertension and cerebral apoplexy on one hand and myocardial infarction on the other, let us review some figures on the overall prognosis of the hypertensive patient.

The data available on the spontaneous course of hypertension are limited, particularly for *severe* forms of the disease, as it would be irresponsible to deprive these patients of necessary treatment simply to study the untreated course of the disease. Therefore, one must resort to earlier observations made at a time when effective antihypertensive drugs were not yet available or were still undergoing clinical testing. Leishman[33] did a very detailed analysis by following over a period of 5 years the fate of 124 untreated hypertensive individuals with diastolic blood pressures above 120 mm Hg. Figure 1 shows clearly that survival rates decrease with increasing blood pressure. Whereas all male patients with malignant hypertension died within 1 year, the survival rate for the same period was over 40% for men with diastolic blood pressure values of 120–129 mm Hg. Women seem to have better tolerance for high blood pressure; their survival rates were higher than the men's in all blood pressure groups.

A study of causes of death yielded the following picture:[33] In male hypertensives with diastolic pressures above 149 mm Hg, death results mainly from cerebral complications, usually in the form of a massive hemorrhage occurring within the first year. Patients with diastolic blood pressure between 130 and 149 mm Hg die mainly from renal failure, usually within 3 years. In the group characterized by diastolic blood pressure readings between 120 and 129 mm Hg, the cerebral complication is again the principal cause of death, occurring exclusively in the

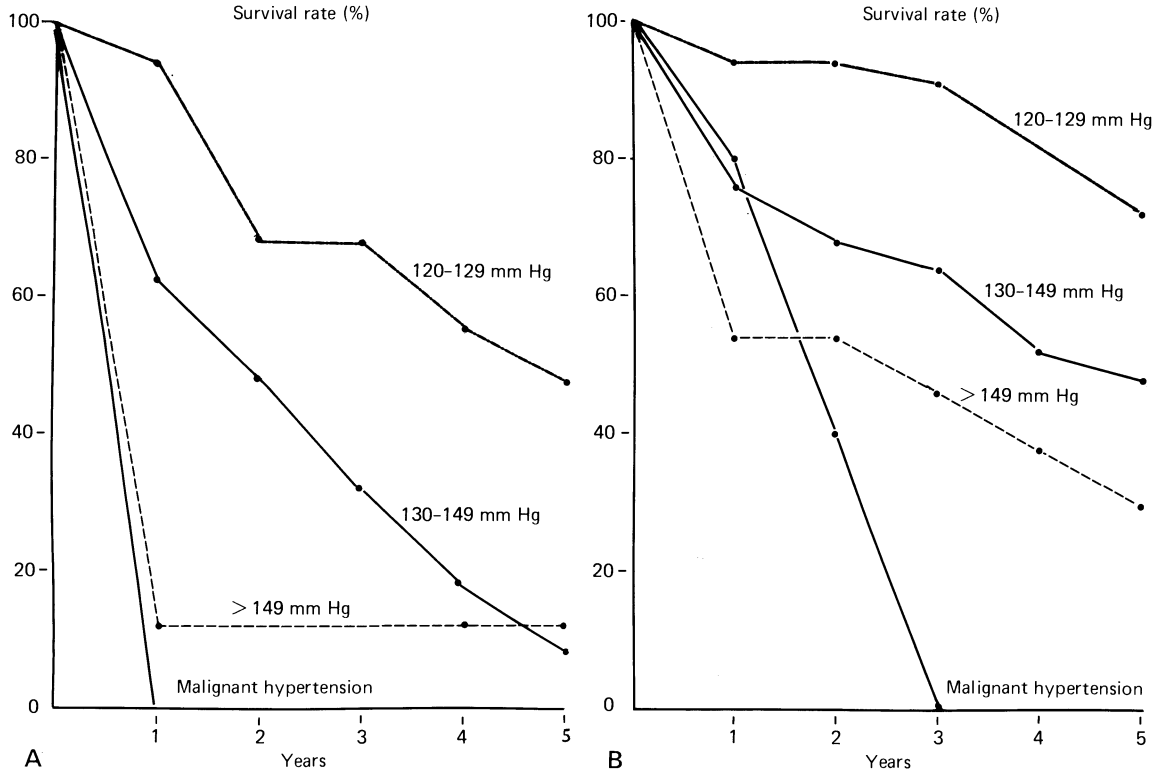


**Figure 1.** Survival rates of hypertensive patients (**A**, male; **B** female) as a function of diastolic blood pressure. From Leishman AW, ref 33

later course (3 to 5 years or more); it is usually the result of softening secondary to cerebral infarction.

In women, the highest mortality is from cerebral complications in all hypertensive groups. Thus, the hypertensive patient with diastolic blood pressure over 150 mm Hg succumbs to massive cerebral hemorrhage even before renal failure or a stenosing coronary artery sclerosis has had a chance to develop.[9]

Since the introduction of effective antihypertensive drugs, and with their consistent use, cases of *severe* hypertension are becoming less frequent, and medical attention has shifted increasingly to the large group of *mild* to *moderate* hypertension cases. Representative values for these groups were compiled in the Build and Blood Pressure Study[8] released in 1959 by 26 American and Canadian insurance companies and based on data of 3,900,000 living and 102,000 deceased policy holders (age at insurance, 15–69 years) between 1935 and 1954. Figure 2 shows a clear rise of excess mortality with increasing blood pressure even in mild to moderate hypertension (upper limit 168–177 mm Hg systolic and 103–113 mm Hg diastolic). Excess mortality is defined as the percentage increase of mortality within a given group—in our case, the different blood pressure groups—relative to the normal population. Qualitatively, the dependence of excess mortality on blood pressure is similar in men and women. However, the women display a markedly lower excess mortality than men in all blood pressure groups. No difference in prognostic value between systolic and diastolic blood pressure can be ascertained. The study further indicates that there is no "normal blood pressure" in the epidemiologic sense; rather, the risk of degenerative vascular disease increases steadily over the entire blood pressure range.

As a result of antihypertensive therapy, massive cerebral hemorrhage and renal failure are becoming less important as complications of high blood pressure. Medical interest is increasingly being focused on the consequences of mild to moderate hypertension—stroke with encephalomalacia and, above all, myocardial infarction. In the sections below we shall review the epidemiologic correlations between blood pressure and these two important syndromes of atherosclerotic origin.

## Blood Pressure and Stroke

Stamler[47] reported on a study of 110 Chicago citizens who died between ages 45 and 64 and in whom stroke was the direct cause of death or at least a con-

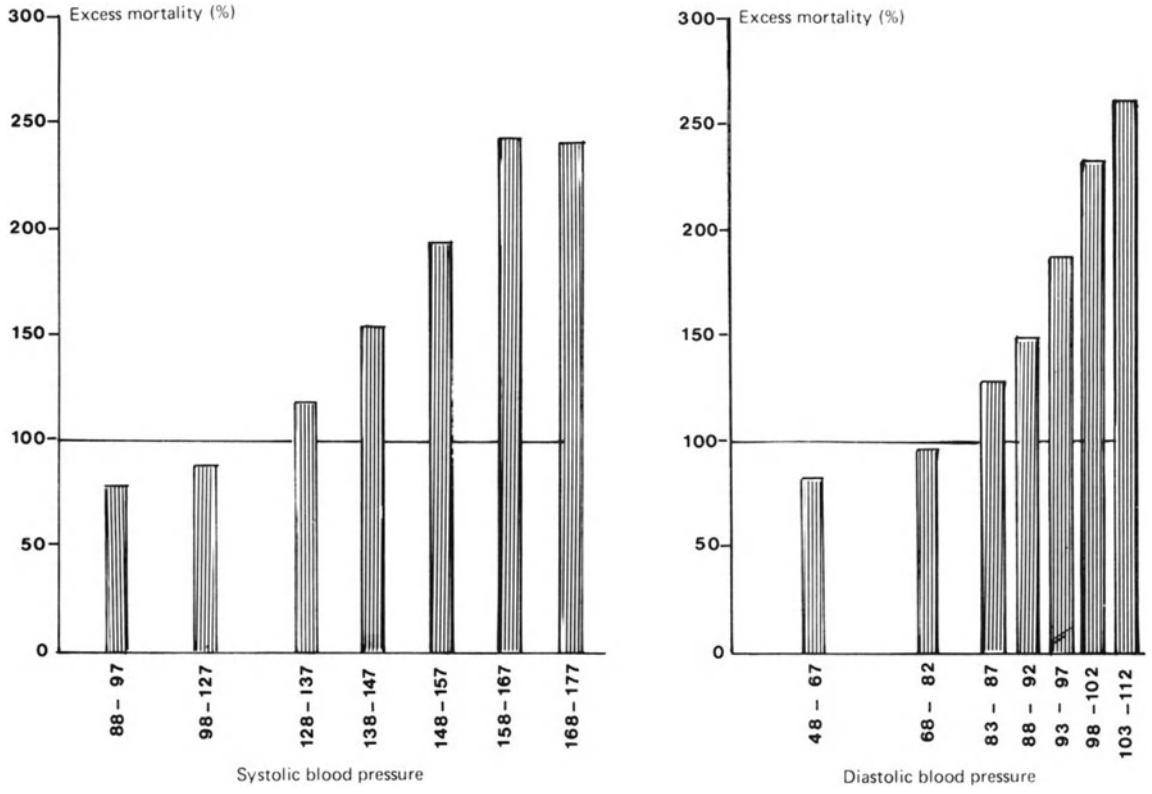


**Figure 2.** Excess mortality of the hypertensive patient as a function of systolic and diastolic blood pressure. From Build and Blood Pressure Study, ref 8

tributing factor. Progressive hypertension could be confirmed in 69% of the cases, either by statements on the death certificate or by questioning the attending physicians.

Results of the Peoples Gas Light and Coke Company Study done on 1329 men, 40 to 59 years old, who were healthy at the start of the study, showed over a 6-year observation period a five times higher death rate from cerebrovascular disease in the group with diastolic blood pressure values of 95 mm Hg or more than in the group with values below 80 mm Hg.[6]

The North American insurance companies Build and Blood Pressure Study[8] confirms the marked increase in cerebrovascular accidents with rising blood pressure.

In summary, it can be said that hypertension—even in its mild forms—must now be considered one of the most important risk factors in apoplectic stroke.

## Blood Pressure and Ischemic Heart Disease

A large number of epidemiologic studies show a clear correlation between blood pressure and ischemic heart disease. From the abundance of data, we shall cite some figures given by the American Pooling Project,[30] a summary of several prospective studies. A total of 7581 white men, aged 30 to 59 years at the beginning of the study and initially free from clinically demonstrable heart disease, were followed over a 10-year period. Figure 3 shows a marked increase of ischemic heart diseases (fatal and nonfatal myocardial infarction, including sudden death) with rising diastolic pressure. Compared with the group with low diastolic readings (below 84 mm Hg), the risk of ischemic heart disease is twice as high in the group with diastolic values of 95–104 mm Hg, and almost four times as high in the group with values above 105 mm Hg. A similar correlation between blood pressure and cardiovascular disease is seen for systolic values. Figure 4 shows corresponding results from the Framingham Study based on observations in 4994 men and women (age 30–59 at the beginning of the study) over a period of 10 years.[31]

Stamler[49] confirms the equivalent prognostic value of the diastolic and systolic blood pressures. In the Peoples Gas Company Study, the diastolic and systolic blood pressure readings have an equal prognostic value in terms of cardiovascular disease

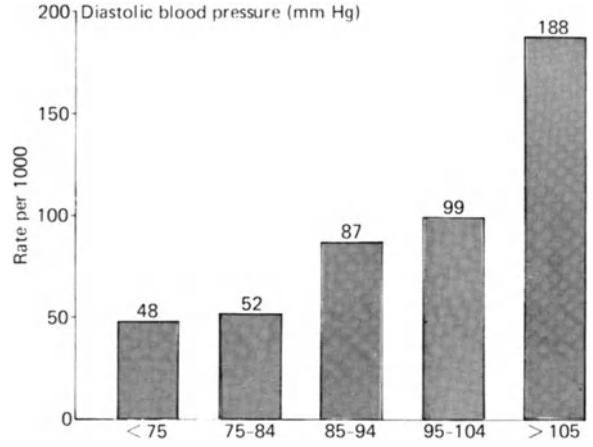


**Figure 3.** Correlation between rate of myocardial infarction and diastolic blood pressure. From Pooling Project, ref 3.

risk. If both the diastolic and systolic pressure are considered simultaneously, then men with elevated diastolic values—with or without a concomitant rise of systolic pressure—run a higher cardiac risk than normotensive men. In most cases, however, rises in diastolic pressure are accompanied by a corresponding rise of systolic pressure. An elevation of the systolic blood pressure with no accompanying rise of diastolic pressure—a condition called "pure systolic hypertension"—is found in 15% of the hypertensive men. As this form of hypertension develops in most cases from a marked reduction in the elasticity of the large arteries secondary to severe arteriosclerosis, it can be understood why this group runs a higher risk than expected from the diastolic values. Furthermore, this study indicates that the risk of

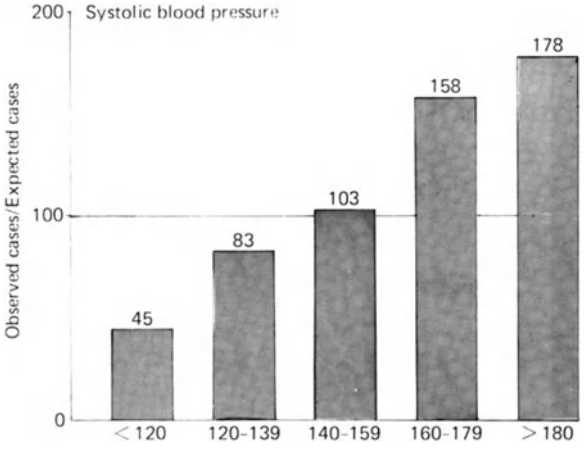


**Figure 4.** Correlation between ischemic heart disease and systolic blood pressure. From Framingham Study, ref 31

cardiovascular mortality increases if—most probably as a direct consequence of hypertension—signs of manifest or presumed cardiac damage (e.g., nonspecific ECG abnormalities) are present in addition to the elevated blood pressure.

## Labile Hypertension in Adolescence

The view that adolescents usually have a labile hypertension that requires no medical attention must definitely be corrected. Stamler[48] reports on 764 employees of the Peoples Gas Company in Chicago whose blood pressure readings at the start of employment were compared with readings taken 20 years later. A close correlation was found between individual readings, i.e., persons who had hypertensive blood pressures when examined initially were still in the hypertensive range 20 years later.

Heyden[29] conducted a study in Evans County, Georgia, in which over one-third of the 30 juvenile labile hypertensives were found to have developed established hypertension with vascular complications after 8 years of observation. During this period, two young women died of cerebral hemorrhage during childbirth. One-third of the subjects became normotensive, while the rest showed no change in their labile blood pressure values. In the normotensive control group, on the other hand, only 4 of 30 adolescents showed a rise of blood pressure; there was not a single case of established hypertension with vascular complications. These figures show that while not every labile hypertensive develops established hypertension, adolescents with labile blood pressures definitely warrant supervision to determine whether therapeutic intervention is needed.

## Effects of Chronic Antihypertensive Therapy

### Severe Hypertension

When we view the effects of adequate antihypertensive therapy against the consequences of untreated hypertension, there is no longer any doubt that the mortality of patients with severe hypertension, especially of the malignant form, has been dramatically lowered. This has been clearly demonstrated in numerous studies.

From the abundance of examples, one may cite the study of Hany et al.,[24] in which 97 patients with malignant hypertension were followed over 8 years. Of the 97 patients, 53 received adequate and regular

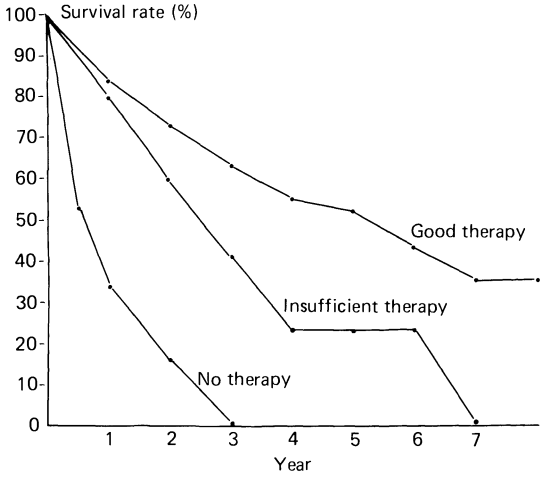


**Figure 5.** Dependence of survival rates of malignant hypertensive patients on therapy. From Hany A et al., ref 24

therapy; 20 patients received inadequate medication at irregular intervals, and 24 received no treatment. The result: all 24 of the untreated patients had died after 3 years, over 40% of the inadequately treated group and over 60% of the adequately treated group were still alive after the 3-year period (Fig. 5).

Very similar results were reported in a Mayo Clinic study.[16] Sixty-four patients with malignant hypertension (grade IV fundus) and 97 with pronounced benign hypertension (grade III fundus) received antihypertensive treatment for 6 years. The results were compared with those of Keith et al.[32] on the spontaneous course of comparable hypertensive

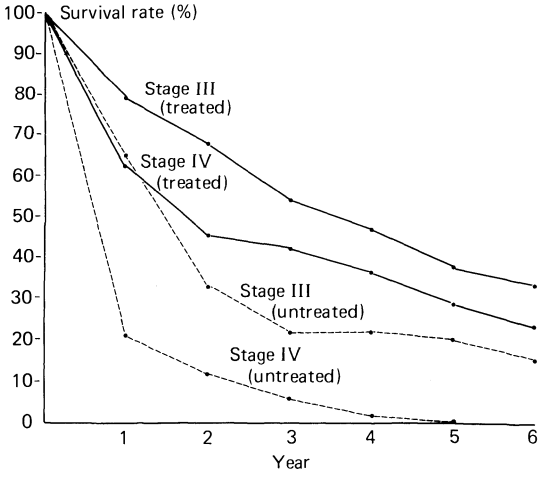


**Figure 6.** Survival rates of treated malignant (stage IV) and benign (stage III) hypertensive patients, compared with untreated malignant hypertensives. From Mayo Clinic Study, ref 16

groups (Fig. 6). It was found that survival rates were markedly improved by antihypertensive therapy. As expected, the therapeutic benefit was greatest in the group with malignant hypertension. After 3 years, over 90% of the untreated patients in the Keith et al. study had died, while over 40% in the treated group (grade IV fundus) were still alive.

The impressive reduction of mortality achieved by antihypertensive therapy in these severe forms of hypertension is attributable to a drastic reduction of massive cerebral hemorrhage in particular, as well as of progressive renal failure.

## Mild and Moderate Hypertension

The Veterans Administration Cooperative Study[52,53] shows a convincing reduction of morbidity and mortality by antihypertensive therapy in men with diastolic blood pressures between 115 and 129 mm Hg at the beginning of the study. In 70 hypertensives treated by placebo (average blood pressure 187 mm Hg systolic and 121 mm Hg diastolic at start of study; no significant fall of blood pressure under placebo therapy), 27 cases of severe cardio-, cerebro- and renovascular disease developed, 4 of which had fatal outcomes. In the group of 73 men (average blood pressure 186 mm Hg systolic and 121 mm Hg diastolic at start of study) who received active treatment there were no deaths and there was only one case of cerebrovascular thrombosis and another of serious drug intolerance. Systolic and diastolic blood pressure could be lowered promptly and remained at a relatively low level during the study. After 24 months, mean reductions in blood pressure of 43 mm Hg systolic and 30 mm Hg diastolic were demonstrated, corresponding to a mean therapeutic blood pressure of 143 mm Hg systolic and 92 mm Hg diastolic. In view of these highly significant results, it became necessary to put the placebo group under active therapy as well. Therefore, the study of the placebo group ended sooner than planned with a mean observation period of only 18 months. A significant lowering of the morbidity and mortality risks by antihypertensive therapy was also reported among men in the quite common blood pressure range of 90–114 mm Hg diastolic. During a mean observation period of 40 months, the placebo group of 194 patients had 56 cases of severe cardio-, cerebro- and renovascular disease and 19 deaths; 20 patients developed diastolic blood pressures in excess of 124 mm Hg and had to be transferred to active therapy. In the 186 actively treated patients there were only 22 cases of cardio- and cerebrovascular disease and 8 deaths. Calculations based on mortality curves for a 5-year observation period show that

the morbidity risk was reduced from 55% to 18% by antihypertensive therapy.

Before drawing any general conclusions from these results, some restrictions must be noted and clarified. Antihypertensive therapy is unequivocally successful only against complications associated directly with hypertension: Diseases such as cardiac failure, progressive renal damage, progressive hypertension with neuroretinopathy or encephalopathy, massive cerebral hemorrhage, and aortic aneurysm were found only in the control groups. Complications associated with arteriosclerosis, such as ischemic myocardial disease, conduction disturbances and atrial fibrillation, occurred with comparable frequency in both groups (13 cases of ischemic heart disease in the placebo group as opposed to 11 in the therapy group). This may be explained in part by the short duration of the study and the high average age of the patients (51 years) at the beginning of the study.

If the patients are divided into two blood pressure subgroups, the efficacy of therapy as related to overall morbidity is limited to the group with moderate hypertension (105–114 mm Hg diastolic). In patients with slight elevations of blood pressure (90–104 mm Hg diastolic), the therapeutic results are slightly but not significantly better than in the control group. The validity of the Veterans Administration Cooperative Study[52,53] is further limited by the small number of selected patients who sought treatment at the VA hospitals and who therefore must be classified as sicker and thus at higher risk than the average population. The study included no women at all and only a small number of young adults.

Smith[46] reports similar results from the US Public Health Service Hospitals Cooperative Study, which was conducted as a double-blind study on 389 patients with mild hypertension (90–115 mm Hg diastolic) over a 7- to 10-year period. The majority of the patients (80%) had relatively low initial diastolic blood pressures of 90–105 mm Hg. Antihypertensive therapy produced an average diastolic blood pressure decrease of 10 mm Hg. No fall of blood pressure was recorded in the placebo group. In contrast to the Veterans Administration Cooperative Study, the US Public Health Service study was done only on patients who were otherwise healthy. The average patient age was 44 years (range 21–55 years) and thus 7 years below that in the Veterans Administration study. Moreover, 20% of the study population were women. Table 2 shows the distribution of initial disease manifestations during therapy. A total of 146 first manifestations were recorded—56 cases (29%) in the active-therapy group and 90 cases (46%) in the placebo group. When these cases are subdivided into direct complications of hypertension (stroke, left ventricular hypertrophy, retinopathy) and direct complications of arteriosclerosis (myocardial infarction, angina pectoris), it is clearly seen that the reduction of morbidity under active therapy is due essentially to the reduction of the complications of hypertension. Results were particularly good for left ventricular hypertrophy, the incidence of which was reduced by more than 50% with antihypertensive therapy. No difference was found in the rate of arteriosclerotic complications; 7 myocardial infarctions occurred in the active-therapy group, and 6 in the placebo group.

**Table 2.** First Manifestations of Disease during Active Therapy vs. Placebo Therapy

| | Active Therapy | | Placebo | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Total number of patients | 193 | | 196 | |
| Number of disease cases | 56 | 29 | 90 | 46 |
| *Complications of hypertension* | 29 | 15 | 65 | 33 |
| Stroke | 0 | | 2 | 0.5 |
| LVH | 9 | 5 | 23 | 12 |
| Repolarization disturbance | 10 | 5 | 22 | 11 |
| Cardiac enlargement in x-ray | 10 | 5 | 15 | 8 |
| Retinopathy | 0 | | 3 | 2 |
| *Complications of arteriosclerosis* | 27 | 14 | 25 | 13 |
| Myocardial infarction (nonfatal) | 6 | 3 | 5 | 3 |
| Myocardial infarction (fatal) | 1 | 0.5 | 1 | 0.5 |
| Sudden death | 1 | 0.5 | 1 | 0.5 |
| Angina pectoris (CHD) | 18 | 9 | 18 | 9 |
| Transient cerebral ischemia | 0 | | 0 | |
| Intermittent claudication | 1 | 0.5 | 0 | |
| Malignant hypertension (>130 mm Hg diastolic) | 0 | | 11 | 6 |

From Smith WM, ref 46.

Twelve patients in the placebo group showed a malignant rise of blood pressure (> 130 mm Hg diastolic) during the observation period; with antihypertensive therapy, no such elevations occurred (Table 2).

## Conclusions

Many epidemiologic studies show that the risks of cardio- and cerebrovascular morbidity and mortality increase in direct proportion to the rise of blood pressure, even at relatively low levels. Besides the direct damage caused to the heart and circulation, hypertension (combined with a high cholesterol level) accelerates the development of arteriosclerosis, which is responsible for the majority of cardiovascular and cerebrovascular complications. The Veterans Administration Cooperative Study[52,53] and the US Public Health Service Hospitals Cooperative Study[46]—so far the only completed prospective, controlled therapy studies—clearly show that antihypertensive therapy is capable of significantly reducing the direct consequences of hypertension, such as congestive heart failure, renal failure, and cerebrovascular accident, which have a high incidence when diastolic pressures exceed 104 mm Hg.

In the wide field of borderline hypertension (90–104 mm Hg diastolic) where arteriosclerosis-induced complications such as myocardial infarction predominate, the question of the indication for drug therapy must remain open. In this large group, therapy must be individualized with consideration for additional factors such as age, sex, family history, and the presence or absence of organ damage. If further risk factors are present such as hypercholesterolemia, cigarette smoking, and diabetes, the prognosis is much less favorable and therapy therefore more urgent. The prognosis is likewise poor in the presence of organ damage already caused by hypertension. ECG abnormalities such as left ventricular hypertrophy, diffuse ischemic signs, and arrhythmias are particularly frequent. Optic fundus changes and renal injuries are rare in this blood pressure group. Angina pectoris and transient cerebral ischemia indicate an already severe arteriosclerosis and warrant careful antihypertensive therapy. Further large-field studies are needed; some, like the Hypertension Detection and Follow-Up Program,[56] will be concluded shortly.

Three important questions remain to be answered concerning the connection between hypertension and arteriosclerosis:

First, is antihypertensive therapy started in adulthood too late, and would it be possible with proper treatment, to at least slow the progress of arteriosclerosis in the juvenile hypertensive?

Second, does the treatment of *mild* hypertension in adults in whom considerable arteriosclerosis is already present have a negative rather than positive effect owing to the further iatrogenic restriction of circulation?

In the Veterans Administration Cooperative Study,[52,53] the therapy group included five surviving myocardial infarction patients, while the placebo group had only two. Stewart[50] makes similar observations. Breckenridge et al.[7] report an increase in myocardial infarctions and sudden deaths as well as a decrease in cerebrovascular complications in a group of patients treated with various antihypertensive drugs. In hypertensive patients treated with postganglionic sympathetic blocking agents, Goldberg and Raftery[20] found signs of impaired cerebral and coronary arterial blood flow which they interpreted as a predisposition to cerebral and myocardial infarction.

Third, the drugs administered must be tested individually for as-yet-known side effects during long-term use. Especially in mild hypertension there is danger that therapeutic gains might be offset by side effects.

In antihypertensive therapy with diuretics, Ames and Hill[1] observed a rise of cholesterol levels with no accompanying hemoconcentration. A promising new therapy has been offered by the introduction of $\beta$-blocking drugs. Stewart[51] reports on a therapy study in 169 hypertensive patients (average diastolic pressure 124 mm Hg before therapy and 101 mm Hg during therapy) in whom the myocardial infarction rate over a 5-year observation period could be reduced from 31% without propranolol to 7.5% with propranolol as the basic medication.

Even if an effective long-term drug therapy is found for mild forms of hypertension, it remains to be determined whether human, technical, and financial resources, as well as public cooperation, could be mobilized to the degree necessary to institute high-quality diagnosis and treatment on a broad scale. Only if this broad base is established can preventive medicine be fully effective.

## Addendum

Since this book went to press, the results of the Hypertension Detection and Follow-Up Program (HDFP), the largest and most costly blood pressure study done to date, have been made public. In view of the tremendous importance of these results regarding the previously controversial range of mild hypertension, their discussion should not be omitted.[29a]

A total of 10,940 patients with diastolic blood

pressures (DBP) of 90 mm Hg or more took part in the program. At the start of the study, which ran for 5 years, the participants ranged in age from 30 to 69 years (mean age 51 years). They were randomly assigned to two groups. The first group of 5485 patients was given intensive treatment in 14 special centers according to a "stepped care" regimen (SC group), which began with a diuretic, followed by the stepwise addition of reserpine or methyldopa, vasodilators, and antiadrenergic drugs. The goal of this regimen was to reduce the DBP to 90 mm Hg in patients entering with pressures of 100 mm Hg or more, and to obtain a 10-mm decrease in those entering with pressures of 90 to 99 mm Hg, so that the lowest goal DBP was 80 mm Hg. Treatment was administered by specially trained nurses and paramedical personnel in accordance with a detailed manual. The center physician was called upon only in cases requiring a therapeutic or diagnostic decision that was beyond the scope of the manual. This was seldom necessary.

The 5455 patients of the second group were informed of their high blood pressure as measured at entry and were advised to consult their personal physicians for treatment. This was the "referred care" or RC group. In both groups a thorough clinical examination was performed by the center physician at entry and after 2 and 5 years.

Two points should be noted that distinguish the HDFP from other blood pressure studies. First, there were no restrictions in the selection of participants, i.e., the study included healthy persons as well as those suffering from disease (including cardiovascular diseases). Thus, the participants constituted a representative cross-section of the population. Second, there was no control group in the traditional sense, for no placebos were administered. Nevertheless, it could be assumed when planning the study that the RC group would receive less intensive therapy from their family physicians, thus permitting a comparison to be made with the SC group.

The hypertensive patients were divided into three subgroups (strata I–III). The great majority (72%) were in stratum I, the "mild" range, with DBPs of 90–104 mm Hg (Table 3). After 5 years the average DBP in the SC group was 84 mm Hg, and in the RC group, 89 mm Hg.

**Table 3.** Assignment of Hypertensive Patients into Three Blood Pressure Groups at Entry

| Stratum | DBP (mm Hg) | Sample Size | |
|---|---|---|---|
| | | No. | % |
| I | 90–104 | 7825 | 71.5 |
| II | 105–114 | 2052 | 18.8 |
| III | 115+ | 1063 | 9.7 |

From HDFP, ref 29a.

The results of the study show that the 5-year all-cause mortality was 17% less for all SC participants compared to RC participants as a result of systematic, intensive antihypertensive therapy. When considered by blood pressure subgroup, the greatest reduction of mortality, 20%, was obtained in the mild hypertensives (90–104 mm Hg diastolic). The mortality reduction was lower in the subgroups with higher DBPs: 13% in the group with 105–114 mm Hg and 7% in the group with 115 mm Hg or higher (Table 4).

This result, which may seem curious at first, is explained by the fact that the referred patients with more severe hypertension received more energetic treatment from their personal physicians than did those with mild hypertension, thus reducing the differences between the two groups.

When the patients were subdivided by race, sex, and age, no reduction of overall mortality was found among white women or in the 30–49 age group (Table 5). In the case of white women, this is explained in part by their lower hypertension-related cardiovascular mortality compared to men, and by the superior blood pressure reduction in white women of the RC group as compared to the other groups. Thus, the blood pressure of the white

**Table 4.** Mortality from All Causes for Stepped Care (SC) and Referred Care (RC) during 5-Year Period by Diastolic Blood Pressure (DBP) at Entry

| DBP at Entry (mm Hg) | Sample Size (No.) | | Deaths (No.) | | Death Rates (%) | | Reduction of Mortality for SC Group (%) |
|---|---|---|---|---|---|---|---|
| | SC Group | RC Group | SC Group | RC Group | SC Group | RC Group | |
| 90–104 | 3903 | 3922 | 231 | 291 | 5.9 | 7.4* | 20.3* |
| 105–114 | 1048 | 1004 | 70 | 77 | 6.7 | 7.7 | 13.0 |
| 115+ | 534 | 529 | 48 | 51 | 9.0 | 9.7 | 7.2 |
| Total | 5485 | 5455 | 349 | 419 | 6.4 | 7.7* | 16.9* |

*$p < 0.01$.
From HDFP, ref 29a.

**Table 5.** Mortality from All Causes for Stepped Care (SC) and Referred Care (RC) During 5-Year Period by Race, Sex, and Age at Entry

| Race, Sex, or Age | Sample Size (No.) | | Deaths (No.) | | Death Rates (%) | | Reduction of Mortality for SC Group (%) |
|---|---|---|---|---|---|---|---|
| | SC Group | RC Group | SC Group | RC Group | SC Group | RC Group | |
| Black men | 1064 | 1084 | 112 | 140 | 10.6 | 13.0 | 18.5 |
| Black women | 1344 | 1354 | 70 | 98 | 5.2 | 7.2 | 27.8 |
| White men | 1892 | 1861 | 109 | 126 | 5.8 | 6.8 | 14.7 |
| White women | 1185 | 1156 | 58 | 55 | 4.9 | 4.8 | −2.1 |
| Ages 30–49 | 2429 | 2374 | 81 | 82 | 3.3 | 3.5 | 5.7 |
| Ages 50–59 | 1852 | 1909 | 115 | 159 | 6.2 | 8.3 | 25.3 |
| Ages 60–69 | 1204 | 1172 | 153 | 178 | 12.7 | 15.2 | 16.4 |

From HDFP, ref 29a.

women in the RC group was consistently below 90 mm Hg, which was not the case in any other group. In the 30–49 age group, the death rates were so low—3.3% in the SC group and 3.5% in the RC group—that no difference could be discerned. By contrast, in the older patients and the other race and sex groups, the all-cause mortality was found to be markedly reduced by antihypertensive therapy (Table 5).

On analysis of cause-specific mortality it was

**Table 6.** Number of Deaths by Cause for All Blood Pressure Ranges and for Stratum I

| Cause of Death | Strata I–III | | Stratum I | |
|---|---|---|---|---|
| | SC Group | RC Group | SC Group | RC Group |
| Cerebrovascular diseases | 29 | 52 | 17 | 31 |
| Myocardial infarction | 51 | 69 | 30 | 56 |
| Other ischemic heart diseases | 80 | 79 | 56 | 51 |
| Hypertensive heart disease | 5 | 7 | 5 | 5 |
| Other hypertensive diseases | 4 | 7 | 2 | 3 |
| Other cardiovascular diseases | 26 | 26 | 12 | 19 |
| *All cardiovascular causes of death* | 195 | 240 | 122 | 165 |
| Renal diseases | 15 | 10 | 7 | 5 |
| Diabetes mellitus | 5 | 10 | 4 | 8 |
| Neoplastic diseases | 61 | 74 | 45 | 57 |
| Breast cancer | 2 | 5 | 2 | 4 |
| Gastrointestinal diseases | 11 | 20 | 9 | 15 |
| Respiratory diseases | 13 | 17 | 9 | 10 |
| Infectious diseases | 6 | 3 | 4 | 2 |
| Accidents, suicides, and homicides | 26 | 25 | 20 | 17 |
| Other noncardiovascular diseases | 17 | 20 | 11 | 12 |
| *All noncardiovascular causes of death* | 154 | 179 | 109 | 126 |
| Total | 349 | 419 | 231 | 291 |

From HDFP, ref 29a.

found that the reduction was due mainly to a decline in the number of deaths from cerebrovascular diseases and myocardial infarction. Thus, in stratum I (90–104 mm Hg) there were 31 deaths from cerebrovascular disease and 56 deaths from myocardial infarction in the RC group, compared to only 17 and 30 deaths from respective causes in the SC group (Table 6). There was also a marked decline of noncardiovascular mortality in the SC group compared to the RC group. The reason for these findings remains unexplained.

The HDFP has resolved the controversial question of whether mild hypertensives are in need of treatment, demonstrating the benefits of a program of systematic, intensive therapy. A further study, the Australian Therapeutic Trial in Mild Hypertension,[57] confirms and supplements the findings of the HDFP. In addition to the expected reduction in cerebrovascular complications, a significant decline in the rate of myocardial infarction could also be obtained, thus contrasting with earlier studies (Veterans Administration Cooperative Study and U.S. Public Health Service Hospitals Cooperative Study). The practice of differentiating between hypertension-related and atherosclerosis-related complications, on the assumption that only the former can be prevented by antihypertensive therapy, is no longer tenable.

The data of the HDFP also indicate that a reduction below the previously assumed limit of 90 mm Hg diastolic (the SC group had a mean DBP of 84 mm Hg after 5 years) is both feasible and prudent.

The HDFP further demonstrates that antihypertensive therapy can be successfully administered for the most part by nurses and paramedical personnel. This finding is important for it is impossible as well as economically impractical for the vast population of hypertensive patients to be treated by physicians alone. From the standpoint of patient compliance, there appears to be no problem, at least in the United States, as demonstrated by the excellent compliance rate in the HDFP.

The HDFP was designed as a unifactorial drug intervention study; no attempt was made to influence other factors such as overweight, hypercholesterolemia, smoking, salt intake, and physical activity. This was necessary in order to obtain meaningful results. This does not mean, however, that the other risk factors may be ignored, or that mild hypertensives must be given immediate drug therapy. The important finding of the HDFP is that mild hypertension should be treated. The form of the treatment must be individualized. Naturally, an attempt at weight reduction in overweight patients and a restriction of salt intake are indicated. But if hypertension persists, the institution of systematic drug treatment should not be delayed.

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# Hypertension and Diabetes Mellitus

# 6

S. Raptis

One of the most serious consequences of the growth of civilization and technology may well be the alarming increase in the "diseases of civilization." Important among these, owing to their prevalence and grave complications, are essential hypertension and diabetes mellitus. It is considered probable that hypertension, diabetes mellitus, and obesity are all based on common pathophysiologic mechanisms.

Next to cardiovascular disease, hypertension, obesity, and diabetes mellitus have become the most common clinical diagnoses. An abnormal glucose tolerance or (sometimes mild) elevation of blood pressure, as well as hyperuricemia, can often be demonstrated in patients with generalized arteriosclerosis and metabolic disturbances. Epidemiologic studies have proved that these syndromes occur simultaneously with a frequency considerably higher than chance would predict.

## Prevalence

Pell and D'Alonzo showed in 1967 that hypertension occurs 50% more frequently in diabetics than in nondiabetics.[44] Very often, hypertension will develop long before clinical signs of diabetes mellitus appear.

In our own retrospective study of 814 myocardial infarction patients, we found a pathologic glucose tolerance in 423 (52%), overweight in 480 (59%), and hyperlipidemia in 578 (71%). Smoking was present as a risk factor in 317 (39%). Finally, 98 patients (12%) had overt diabetes. Of these overt diabetics, 6.2% were treated with sulfonylureas and the remaining 5.8% with insulin. When the latent and overt diabetics were investigated for hypertension, it was found that 72% had a history of high blood pressure. Among the patients with overweight, hyperlipidemia, or nicotine abuse but no disturbance of carbohydrate metabolism, only 39% were hypertensive.

Numerous studies, mainly prospective (Framingham, Albany, Los Angeles, Tecumseh, Chicago, Minneapolis), have clearly shown that elevated blood pressure is the strongest risk factor for increased morbidity and mortality from cardiovascular disease. Thus, arterial hypertension appears to play a central pathogenic role in myocardial infarction, analogous to that of obesity in diabetes mellitus.

## Correlations

The positive correlation between obesity and high blood pressure is statistically significant.[36] It has been estimated that weight normalization would reduce the incidence of essential hypertension by 50% among the white population of the United States.[60]

With the direct correlation between obesity and hypertension on the one hand[6,31,36,60] and obesity and diabetes mellitus on the other, it may be assumed that hypertension, diabetes, obesity, and the most frequent accompanying symptoms such as hyperlipidemia and hyperuricemia represent a syndrome which can be considered the precursor of arteriosclerosis and subsequent vascular complications. Weight reduction can normalize not only the blood pressure, but also the diabetic metabolic state. For example, Sarre reported that the percentage of hy-

pertensives among the patients at the University Medical Clinic in Freiburg, West Germany, decreased to 9.5%–11% during the period 1945–1947.[29] It later rose to 14% in 1948 and to 22% in 1964. Similar observations were made with respect to obesity and diabetes mellitus. Himsworth et al. showed in their retrospective study of England and Wales between 1900 and 1949 that the morbidity and mortality from diabetes declined significantly in these countries whenever food rationing was instituted during war or economic crisis.[28] Moreover, Danopoulos and Angelopoulos reported a decline in diabetic consultations at the Second University Medical Clinic in Athens, Greece, during the famine years of 1941–1942.[15] Our own investigations in 17 latent diabetics with hypertension showed that a reduction of more than 50% of excess weight in these patients led to a normalization of blood pressure and a marked improvement of glucose assimilation without medical therapy.[48]

Reisin et al. recently demonstrated in a controlled study that simple weight reduction in overweight patients leads to blood pressure normalization.[49] The patients in this study followed a reducing diet but had no restriction of salt intake. This refutes the hypothesis of Dahl[14] that the blood pressure decrease in overweight patients on a reducing diet is the result of diminished salt intake. In all probability, the problem is a mechanical one. It is known, for example, that approximately 9 m of blood vessels is required to nourish each kilogram of excess weight. A weight reduction of 10 kg, therefore, will lead to a "vascular saving" of 90 m. The result is a lower peripheral resistance and a significant fall of blood pressure. The effect of nutritional state on blood pressure not only has been statistically verified, but has solid scientific support as well. In men, each kilogram of weight gain is accompanied by a blood pressure increase of 0.63 mm Hg.[22] The age-dependent increase, by comparison, is 1.1 mm Hg per year. Diabetes can also be improved by a reduction of body weight, or even cured if the weight loss is sufficient.[17,45]

The problem of the course of hypertensive disease is an extremely complex one, as illustrated by the observations of P. D. White in Africa.[53] He observed many patients who had pyelonephritic hypertension but never developed myocardial infarction. He attributed this to chronic malnutrition. Thus, hypertension unaccompanied by overweight, latent or overt diabetes, hyperlipoproteinemia, or hyperuricemia apparently does not predispose to myocardial infarction or arteriosclerosis.

Numerous efforts have been made in recent years to clarify the pathophysiologic mechanism which may be common to both hypertension and diabetes mellitus. As is known, approximately 70% of all hypertensive patients can be classified as essential hypertensives. Owing to the rapid increase in the morbidity rates for hypertension and adult-type diabetes mellitus, the need for early detection and treatment is becoming increasingly urgent. The discovery of a common etiologic mechanism is of prime concern. Experiments with laboratory animals have indicated that the cerebral visceral systems for regulating blood pressure and carbohydrate metabolism may become activated in states of stress. Working from these results, Baumann and Graff performed studies in 266 patients with essential hypertension to determine whether an association with latent or asymptomatic diabetic metabolic disturbances is present in the early stage of hypertension.[3,4] While 5% of these patients exhibited overt diabetes, 45% displayed a "protodiabetic" metabolic state.[45] All patients in the latter group were overweight and suffered from hyperlipidemia and pathologic liver function; the histologic changes corresponded to the picture of fatty infiltration of the liver. Thus, we again encounter obesity as a key factor. Whether this is attributable to an abnormality of central nervous regulation, as many authors claim, or to an increase in effective and relative caloric consumption, as we believe, must remain an open question.

## Importance of the Renin-Angiotensin System

Many authors have attempted to clarify glucose assimilation and insulin secretion in patients with essential or renal hypertension. For example, Welborn et al.[61] and Dieterle et al.[16] found a normal glucose tolerance with an elevated insulin level in some patients with essential hypertension, but a decrease in both glucose assimilation and insulin secretion in others. Findings on glucose consumption and insulin secretion also vary in patients with renal hypertension.[55,56]

Experimental studies in rats with genetically determined spontaneous hypertension, with renal hypertension of the "one-clip, one-kidney" type, and with hypertension induced by mineralocorticoids have shown that in animals with severe spontaneous hypertension, the usual age-dependent decline of glucose assimilation and insulin secretion is more pronounced than in the controls.[62] In the young hypertensive rats, the authors found a marked hyperinsulinism with a more or less unchanged glucose tolerance relative to control animals of equal age. A similar insulin-glucose constellation very often ap-

pears in overweight humans and animals. One deficiency of this study and of all the aforementioned studies in humans is that the body weight was never adequately taken into account. It is quite possible that the differences found were not directly related to hypertension, but to differences in body weight.

In rats with DOCA- and salt-induced hypertension, a depression of glucose assimilation and insulin secretion was observed. Rats with renal hypertension showed a depression of glucose tolerance with no change in insulin secretion.[67] These findings suggest the possibility that vasopressor substances are released which promote the development of a diabetic metabolic state. In this connection, many authors have explored the link between the renin-angiotensin system and catecholamines on the one hand and hypertension, experimental diabetes, and clinical diabetes on the other.[7,9,10,23–25,50] In rats with severe alloxan-induced diabetes, a highly significant correlation was found between blood pressure and plasma glucose, as well as between blood pressure and urea level.[7] No significant correlations were found between the mildly diabetic animals and the controls. The plasma renin and renal renin showed significantly lower levels. In addition, the cardiovascular response to angiotensin II infusion was more pronounced in the severely diabetic rats than in the controls.

The plasma renin activity was also measured in diabetic patients. It was found that in long-standing diabetics with diabetic complications such as retinopathy and nephropathy, the renin-angiotensin system is suppressed. In patients without apparent complications, on the other hand, the renin-angiotensin system appears to be intact. As in the animal study, patients with long-standing diabetes show a more pronounced blood pressure increase after angiotensin II than patients without complications. Christlieb et al. have attempted to correlate the observed aberration of plasma renin activity, the serum potassium, and the glucose level.[11] They found that the renin-angiotensin system generally responds normally in diabetics without renal involvement and subnormally in patients with nephropathy. Diabetics with nephropathy show an increased incidence of hyporeninemic hypoaldosteronism with hyperglycemia and hyperkalemia. In diabetics with hyperglycemia, an expansion of the blood volume is observed.[8] The hypervolemia, together with the increased peripheral vascular resistance, leads to a hyalinization of the renal arterioles. This causes hypertension accompanied by a fall of plasma renin activity and aldosterone levels in the blood. Thus, it would appear that the hypertension in diabetes mellitus shows similarities to the pathogenic mechanisms of hyporeninemic essential hypertension, which affects about 30% of all essential hypertensive individuals.

Christlieb and Munichoodappa also investigated the plasma renin activity in diabetics with orthostatic hypotension and other complications such as retinopathy and nephropathy.[12] The renin values were markedly elevated compared to patients without complications. Interestingly, nondiabetic patients with idiopathic orthostatic hypotension exhibit normal renin values.[34] The latter findings show that the autonomic nervous sytem cannot be responsible for the low renin values observed in the diabetic patient.

There has been increasing evidence in recent years that, aside from diabetic nephropathy, connections exist between diabetes mellitus and the kidney. For example, Kahn et al. cited biopsy findings to show that the kidneys are significantly larger in diabetics than in nondiabetics.[30] They found no correlation between the type, duration, and severity of the diabetes and kidney size. The authors attributed this enlargement to the overproduction of growth hormone in diabetics reported in earlier studies.[26,35,57]

## Importance of Growth Hormone

Our own studies, by contrast, have shown that the secretion of growth hormone after arginine in the diabetic does not differ significantly from that in persons with a normal metabolism.[47] In more recent studies, we found that somatostatin led to a highly significant reduction of the daily insulin requirement as assessed by artificial $\beta$ cell in diabetics with total pancreatectomy, but not in diabetics with total hypophysectomy.[46] Thus, it appears that growth hormone indeed plays a certain role in the regulation of carbohydrate metabolism. According to studies by Ditschuneit et al., growth hormone is also responsible for the origin and development of arteriosclerosis—yet another reference to the close association between diabetes, hypertension, and arteriosclerosis.[18] If we accept the fact that a pathogenic relationship exists between growth hormone and the severity of diabetes mellitus (i.e., diabetic macro- and microangiopathy), then these complications should be absent in diabetics with growth-hormone deficiency. Indeed, Merimee found an absence of retinopathy on ophthalmoscopic examination of growth-hormone–deficient dwarfs with diabetes mellitus.[41] Moreover, these patients had significantly fewer hypertensive blood pressure readings and ischemic ECG changes than diabetics with normal growth hormone.

Of course, growth hormone cannot be held solely responsible for the vascular complications of diabetes mellitus and the resulting hypertension, nor can it be claimed that chronic hyperglycemia and hyperlipidemia play no role in this process. Hyperglycemia and the associated anomalies of cell metabolism in the intimal and medial cells of the arteries and the capillary-wall cells could contribute to the angiopathy in diabetes, but, according to Merimee's studies, only if pituitary function is intact. Thus, the hyperglycemic syndrome is never as severe in diabetic pituitary dwarfs as in other diabetics, owing to their deficiency of growth hormone. This deficiency also appears to give protection against cholesterol- and triglyceride-associated atherosclerosis. Moreover, the hypervolemia from growth-hormone hypersecretion observed by us earlier [unpublished finding] aggravates the hyperglycemic hypervolemia already described by Christlieb et al.,[8] thereby increasing the severity of the hypertension. Thus, it appears that the increased incidence of hypertension in diabetes mellitus can be attributed mainly to the frequent occurrence of arteriosclerosis.

## The Problem of Arteriosclerosis

Numerous epidemiologic studies in humans have shown that diabetes mellitus is a major factor in the development of arteriosclerosis,[21,42] and is very often accompanied by hypertension.[21,43] The cause has been sought in the observed aberrations of metabolism in the vascular-wall cells[59] and the change in circulating lipoproteins[2,21,42] that occur in diabetes mellitus; nor has the genetic basis of the prevalence of arteriosclerosis in diabetes mellitus been neglected.[37] On the other hand, hypertension is very probably the greatest risk factor for the development of arteriosclerosis and its sequelae.[32] The cause, according to one theory, lies in an increase in vascular-wall permeability to many circulating proteins and cholesterol.[19,62] This is reflected in the increased uptake of circulating material into the cell and the stimulation of lysosomes in the vascular smooth-muscle cells.[65,66] Indeed, Wolinsky et al. have described a combined effect of the two risk factors—hypertension and diabetes mellitus—on the biochemical development of arteriosclerosis on a cellular level.[63,64] They found that the hydrolase activity in the smooth-muscle cells was significantly lower in hypertension combined with diabetes mellitus than in hypertension alone.

Diabetes mellitus can be observed in all types of hypertension, even surgically correctable forms such as Conn's syndrome and Cushing's syndrome. That occurring in Conn's syndrome is easily explained by the presence of hypokalemia and the reduction of insulin secretion.[13] In Cushing's syndrome, the cause is hypercortisolism. It has even been postulated that essential hypertension leads more frequently to the outbreak of diabetes mellitus as a result of premature sclerosis of the pancreatic vessels with secondary involvement of the islet system. This pathophysiologic concept appears doubtful, because in elderly diabetics regressive changes in the pancreatic parenchyma are due more to general age-dependent involution than to the effects of pancreatic vascular sclerosis.[40] Moreover, the results of genetic studies in diabetics of the juvenile and adult type cannot be reconciled with this concept, since genetic determination in such cases is beyond question.

## Importance of Diabetic Nephropathy

The classic cause of hypertension in long-standing diabetes mellitus is diabetic nephropathy. This term, coined by Aschoff in 1911,[1] is now regarded as a complicated syndrome consisting of three parts: pyelonephritis (inflammatory component), arterio-arteriolosclerosis (microangiopathy), and glomerulosclerosis (macroangiopathy). In one group of hypertensive patients with proven renal artery stenosis, i.e., with macroangiopathy, diabetes mellitus was demonstrated in nearly 50%.[40] This was taken to confirm the thesis that renal artery stenosis usually occurs secondary to essential hypertension, with arteriosclerosis-promoting factors such as diabetes mellitus playing an accessory role. The diversity of these diabetic complications, i.e., of diabetic nephropathy, also accounts for the difficulty of treatment. The treatment of the cause of diabetic nephropathy is not possible under these circumstances. The major effort is directed toward prophylaxis. As a rule, it can be said that nephropathy is less common in the adequately adjusted diabetic. The hypertension observed in diabetic nephropathy, which sometimes is malignant and accompanied by hypertensive encephalopathy, is often characterized by elevated renin levels. The treatment of hypertension in diabetic nephropathy must be undertaken with great care, and the use of thiazide preparations, which impair carbohydrate metabolism,[52] should be avoided if possible. Besides potassium deficiency and impaired insulin secretion and glucose assimilation, thiazides lead to a relative or absolute thiamine deficiency, with adverse consequences for carbohydrate metabolism.

There are two theories as to the cause of diabetic glomerulosclerosis, particularly microvascular ab-

normalities, in this state. The first postulates a genetic cause which is independent of the insulin deficiency. This theory is based on the fact that such microvascular lesions have also been described in patients with a normal glucose tolerance.[27,33] In addition, other authors have observed a thickening of the glomerular basement membrane, the early histologic sign of diabetic glomerulosclerosis, immediately after the discovery of diabetes mellitus[51] and in prediabetics.[5] Advocates of the metabolic theory see the diabetic microangiopathy in the kidney as a direct result of the metabolic abnormality arising from the absolute or relative insulin deficiency. As a result of this, the basement membranes of the glomeruli contain an abundance of glucoproteins.[58] In view of the fact that healthy kidneys which are transplanted into diabetic patients develop microangiopathy[37] and that the renal vascular lesions are reversible by pancreatic islet transplantation,[20,39] the metabolic theory appears to be more probable. Recently, Mauer et al. showed in animal studies that a change in renal hemodynamics combined with a diabetic state leads to a marked acceleration of diabetic glomerulopathy.[38]

## Conclusions

In summary, it can be said on the basis of the above findings that hypertension is more frequent in the diabetic than in the nondiabetic. The hypertension that complicates long-standing, poorly adjusted diabetes mellitus is attributable to diabetic microangiopathy in the setting of diabetic nephropathy and is more common in juvenile diabetics. Systolic hypertension is a result of the arteriosclerosis that frequently accompanies diabetes.

Essential hypertension occurs most frequently in the diabetic and apparently has a complex cause. It is either associated with overweight, hypersecretion of growth hormone, or suppression of the renin-angiotensin-aldosterone system or, as biochemical findings on a cellular level suggest, it is the result of a subtle arteriosclerosis with no obvious manifestations.

True endocrine hypertension in the setting of Conn's syndrome, Cushing's syndrome, pheochromocytoma, or hyperthyroidism is observed no more frequently in the diabetic than in the nondiabetic.

With the exception of thiazide preparations, antihypertensive therapy of the diabetic patient does not differ from that of other hypertensive patients, although particular care is warranted because of the danger of hypoglycemia with the use of $\beta$-blocking drugs.

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# Role of the Central Nervous System in the Control of Arterial Blood Pressure and in the Pathogenesis of Arterial Hypertension

7

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The brain plays a fundamental role in the regulation of arterial blood pressure. Information concerning changes in arterial pressure, blood volume, or blood chemistry, discerned by specific receptors (baroreceptors, atrial receptors, chemoreceptors), reaches central structures which readjust circulatory parameters by reflex mechanisms. This explains the ability of the organism to withstand various local and generalized insults. This neurogenic aspect of blood pressure regulation, which assures homeostasis in the whole organism, complements local regulating mechanisms that adapt local blood supply according to the needs of the organism, the most simple of which is the regulation by metabolism.

In the reflex regulation of blood pressure exerted by the brain, direct effects on central structures also play a role. It is possible to observe modifications of arterial blood pressure in situations such as physical effort or so-called "stressful" situations in which the baroreflex arc seems to be inhibited by suprabulbar structures.

The relationship which may exist between arterial hypertension and central mechanisms can be clearly demonstrated after bilateral destruction of the nucleus of the solitary tract (NTS) or by the stimulation of pressor zones, which appear to be restricted to certain well-defined brain areas. Differences between the monoamines in various brain regions can be demonstrated in a number of experimental models of hypertension. Such facts, to some degree difficult to interpret since it is still not known whether they are the cause or the result of hypertension, nevertheless allow the reconsideration of hypertension from a pathogenic aspect involving the nervous system. In essential hypertension in humans, several arguments, such as the observation of elevated plasma catecholamines and the central mechanism of action of antihypertensive drugs such as $\alpha$-methyldopa or clonidine, suggest a relationship between disturbances of the autonomic nervous system and elevated blood pressure.

We shall consider in sequence cerebral regulatory function, the influence of circulating compounds on cerebral activity, and the role of the brain in physical and emotional situations recently studied. [40,54,70] Finally, we shall examine the role of the central nervous system in various models of experimental hypertension and in essential hypertension in humans.[2,6,15]

## Reflex Arcs in Blood Pressure Regulation

### The Medullary Baroreflex

Peripheral receptor organs are located in the media and adventitia of the internal carotid artery at its origin (the carotid sinus) and in the aortic arch. These structures, called baroreceptors, are activated by the pulsatile distension of the arterial wall. This excitation gives rise to an increased discharge in the afferent loop of the baroreflex arc. These specialized nerve cells form the carotid sinus and the aortic nerves. Their pseudounipolar cell bodies are situated in the plexiform ganglion. The nerve fibers then travel with cranial nerves 9 and 10 and enter the medulla via the collateral groove at the level of the obex (at the caudal end of the fourth ventricle). They cross the motor fibers of the fifth cranial nerve to join the solitary tract. Some of the fibers decussate to join the solitary tract of the opposite side.

The first synapse is situated at the level of the solitary tract. They become localized on both sides of the obex, extend in a posterior and superficial direction, and then run caudally and medially. The first junction was identified by degenerative studies of the medullary axons secondary to ablation of the plexiform ganglion, by the section of the ninth and tenth pairs of cranial nerves,[56] and by the recording of electrical activity in the medulla during stimulation of baroafferent fibers.[38,69]

Distension of the baroreceptors or direct stimulation of the NTS results in arterial hypotension and bradycardia associated with a depression of sympathetic activity and an increase of vagal tone. These effects imply synaptic connections between the NTS and visceromotor fibers of the vagus and sympathetic tract.

The origin of the vagal fibers to the heart is disputed. At least in the cat it is not the dorsal motor nucleus of the vagus, situated just behind the NTS, that seems to be involved, but the nucleus ambiguus located in the reticular formation. Indeed, stimulation of the nucleus ambiguus results in bradycardia, the opposite of stimulating the dorsal motor nucleus.[72] In the same way, the antidromic stimulation of the vagal efferents to the heart results from an activation of the nucleus ambiguus, whereas the dorsal nucleus is activated only by the retrograde stimulation of efferent fibers not destined for the heart.[45]

The bulbospinal fibers destined to regulate the activity of the preganglionic sympathetic neurons originate in the reticular formation of the medulla oblongata.

A lateral area in the region of the lateral nucleus of the reticular formation can be distinguished and is named area $A_1$ according to the classification of Dahlström and Fuxe.[12] The letter A designates catecholaminergic cell groups. Noradrenergic fibers originate in area $A_1$ and travel in the ventral parts of the lateral columns of the spinal cord before crossing the midline to reach the preganglionic sympathetic fibers. This lateral area corresponds to what neurophysiologists call the medullary pressor area, so named because of the observed increase in blood pressure and sympathetic activity when it is stimulated.[29]

The median region, which corresponds to the serotonergic areas of the raphe (area B), gives origin to serotonergic fibers which travel in the dorsal parts of the lateral columns of the cord before crossing the midline to reach the sympathetic nerve cells. The control exerted by these serotonergic fibers on the activity of preganglionic sympathetic fibers depends on the particular B area involved.[1] In response to a distension of the baroreceptors, a decreased activity of sympathetic fibers is seen which appears to be modified by the previously described bulbospinal fibers. The cell bodies of the preganglionic sympathetic neurons extend between the first thoracic and second lumbar segments in the intermediolateral columns of the spinal cord. The axons of the cells leave the cord via the ventral nerve roots and then form cholinergic synapses in the paravertebral sympathetic ganglion chains. From there, the postganglionic sympathetic fibers leave for peripheral organs (heart, blood vessels, kidneys, etc.). Released norepinephrine stimulates cardiac contraction (cardiac $\beta_1$-adrenergic effect), increases the peripheral resistance (vascular $\alpha$-adrenergic effect), and induces the secretion of renin (renal $\beta_2$-effect). The sympathetic fibers arising in the medulla oblongata and destined for the adrenal medulla form connections (cholinergic synapses) in the gland itself. These fibers regulate the release of adrenal catecholamines (norepinephrine and, especially, epinephrine).

Three important facts should be mentioned in relation to medullary baroreflex function. First, blood pressure readjustment brought about by the baroreflex is limited by the sensitivity of the baroreceptors. Large variations in blood pressure are not able to produce a greater signal then the maximum already achieved by moderate (50–60 mm Hg) changes in blood pressure.[40] One can readily appreciate the importance of other reflex arcs in the correction of large variations in blood pressure. Second, in the case of chronic elevations of blood pressure, medullary baroreflex function is normal and appears to readjust blood pressure to the new level.[46] This fact, the mechanism of which is still unknown, could play a role in the pathogenesis, or at least in the maintenance, of arterial hypertension. Finally, we have emphasized the medullary integration of changes in blood pressure. These variations are also integrated at higher levels (a mechanism to which we shall return in relation to "stress")and at lower levels. The persistence of cardiovascular reflexes in the spinal animal or in tetraplegic humans indicates the existence of a spinal control of sympathetic neurons.[10] It appears that in the intact animal the medullary centers dominate the spinal vasomotor centers, since there is a clear diminution of spinal somatosympathetic reflexes after high section of the spinal cord.[58]

## The Chemoreflex

The chemoreceptors located in the carotid artery and the aortic arch are sensitive to variations in pH and the arterial partial pressure of oxygen ($pO_2$) or carbon dioxide ($pCO_2$) and modify respiration in

such a way as to correct the initial derangement of blood chemistry. Furthermore, hypoxia or hypercapnia restricted to chemosensitive areas results in an elevation of peripheral resistance.[57] In severe hypoxic states associated with anoxia, this mechanism could contribute to the reestablishment of blood pressure. In another respect, sympathetic hyperactivity resulting from an inhibition of the baroreflex arc could be a contributing factor to anoxia by the mere fact of a reduction in the blood supply to the carotid body.[37] The neural pathways utilized by the chemoreceptors to reduce variations in blood pressure are superimposed on those of the medullary baroreflexes.

### The Cardiac Reflexes

Receptors found in the atria are sensitive to variations in atrial pressure and in this way recognize changes in blood pressure. Atrial distension produces vagal bradycardia and vasodilatation via a decrease in sympathetic activity associated with a diuretic and a natriuretic response. The reduced secretion of the posterior pituitary antidiuretic hormone (ADH) by the neurohypophysis could explain the increased diuresis. In the hypovolemic state the reverse situation is seen. Nevertheless, it seems that sympathetic hyperactivity secondary to hemorrhage is not the direct consequence of the activation of the baroreflex via the atrial receptors. In fact, vagotomy, which interrupts the afferent limb of this arc, does not suppress the elevation of catecholamines secondary to hemorrhage. Sympathetic hyperactivity could be the consequence of a central action of angiotensin which forms from the renin released by the kidney following hemorrhage.[23]

Ventricular receptors appear to be equally sensitive to distension, but they are of two types: (1) epicardial receptors, the best known, transmit impulses via the vagus to the medulla which, in response to an increase in muscular tension, causes a vagal bradycardia (the Bezold-Jarisch reflex) and a reduced sympathetic tone; (2) myocardial receptors connected with the sympathetic afferents evoke opposite responses.

### Other Reflexes

There exist a large number of receptors whose stimulation produces cardiovascular responses. Among these are the pulmonary receptors which produce venous constriction during deep inspiration,[21] muscular receptors activated by physical exertion, cutaneous receptors activated by painful stimuli (which result in increased sympathetic tone) or by variations in temperature,[33] and receptors in the urinary bladder and gastrointestinal tract.

## The Influence of Variations in Blood Chemistry on Cerebral Activity

The brain, with its role in reflex activity, appears capable of modifying the activity of efferent neurons in response to direct central stimuli such as metabolic changes or variations in circulating hormones.

Cerebral ischemia can, in extreme cases (when autoregulation and metabolic regulation of cerebral blood flow are very active), generate extreme sympathetic hyperactivity. It may be that the observed response originates with the ischemia of one chemosensitive zone in the medulla such as the area postrema. Hyperglycemia leads to sympathetic hyperactivity. Temperature variations in central structures also influence the activity of the cardiovascular nerve cells.[33] The thermosensitive structures are probably located at the level of the hypothalamus.

Circulating hormones do not appear to have an important effect on the brain, since the blood-brain barrier restricts the passage of molecules from the bloodstream into the brain, admitting only those that are lipid-soluble. Nonetheless, certain densely vascularized structures are devoid of a blood-brain barrier. Circulating angiotensin acts centrally at the level of one of these areas, namely the area postrema. This area forms the two borders of the caudal tip of the fourth ventricle (obex) and is connected with the neighboring cardiovascular structures of the medulla. Stimulation of the area postrema by circulating angiotensin results in increased sympathetic tone and decreased vagal tone. Bilateral ablation of the area postrema reduces the pressor effects of a continuous intravenous infusion of exogenous angiotensin or endogenous angiotensin produced by hemorrhage or stenosis of the renal artery.[39,67,68] The only vasoactive effects observed are associated with the direct constrictive action of the hormone on smooth vascular muscle. Angiotensin possesses other central effects which contribute to blood pressure regulation.[5,20,25] It stimulates water intake (and to a lesser degree salt intake) and liberates ADH from the posterior pituitary, resulting in antidiuresis.

## The Physiologic Role of the Central Nervous System

In this section we shall describe the mechanisms whose function it is to maintain a stable arterial

blood pressure in the face of peripheral circulatory changes. These mechanisms depend on the reflexes previously described. We shall also consider cerebral mechanisms which bring into action suprabulbar systems capable of modifying the baroreflex functions. The modulation of the baroreflex explains the maintenance of blood pressure variations in particular situations.

### Orthostatism

In humans, the change from a recumbent to an upright position causes about half a liter of blood to pool in the dependent areas of the body. This results in decreased venous return and orthostatic hypotension. Before this amount of blood can be mobilized by muscular contraction or respiratory movements, a rapid correction of the blood pressure takes place under the influence of increased sympathetic tone and vagal depression. These effects are the reflex consequences of a reduction in atrial pressure and a reduction in the discharge of the baroreceptors related to their relaxation. The renin-angiotensin-aldosterone system and ADH intervene secondarily. The pressor effect of stimulation of the fastigial nucleus of the cerebellum[47] has given rise to another hypothesis: It is possible that stimuli resulting from the postural changes of orthostatism, arriving at the cerebellum, activate this nucleus and evoke a pressor response.

### Physical Activity

Physical exertion leads very rapidly (within a second of commencing exertion) to a considerable increase in cardiac output with tachycardia and a rise of arterial blood pressure. The swiftness of these hemodynamic changes suggests a nervous origin. Certainly, inhibition of the baroreflex could be the main cause of the tachycardia and elevated blood pressure. This inhibition could be a result of the activation of the motor or premotor cortex, which would explain the tachycardia preceding the onset of physical effort. According to other researchers, the rise in blood pressure with tachycardia seen with muscular contraction could be due to a sympathetic reflex activated by a release of metabolites from muscle which are able to stimulate muscular chemoreceptors.[8,44] This hypothesis could explain the maintenance of the elevated blood pressure in terms of the slow inactivation of these metabolites. The moderate change in total peripheral resistance could be due to a generalized increase in sympathetic tone (baroreflex inhibition or reflex of muscular origin) and to a vasodilation restricted to the contracted muscles (especially a functional hyperemia, the possible activation of a muscular vasodilator nerve bundle; see below).

### Sleep

In a large number of species, and especially in humans and cats, there is a moderate decrease in arterial pressure and heart rate during sleep, which is most marked during periods of paradoxical sleep.[31] These changes can be interpreted as resulting from changes in the activity of the reticular formation of the brainstem, thus affecting the activity of the cardiovascular neurons.

### Stress

Certain emotional states (e.g., vasovagal syncope in humans) are characterized by bradycardia and a fall of blood pressure. However, in most cases, emotion produces a marked tachycardia, a rise of arterial blood pressure, an increase of muscle tone in the visceral organs, and an increase in muscular blood flow, which can be interpreted as a preparation for muscular exercise. These hemodynamic changes have been studied in experimental animals by the stimulation of central structures which evoke an attack, flight, or defense response. The integrating structures, or centers, are localized in the medulla, the mesencephalon, and the "defense area" of the hypothalamus and form part of the ascending activating system of the reticular formation.[36] These structures receive information from the periphery (extralemniscal system for pain and temperature stimuli) or from the cerebral cortex (via the rhinencephalic amygdala). These centers trigger not only defense and attack reactions, but also neuroautonomic functions such as the inhibition of the baroreflex.[34] This baroreflex inhibition, which arises in the suprabulbar areas, explains the tachycardia and the visceral vasoconstriction. As for muscular vasodilatation, this could be connected with the stimulation of a vasodilator nerve bundle arising in the hypothalamus.[35] This pathway, which does not synapse at the level of the medulla, is cholinergic in the cat[65] but not in the monkey.[66] The example of "stress" demonstrates the complexity of the medullary baroreflex, a key reflex arc in the regulation of blood pressure, whose activity apparently can be modified by suprabulbar afferent fibers arising mainly in the hypothalamus. The hypothalamus is also informed about changes in blood pressure.[51,71] Thus the hypothalamus can be pictured as a higher regulatory center capable of influencing the activity

of the medullary center, which in turn controls the cardiovascular centers of the medulla.

### Conditioned Cardiovascular Regulation

It has recently been shown that learning processes produce changes in the activity of the autonomic nervous system and thus that this activity should be regarded not as purely autonomic but as a part of the behavioral pattern. For example, a monkey conditioned to receiving electrical stimuli, instead of responding with a rise in blood pressure, will develop a chronic hypotensive state, which can be attributed to learning.[3] Such experience has prompted research into conditioned antihypertensive activity in which a compensatory lowering of blood pressure has followed repeated pressor stimuli.[4]

## Central Mechanisms in Arterial Hypertension

Neurophysiologic experiments, such as the section, ablation, or stimulation of cerebral structures, have led to a better understanding of the role of these central structures in the regulation of arterial blood pressure. Recent technical developments in neurochemistry and neuropharmacology help to clarify the extent to which derangements in cerebral function might play a role in arterial hypertension. At the neurochemical level it is possible to study the monoamine levels in specific brain regions selected because of their relationships to central monoaminergic pathways.[73,74] With this methodological approach, however, it is difficult to determine whether the changes observed in the neurotransmitters are responsible for the arterial hypertension or are the result of the elevated blood pressure, inasmuch as changes in transmitter levels may occur simultaneous to the development of hypertension without being directly related to it. At the neuropharmacologic level, even the local application of stimulating or blocking drugs and the use of inhibitors of transmitter synthesis or neurotoxic compounds permit a precise evaluation of the role of these connecting pathways in hypertension. These techniques are limited, however, by the lack of absolute specificity of the neurotoxic drugs and by the uncontrolled distribution of the injected drugs.

In the next section we shall consider some neurologic data from experimental hypertension, followed by some observations in humans based on indirect studies of the activity of the autonomic nervous system.

### Neurogenic Hypertension

Denervation of the baroreceptors frees the activity of the medullary centers from the inhibitory influences of the afferent fibers and leads to an oscillation of the blood pressure.[11] De-afferentation causes an increase of norepinephrine synthesis in both the heart and adrenal glands, but the level of endogenous norepinephrine in these organs remains unchanged.[16] This may correspond to an increase of norepinephrine release which could lead to hypertensive episodes.

Arterial hypertension also results after bilateral destruction of the NTS.[17] The fulminating hypertension observed in this situation is related to an increase in sympathetic tone, which can be explained by the destruction of a center which normally exerts an inhibitory effect on the sympathetic pathway. It is certainly associated with the abolition of the baroreflex, since the first relay station is destroyed.

These experimental models make it possible to analyze the role of bulbospinal monoaminergic pathways in relation to the spinal sympathetic neurons. In considering the contribution of catecholamines in neurogenic hypertension, one should note the effects of 6-hydroxydopamine (6-OHDA). This compound destroys monoaminergic nerve cells, especially noradrenergic neurons. When introduced into the cisterna magna, it causes a decrease in spinal catecholamine levels, which is attributable to a destruction of the bulbospinal catecholaminergic pathway. The administration of 6-OHDA can now prevent (or correct) the hypertension produced by sinoaortic denervation or bilateral destruction of the NTS.[7,18] It can be concluded that the bulbospinal catecholaminergic pathway is activated in this model and that it may stimulate the spinal sympathetic nerve cells.

In support of the role of serotonin in blood pressure regulation, one can cite the effects of 5,6-dihydroxytryptamine (5,6-DHT), which destroys serotonergic nerve cells. Administered intracisternally, it prevents (or reduces) the hypertension produced by denervation.[75] The serotonergic bulbospinal fibers seem to be activated in a similar manner in this model and apparently stimulate the spinal sympathetic neurons in the same way as the catecholaminergic pathways. Both of these sets of data, which indicate an excitatory action of catecholamines and serotonin on the spinal sympathetic neurons, are nonetheless at odds with other results which have led researchers to conclude that the two amines have an opposite effect on spinal sympathetic neurons.[9,32,52,62]

In another experiment, 6-OHDA was injected locally into the NTS of normal rats or cats.[61] The af-

ferent catecholaminergic fibers of the NTS, particularly those arising from the baroreflex control centers above the medulla and area $A_2$ of the medulla, were thus destroyed. The result was an unstable blood pressure with no apparent disturbance of the baroreflex arc. The catecholaminergic innervation of the NTS, therefore, appeared to modulate the baroreflex and contribute to the stability of the blood pressure.

### Hypertension Based on Desoxycorticosterone Acetate (DOCA) and Salt

Severe arterial hypertension is seen when a high salt intake is combined with the administration of a mineralocorticoid (such as DOCA), thus providing salt retention. Unilateral nephrectomy accelerates the positive sodium balance, which appears to be responsible for the hypertension. Other types of experimental hypertension, such as one-kidney Goldblatt hypertension (stenosis of the renal artery with unilateral nephrectomy), the hypertension due to the perinephritis resulting from renal encapsulation, and finally the hypertension resulting from bilateral nephrectomy, are also accompanied by a positive salt balance. The sodium excess initially increases the blood volume and cardiac output, an action which may initiate arterial hypertension. During the chronic phase of mineralocorticoid hypertension, an increase in peripheral resistance is solely responsible for the raised blood pressure. The peripheral vasoconstriction could be explained by an increased sympathetic tone.[13,60] Bilateral adrenalectomy or chemical sympathectomy induced by intravenous 6-OHDA lowers this elevated blood pressure.[14] The increased sympathetic tone is apparently dependent on a supraspinal mechanism since section of the cervical cord relieves the hypertension. The preventive effect of the intraventricular injection of 6-OHDA on mineralocorticoid hypertension suggests that central catecholaminergic fibers play a role.[24,42] Also, the increased activity of phenylethanolamine N-methyltransferase (PNMT) (the enzyme catalyzing the methylation of norepinephrine to epinephrine in area $A_1$ of the medulla[63]) could explain the activation of adrenergic bulbospinal fibers which arise at this level and control the spinal sympathetic fibers. This activation of area $A_1$ could itself depend on the variations in activity of the bulbospinal monoaminergic pathways, as suggested by the reduced turnover of norepinephrine in the hypothalamus and brainstem of DOCA-salt hypertensive rats.[50] The initial site of action of sodium could be the hypothalamus, but its mechanism of action is unknown. Central serotonergic fibers do not seem to be involved in this hypertensive model, since the intracisternal administration of 5,6-DHT does not influence mineralocorticoid hypertension.[48]

### Experimental Renovascular Hypertension

In the previously cited models of renal hypertension associated with a positive sodium balance, central and peripheral adrenergic changes are seen which are identical to those of mineralocorticoid hypertension. Two-kidney Goldblatt hypertension is very different since it is mainly dependent on the renin-angiotensin system. As previously mentioned, angiotensin has several central actions in addition to its powerful vasoconstrictive effect. The stimulation of the area postrema by circulating angiotensin originating from stenosis of the renal artery could play a role in this model; in the dog, the bilateral destruction of the area postrema reduces the elevated blood pressure secondary to renal artery stenosis.[67] Nevertheless, in the rat the level of plasma norepinephrine is normal after clamping of the renal artery, a fact which argues against neurogenic mechanism for two-kidney renovascular hypertension in the rat.[59]

### Genetic Hypertension in the Rat

The biochemical changes seen in spontaneous hypertension in the rat are difficult to interpret. Indeed, the method of selecting spontaneously hypertensive rats may select rats which carry biochemical anomalies unrelated to arterial hypertension. For this reason rats used as controls must have a maximum genetic similarity to the hypertensive rats. A further difficulty arises from the numerous strains of genetically hypertensive rats. The most studied is the Japanese strain, which has displayed various irregularities that have yet to be described.

The development of hypertension is clearly influenced by environmental factors such as stress and salt consumption.[77] However, young rats display a high level of sympathetic nervous discharge[55] and an elevation of plasma norepinephrine.[30] It would appear that this sympathetic hyperactivity is indispensable to the genesis of the hypertension, for sympathectomy arrests the development of the hypertensive state.[76] The preventive effect of the intraventricular administration of 6-OHDA on the development of spontaneous hypertension suggests that central catecholaminergic fibers play a role.[24] In addition, an increase in PNMT activity is seen in areas $A_1$ and $A_2$ of the medulla when compared to the controls.[63] These changes could account for an activation of the adrenergic bulbospinal fibers which

control the spinal sympathetic fibers. This catecholaminergic activation of the medulla may depend on monoaminergic pathways originating in the hypothalamus. In the young spontaneously hypertensive rat, some researchers have described a reduced synthesis of norepinephrine in the anterior hypothalamus,[64] while others have found an increased synthesis of serotonin in the whole hypothalamus.[49]

Spontaneous hypertension in the adult rat, in contrast to that in the young rat, appears less dependent on neurogenic factors since some residual hypertension persists after sympathectomy.[53] Similarly, at the central level, PNMT activity appears to return to normal in areas $A_1$ and $A_2$ of the medulla, but a reduced rate of norepinephrine synthesis persists at the level of the anterior hypothalamus.[64] The hypothesis of an increased formation of cerebral angiotensin, which could be involved in the pathogenesis of spontaneous hypertension via its central pressor action[28] has not been confirmed.[19]

### Arterial Hypertension in Humans

For a long time the investigation of the sympathetic nervous system was limited by methodological problems. The measurement of catecholamines and their metabolites in the urine permitted only the detection of pheochromocytomas. This tumor, usually of adrenal origin, secretes an excess of catecholamines, thus explaining the symptomatology of this disease. The hypersecretion appears to be accompanied by an increased activity of catecholamine-synthesizing enzymes and a decreased activity of the mitochondria-degrading enzyme, monoamine oxidase.[43]

Today there are radiometric methods with which plasma catecholamines can be accurately and reproducibly measured. The rise in their level with orthostatism attests to the sensitivity of the method and also shows that the method is capable of detecting physiologic variations in sympathetic activity. This represents a true advance over the serum activity measurement of dopamine-$\beta$-hydroxylase (a synthetic granular enzyme released on sympathetic excitation), which did not meet all requirements. Nonetheless, published results on catecholamine levels measured in patients with essential hypertension still permit no final conclusions to be drawn.[2] Since the plasma norepinephrine rises with age, it is important to include normotensive controls matched for age with the hypertensive patients in order to appraise the observed differences.[41]

Most researchers have found an elevation of plasma catecholamines in certain hypertensive subjects under baseline conditions, which was even more obvious during orthostatism when compared to control subjects. A recent study suggests that the elevation of catecholamines in hypertensive patients could be due to the elevation of plasma epinephrine rather than norepinephrine, a fact that would implicate a preferential hyperactivity of the adrenal medulla.[26] It should be noted that benign essential hypertension associated with an increased plasma renin activity (PRA) appears to be associated with an elevation of plasma norepinephrine.[22] Small doses of a beta-adrenergic–blocking drug lower the PRA without affecting the blood pressure, indicating an absence of a pathogenetic role of renin in benign hypertension. In contrast, blockade of the autonomic nervous system reduces the hypertension of patients who have elevated levels of both PRA and norepinephrine, suggesting that increased sympathetic tone plays a role in this situation. A raised PRA may be only a reflection of increased sympathetic activity on the kidney.[22]

Such studies indicate that it may one day be possible to classify arterial hypertension according to group, one group being associated with heightened sympathetic activity. This "sympathetic" form of hypertension might be dependent upon various acquired factors (stress, environment, the direct effect of sodium on the brain) or endogenous factors (cerebral biochemical abnormalities).

## Conclusion

The brain regulates the arterial blood pressure through fast-acting mechanisms, bringing into play changes in the activity of the autonomic nervous system. The activation of these mechanisms depends on reflex arcs, the most important of which is the medullary baroreflex. The variety of changes that can be brought about by hemodynamic shifts are controlled by the cardiovascular centers which extend from the diencephalon to the spinal cord. The hypothalamus integrates inputs of cortical origin carrying autonomic responses evoked mainly by emotional stimuli. The medulla coordinates inputs in relation to the systemic hemodynamic state. The spinal cord integrates impulses from somatic structures (muscles, visceral organs, skin). A hierarchy exists, each center controlling the activity of the center below it. Automation of a center occurs only after de-afferentation of the overlying center. The final common pathway is represented by the autonomic nervous system. Changes in its activity best reflect the total needs of the organism. Thus, circulatory changes, such as those associated with hemorrhage, result in an adjustment of blood pressure via the medulla. In the same way, a stressful situa-

tion would produce, via the diencephalon, a hemodynamic response directed toward preparing the organism for muscular effort and defense. The dominating influence of the diencephalon on the medulla would dampen the effect of stimuli arriving at the medulla from the periphery. This mechanism would explain the maintenance of a raised arterial blood pressure in this case by an inhibition of the baroreflex.

Anatomic data on the organization of central cardiovascular connecting pathways are still fragmentary. Monoamines represent the central transmitters of the pathways, their mode of action depending on the type of amine involved.[27] Here we have mainly considered serotonin and catecholamines, but other neurotransmitters could be involved (histamine, acetylcholine, $\gamma$-aminobutyric acid, enkephalines, and as yet unidentified peptides).

With regard to arterial hypertension, certain arguments suggest that the brain could be an initiating factor. Owing to technological progress, it is now possible to investigate this promising possibility.

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# Endocrine Aspects of Hypertension

# 8

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## Renin-Angiotensin-Aldosterone System

### Historical Review

Around the turn of the century, Tigerstedt and Bergman produced hypertension in dogs by injecting a renal extract that they called renin.[43] Decades later, in their classic experiments, Goldblatt et al. succeeded in demonstrating a relationship between experimentally induced stenosis of the renal artery and hypertension.[23] Page and Helmer were the first to demonstrate that renin is an enzyme that acts on another substance to yield a vasoactive agent.[36] Similar observations were reported by Braun-Menéndez.[9] Later, the structural analysis of angiotensin II was successful, followed in turn by its synthesis.

### Renin

#### Chemistry and sites of formation

Renin is a proteolytic enzyme which has not yet been synthesized in a completely pure form. Recent work has shown that it occurs in human plasma and also in renal extracts in both an active form with a molecular weight of approximately 40,000 and in a relatively inactive form with a molecular weight of about 60,000. Characteristically, the activity of the heavier fraction can be increased by incubation at an acidic pH.

Renin is formed in granule-containing groups of cells at the vascular pole of the glomerulus which are supposedly derived from the smooth-muscle cells of the afferent arteriole.[19,25] The afferent arteriole which contains these cells, together with the efferent arteriole and the granule-containing cells at the vascular pole of the glomerulus, form an anatomical and functional unit called the juxtaglomerular apparatus.

Renin-like enzymes have been isolated thus far from various organs, e.g., the uterus, placenta, adrenal glands, and brain.[2,14,21,22,27,40] These renin-like enzymes are held responsible for the demonstration of renin activity in the plasma of patients without kidneys.[13] The importance of these substances in the regulation of blood pressure is not clear, however.

#### Mechanism of action

Renin itself does not have any physiologic effect. It catalyzes the conversion of its substrate, an $\alpha_2$-globulin formed in the liver (angiotensinogen), to angiotensin I, a nonvasopressor substance. This decapeptide is acted on by "converting enzyme," which splits off two end amino acids to form the octapeptide angiotensin II. This process takes place primarily in the pulmonary circulation,[5,31,32] but can also occur in tissue and plasma.[1]

Angiotensin II has a strong vasoconstricting action and therefore increases the blood pressure. It is rapidly degraded by aminopeptidases (angiotensinase). The resulting angiotensin II fragments probably have no physiologic importance, with the exception of the heptapeptide (angiotensin III). The heptapeptide is considered by some investigators to be the actual stimulus of the adrenal production of aldosterone,[8,24] although its pressor effect is less than that of angiotensin II.

#### Regulation of renin secretion

The exact mechanism leading to the release of renin is not known. However, there are indications that two intrarenal receptors in particular control the

regulation of renin secretion. The first receptor (baroreceptor theory) is of a vascular nature and appears to be located in the afferent arterioles of the juxtaglomerular apparatus. It reacts to changes in the arterial wall tension. The second receptor is the macula densa (macula densa theory), which supposedly reacts to changes in the amount of sodium delivered to the distal tubule. Renin secretion is further influenced by the sympathetic nervous system of the kidney. Finally, various humoral factors can cause a change in the secretion of renin.

***Baroreceptor Theory.*** The baroreceptor theory was advanced by Tobian and co-workers.[44] These investigators were able to demonstrate that an increase in the renal perfusion pressure led to a decrease in the granules in the juxtaglomerular apparatus (an index of the renin stored there). The results of experiments on nonfiltering, denervated kidneys of totally adrenalectomized dogs seem to confirm this theory.[6,7] In these animals, glomerular filtration was cut down by contralateral nephrectomy, temporary ligature of the renal artery, and ligature of the ureter. Influences of the sympathetic nervous system or circulating catecholamines were eliminated by denervation and adrenalectomy. Nevertheless, an increase in renin secretion could be attained in these animals by loss of blood and constriction of the abdominal aorta.

***Macula Densa Theory.*** Vander and Miller observed that renin secretion could be influenced by a change in the sodium content of the distal tubule, independent of the blood pressure.[46] Investigations using microperfusion of rat nephrons were able to show that under perfusion with isotonic saline, an increase occurred in the renin production in the juxtaglomerular apparatus, whereas no such increase occurred with the use of other sodium-free solutions.[26,45] These findings supported the assumption that renin release can be influenced, independent of perfusion pressure, by a change in the sodium content of the distal tubule. However, it remains unclear whether the renin release is stimulated by an increase or a decrease in the sodium content of the distal renal tubule.

***Autonomic Nervous System.*** A number of investigators have documented an influence of the autonomic nervous system on renin secretion. Nerve endings are structurally connected with the juxtaglomerular apparatus.[1,30,33,52] Electric stimulation of the sympathetic neuroplexus leads to an increase in renin production;[28,47] renal sympathectomy leads to inhibition of renin release.[10]

***Humoral Factors.*** The interpretation of the effect of circulating catecholamines on renin release is complicated by the fact that these substances simultaneously influence vascular tone. Studies with cell suspensions and renal tissue, however, were able to demonstrate a direct influence of catecholamines on the production of renin.[29,39] Potassium intake leads to a reduction in renin activity,[11,50] while potassium depletion causes an increase in renin secretion. ADH in physiologic concentrations is capable of suppressing renin release.[42] The site of action of ADH appears to be the juxtaglomerular apparatus, since the hormone also suppresses renin secretion in the nonfiltering kidney.[41]

### Feedback mechanism of renin secretion

An increase in renin secretion can cause a reduction in renin release by various feedback loops.

***Change in Vascular Tone.*** Angiotensin II can increase blood pressure by direct vasoconstriction. Furthermore, it is capable of changing the peripheral vascular resistance by acting on the central nervous system. Both mechanisms lead to a change in the wall tension of the baroreceptors and thereby influence renin secretion.

***Regulation by Aldosterone.*** Angiotensin II (and angiotensin III) is capable of indirectly influencing the blood pressure by stimulating the adrenal secretion of aldosterone. Aldosterone, the most important mineralocorticoid in man, causes increased sodium retention in the distal renal tubule and a consequent rise of blood pressure. As already discussed, renin secretion is then inhibited, either by an increase in the wall tension of the baroreceptors or by a change in the sodium content of the distal renal tubule.

***Circulating Angiotensin II.*** Experiments in sheep have shown that the secretion of renin can be directly influenced by circulating angiotensin II, independent of renal perfusion pressure or the sodium concentration in the distal renal tubule.

***Intrarenal Mechanism in the Nephron.*** Finally, an intrarenal feedback mechanism in the individual nephron has been postulated. Locally produced angiotensin II supposedly leads to vasoconstriction of the afferent arteriole. This, in turn, would result in a decrease in the glomerular filtration pressure with a consequent decrease of the sodium concentration in the distal renal tubule. According to this theory, the reduced level of sodium in the distal tubule would then inhibit the secretion of renin.

### Inhibitors

The renin-angiotensin inhibitors described thus far have shown one of the following characteristics: (1) direct blockade of renin; (2) inhibition of the renin/substrate reaction; (3) inhibition of the converting enzyme; and (4) antagonism of angiotensin II.

Inhibition of the renin-angiotensin system was first achieved with the use of renin antibodies.[17,38,51] However, since the production of specific antibodies is dependent on the purity of the immunogen, and renin could not be produced in a pure form, the antisera obtained with renin extracts showed low specificity. This may explain why the reduction in blood pressure originally observed in experimentally induced renovascular hypertension could not be reproduced by others.

The substances that inhibit the renin/substrate reaction are substrate analogs.[12,37] The use of these inhibitors of the renin-angiotensin system is partially limited by the fact that some of these substances are inactive at a physiologic pH. Converting enzyme inhibitors prevent the conversion of angiotensin I to angiotensin II.[3] These substances are of a peptide character and were originally isolated from snake venom.[20]

Of the inhibitors of the renin-angiotensin system, the angiotensin II analogs have been the most widely used. Recent investigations with these substances, conducted in normal persons and in patients with essential hypertension, renovascular hypertension, or other forms of secondary hypertension, have greatly extended our knowledge of the physiologic and pathophysiologic role of the renin-angiotensin system.

### Aldosterone

Aldosterone is the most important human mineralocorticoid. It is produced in the zona glomerulosa of the adrenal gland. Its primary physiologic importance lies in the exchange of potassium and hydrogen ions for sodium ions in the distal renal tubule. However, aldosterone does not possess renal effects only; it also influences the electrolyte metabolism in other body cells. Thus, its effects can be demonstrated in saliva, sweat, and intestinal secretions. The most important stimulus of aldosterone secretion is angiotensin II and its degradation product, the heptapeptide, angiotensin III.

Other major factors influencing the adrenal secretion of aldosterone are ACTH and changes in potassium metabolism. According to recent findings, the influence of ACTH appears to be modulated by the kidneys and the renin-angiotensin system. Thus, after bilateral nephrectomy, there is little or no demonstrable effect of endogenous ACTH on fluctuations of plasma aldosterone.[49] The infusion of exogenous ACTH causes a much greater increase in the concentration of plasma aldosterone in patients with terminal renal failure than in patients without kidneys.[35]

In normal persons, even a slight increase in potassium intake leads to a stimulation of aldosterone secretion.[18] Vice versa, even slight reductions in potassium intake cause a decrease in the adrenal secretion of aldosterone. There are many indications that the intracellular potassium concentration is the actual determinant of aldosterone synthesis. Thus, an increase in plasma aldosterone was achieved without changing the potassium metabolism by the administration of insulin with a subsequent transfer of potassium into the cells and a fall of serum potassium.[15,34]

The influence of serum sodium on aldosterone secretion is disputed. Animal experiments with infusions of solutions containing sodium were able to demonstrate a direct effect on the adrenal secretion of aldosterone,[16] whereas in nephrectomized patients no significant changes in plasma aldosterone levels could be observed in response to sodium reduction.[4] The contradictory results may be due in part to the fact that the observed changes in aldosterone secretion were not mediated directly by serum sodium, but indirectly through changes in renal renin secretion.

Investigations in nephrectomized patients have shown that possibly still other, unknown factors are involved in the regulation of aldosterone secretion.[48] The physiologic significance of these factors is not known.

## Hypertension Due to Steroid Hormones

The syndromes associated with hypertension induced by steroid hormones include Cushing's syndrome, primary aldosteronism, congenital adrenal hyperplasia, rare mineralocorticoid excess syndromes, and finally those syndromes caused by exogenous administration of steroid hormones or related substances.

The forms of hypertension caused by steroid hormones probably account for less than 1% of all hypertension cases. Nevertheless, their recognition is important because the majority of patients can be cured by surgical treatment. In the rest, an exact diagnosis usually permits specific medical therapy.

## Cushing's Syndrome

### Historical review

The syndrome was first described by Harvey Cushing in 1932.[36] Since then our understanding of its pathophysiology has changed greatly. Although it was once believed that a tumor of the anterior pituitary was the sole cause of the disease, later work showed that abnormally increased activity of hypothalamic centers triggered the disease in most patients.

### Frequency and severity of the hypertension

Over 80% of all patients with Cushing's syndrome have hypertension, the course of which can sometimes be very severe or even malignant.[117] In a considerable percentage of patients, hypertension persists in spite of surgical cure of the underlying disease. Thus, after bilateral adrenalectomy, 7 of 27 patients still had abnormally elevated blood pressure values.[110] In some of these cases, this was due to nephrosclerosis that had developed secondary to the hypertension.

### Forms of the disease

The syndrome can have the following forms:

***Hypothalamic-Pituitary Forms.*** In approximately 70% to 80% of the patients, there is increased production of ACTH. In some cases, the disease is caused by a basophilic adenoma of the anterior pituitary. In most patients, however, increased secretion of corticotropin releasing factor (CRF) is now considered responsible. The elevated CRF activity leads to an increase in the secretion of ACTH (corticotropin) with subsequent bilateral hyperplasia of the adrenal cortex and increased production of cortisol.

***Adrenal Forms.*** In about 20% of the patients, an adenoma or a carcinoma of the adrenal cortex causes an autonomous increase in the secretion of cortisol. Owing to the primary elevated secretion of cortisol, the production of ACTH is typically suppressed in these patients.

***Ectopic ACTH Syndrome.*** In the ectopic ACTH syndrome, autonomous production of ACTH-like peptides leads to bilateral hyperplasia of the adrenal cortex. Ectopic (paraneoplastic) production of ACTH-like peptides is found primarily in oat cell carcinoma of the lung, bronchogenic carcinoma and bronchoadenoma, and carcinoma of the thymus gland. The tumors are attributed to the APUD (amine precursor uptake and decarboxylation) system.[113] The tumors of the APUD system are of neuroectodermal origin. The majority of the peptide-producing tumors, collectively called apudomas, are derived from this system.[144] The ectopic ACTH syndrome differs from the other forms of Cushing's syndrome primarily in that the biochemical abnormalities of the oversecretion of cortisol are more evident than the clinical abnormalities. Thus, pronounced hypokalemic alkalosis is the leading symptom of ectopic ACTH syndrome.

### Pathogenesis of hypertension

The exact pathogenic mechanism in over 80% of hypertensive patients has not been established as yet. A possible cause of the increase in blood pressure is an elevated production of other steroids, chiefly mineralocorticoids, or a mineralocorticoid effect of high cortisol levels. The main proponents of the mineralocorticoid theory are Biglieri et al.[14] Indirect evidence in support of such a pathogenesis would be a more or less pronounced hypokalemic alkalosis resulting from the renal effect of mineralocorticoid hormones.[14] Abnormally low serum potassium concentrations are, in fact, observed in some of the patients; however, normal values also occur (Table 1). Increased production of mineralocorticoid steroids, such as aldosterone, desoxycortisone (DOC), 11-desoxycortisol, and corticosterone, is apparently not solely responsible for the hypertension, since the levels of these substances can be either normal or elevated in patients with Cushing's syndrome.[35,109,120]

A further mechanism that could be responsible is a glucocorticoid-induced increase in vascular responsiveness to circulating catecholamines. Thus, studies in animals[74] as well as investigations in normal persons and patients with Cushing's syndrome[96] were able to show that the response of vascular smooth muscle to norepinephrine is heightened in the presence of a cortisol excess. Cortisol apparently inhibits the enzymatic catabolism of norepinephrine in the wall of the blood vessel.

In recent investigations it has been postulated that the renin-angiotensin system is involved in the pathogenesis of hypertension.[82] In patients with hypercorticism, the cortisol excess first causes an increase in the renin substrate produced in the liver,[81] which in turn leads to an increased production of the vasopressor agent angiotensin II and, consequently, to hypertension.

To examine the role of the renin-angiotensin system, we infused an angiotensin II antagonist (saralasin) in three patients with Cushing's syndrome, while closely monitoring their blood pressures (Fig. 1). Three patients with primary aldosteronism, an established form of mineralocorticoid hypertension, served as controls. Under the infusion of saralasin,

**Table 1.** Clinical and Laboratory Data in Cushing's Syndrome[a]

| Form of Cushing's Syndrome | Patient No. | Age (years) | Sex | BP (mm Hg) | Serum Potassium (mEq/liter) (normal 3.5–4.5) | Urine Cortisol (μg/24 h) (normal 20–120) |
|---|---|---|---|---|---|---|
| Hypothalamic-pituitary form | 1 | 12 | M | 120/85 | 3.9 | *147* |
| | 2 | 29 | F | 120/70 | 3.5 | *180* |
| | 3 | 12 | M | 140/90 | 3.8 | *1180* |
| | 4 | 22 | F | 150/100 | 4.3 | *520* |
| | 5 | 36 | M | 160/110 | 4.5 | *350* |
| | 6 | 31 | M | 175/120 | 4.9 | *555* |
| | 7 | 26 | F | 140/100 | 4.3 | *240* |
| | 8 | 40 | F | 150/110 | 4.1 | *250* |
| | 9 | 39 | M | 170/110 | 3.7 | *1080* |
| | 10 | 43 | M | 160/110 | 4.1 | *260* |
| | 11 | 60 | F | 150/100 | 4.0 | *180* |
| Adrenal forms | | | | | | |
| Adenoma | 12 | 44 | F | 190/110 | *3.2* | *410* |
| | 13 | 18 | F | 170/115 | 3.9 | *3900* |
| | 14 | 20 | F | 160/130 | *3.0* | *860* |
| | 15 | 48 | F | 160/115 | 4.2 | *220* |
| Carcinoma | 16 | 68 | F | 195/120 | *2.9* | *3600* |
| | 17 | 47 | F | 205/125 | *3.0* | *330* |
| | 18 | 59 | F | 190/110 | *2.6* | *890* |

[a]11 patients with hypothalamic–pituitary dysfunction and 7 patients with adrenal forms (adrenal adenoma n-4, adrenal carcinoma n-3). Pathologic values are in italic.

there was no significant fall of blood pressure in either the patients with Cushing's syndrome or those with primary aldosteronism. Consequently, it appears unlikely that the renin-angiotensin system plays an essential role in the pathogenesis of hypertension in Cushing's syndrome.[141]

## Diagnosis

***Clinical Symptoms.*** The diagnosis of hypertension in Cushing's syndrome usually does not pose major problems once the primary disease has been suspected on the basis of clinical symptoms, i.e.,

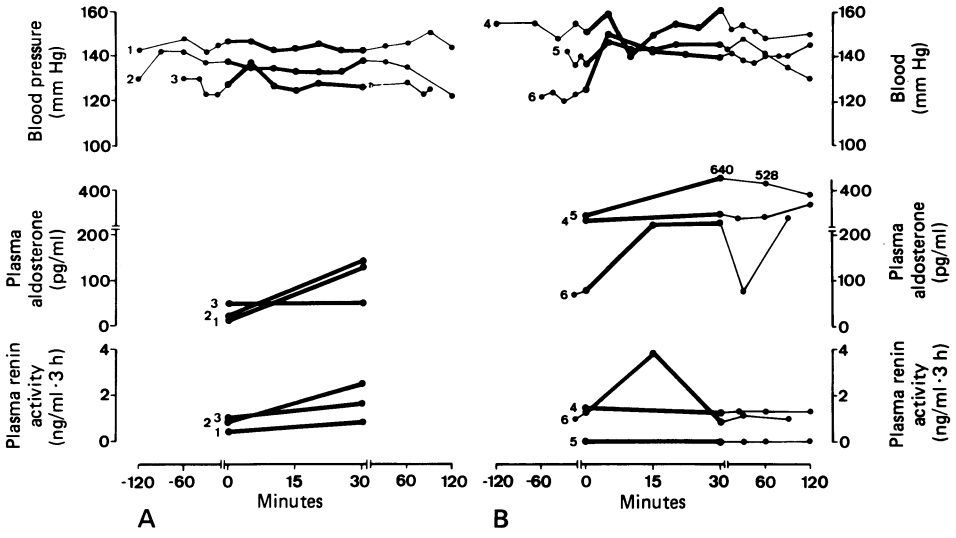


**Figure 1.** Effect of a 30-min infusion of 20 mg of saralasin (I-sar-8-ala-angiotensin-II) on mean arterial pressure, renin activity (ng/ml·3 h) and plasma aldosterone (pg/ml) in three patients with (**A**) Cushing's syndrome (1–3) and three patients with (**B**) primary aldosteronism (Conn's syndrome) (4–6). The duration of saralasin infusion is indicated by thick solid lines.

central truncal obesity, "buffalo hump," purple striae, hirsutism, acne, muscular weakness, and ecchymosis (Fig. 2). In some patients with hypertension and cushingoid aspect, however, differentiation from patients with genuine Cushing's syndrome can be impossible on the basis of the clinical symptoms alone. Analysis of the clinical symptoms of a large number of patients with suspected or established Cushing's syndrome has shown that, as criteria for differential diagnosis, the presence of central truncal obesity, muscular weakness, or ecchymosis should be rated much higher than the demonstration of acne, striae, or hirsutism.[108] In addition, the radiologic demonstration of osteoporosis strongly suggests the presence of Cushing's syndrome.

Clinically, in addition to the characteristic symptoms already listed, the patients exhibit a pronounced elevation of blood pressure, especially diastolic (Table 1). In many cases the hypertension is characterized by a striking resistance to therapy, even with aldosterone antagonists.

***Laboratory Findings.*** Laboratory findings often show hypokalemia, but this is by no means present in all cases (Table 1). A marked decrease in the serum potassium concentration points to the presence of a carcinoma of the adrenal cortex, since this form of Cushing's syndrome often features strongly increased production of steroid hormones with a primary mineralocorticoid effect.

Urinary excretion rates of free cortisol (Table 1) or 17-hydroxycorticosteroid (17-OHCS) are high as a rule; however, normal values are also observed in some cases.[60] Single determinations of the plasma cortisol or 17-OHCS level are not very reliable, since a single normal or increased plasma level by no means excludes Cushing's syndrome. In addition, the episodic secretion of cortisol both in normal subjects and in patients with Cushing's syndrome can cause great fluctuations in the plasma cortisol over a short period of time.[2,64]

The original assumption of several authors that the demonstration of a circadian rhythm of the plasma cortisol indicates the presence of a hypothalamic-pituitary form of the disease, and that the absence of a daily fluctuation can be assigned to an adrenal Cushing's syndrome,[134] could not be confirmed in a relatively large number of patients.[124,137] Thus, most patients with hypothalamic-pituitary Cushing's syndrome showed no circadian rhythm of the plasma cortisol.[137] However, daily fluctuation was never demonstrated in patients with adenoma or carcinoma of the adrenal cortex. The very elaborate protocol by which these investigations are conducted prevents the use of such procedures in the routine evaluation of Cushing's syndrome.

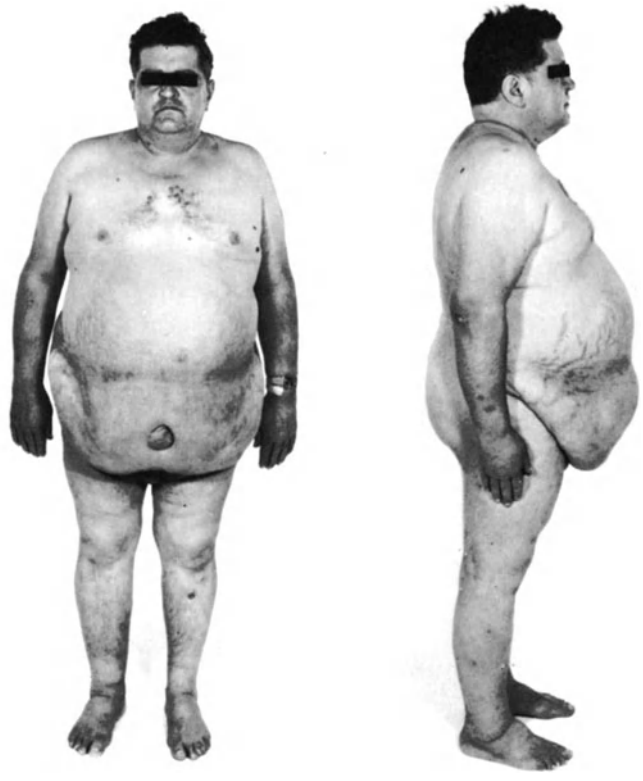

**Figure 2.** Typical cushingoid aspect in a 43-year-old patient with a hypothalamic-pituitary form of the disease.

As a screening test, the overnight dexamethasone suppression test has proved valuable.[107] In this test the patient receives 1 mg dexamethasone orally between 11 and 12 P.M. the night before blood sampling. Normal patients will suppress the morning plasma cortisol (determined at 8 A.M.) to less than 10 μg per 100 ml, whereas the concentration in patients with Cushing's syndrome is considerably above this level. In some patients without Cushing's syndrome, suppression of the plasma 17-OHCS could not be attained, apparently owing to the stress imposed by hospitalization.[33] In contrast, in rare cases, normal suppression has been observed in bilateral adrenocortical hyperplasia.[131]

For the diagnosis of Cushing's syndrome, the 2 mg dexamethasone inhibition test is best-suited. Several years ago Liddle reported that after 2 days of oral administration of 0.5 mg dexamethasone every 6 h, the urinary excretion of 17-OHCS was reduced by more than 50% from the baseline level in normal persons but not in patients with Cushing's syndrome of varying etiology.[85] An extension of the study protocol to 3 days does not increase the reliability of the test.[145]

The type of underlying disorder can usually be recognized by the oral administration of 2 mg dexamethasone every 6 h for 2 days. Within this period of time, patients with adrenal forms of Cushing's syndrome (adenoma, carcinoma of the adrenal cortex) or those with ectopic ACTH syndrome usually do not show suppression exceeding 50% of the baseline level (urinary excretion of free cortisol or 17-OHCS), whereas patients with a hypothalamic-pituitary form do show such a reduction. In some of the cases, there is a paradoxical increase in cortisol excretion as, for example, in adenoma of the adrenal cortex,[70,122,124] in carcinoma,[34,70,122] and—more frequently—in hypothalamic-pituitary Cushing's syndrome.[17,20,53,70,88,122] In patients with a hypothalamic-pituitary form of Cushing's syndrome and a paradoxical response to dexamethasone (8 mg/day), a significant suppression could be attained with very high doses of dexamethasone (32 mg/day).[88]

The paradoxical response to dexamethasone could be attributed to periodic and spontaneous fluctuations in adrenal cortisol secretion in an excellent study by Brown and co-workers.[20] These periodic fluctuations in cortisol synthesis, with temporary normal hormone values, have been repeatedly described in patients with Cushing's syndrome. Histologically, bilateral adrenocortical hyperplasia due to abnormally increased activity of the hypothalamic-pituitary system was usually found in these cases;[5,7,15,17,53] however, a chromophobe adenoma of the pituitary,[20] adenoma of the adrenal cortex,[57] carcinoma,[34] and ectopic ACTH production by a malignant tumor[122] have also been observed.

The metyrapone test or ACTH infusion tests are of only limited use in the evaluation of Cushing's syndrome.

Adrenal venography and determination of cortisol levels in adrenal venous blood were formerly carried out to localize the cortisol-producing tumors. However, these methods are rarely used today. In addition, owing especially to the increased vascular fragility demonstrable in Cushing's syndrome, adrenal venography carries the risk of injury to the adrenal tissue and consequent adrenocortical insufficiency.[8,72]

Of the newer methods, the $^{131}$I-iodocholesterol scintiscan has proved valuable for lateralization of the tumor responsible for overproduction of cortisol.[16,87] In the presence of an adrenocortical adenoma, unilaterally increased uptake of the radioactive compound occurs on the affected side, while there is little or no visualization of the unaffected side (Fig. 3) In the hypothalamic-pituitary form of Cushing's syndrome (Fig. 3) or ectopic ACTH syndrome, the increased production of ACTH or ACTH-like substances leads to bilateral adrenocortical hyperplasia. In these cases, there is enhanced visualization of both adrenals after administration of $^{131}$I-iodocholesterol. Adrenal carcinomas can usually be visualized only weakly, if at all, by $^{131}$I-iodocholesterol.[63,71] In one case, however, it was possible to identify a local recurrence and metastases by means of the scintiscan technique.[52] In another case a metastasis in the pelvic area was visualized, while there was no measurable radioactivity in other metastases in the area of the abdomen and lungs.[42]

There is as yet only limited experience with a new substance (NP-59) that is possibly tumor-specific.[118]

### Treatment

In patients with an adrenal form of Cushing's syndrome (adenoma and carcinoma), unilateral adrenalectomy is performed. Postoperative cortisol replacement is not required. Bilateral adrenalectomy is usually performed in patients with hypothalamic-pituitary Cushing's syndrome. In approximately 10% of these patients, Nelson's syndrome develops postoperatively, regardless of whether irradiation of the pituitary was done before surgery[99] or not.[98] Nelson's syndrome is defined as hyperpigmentation with[92] or without[93] demonstration of a pituitary tumor. Excessively high plasma levels of ACTH are characteristic of patients with Nelson's syndrome. Relatively high recurrence rates are associated with transtemporal hypophysectomy and irradiation of the pituitary in the treatment of the hypothalamic-pituitary form. There is still no extensive experience with transsphenoidal hypophysectomy. However, the results of one study published thus far do appear promising.[24]

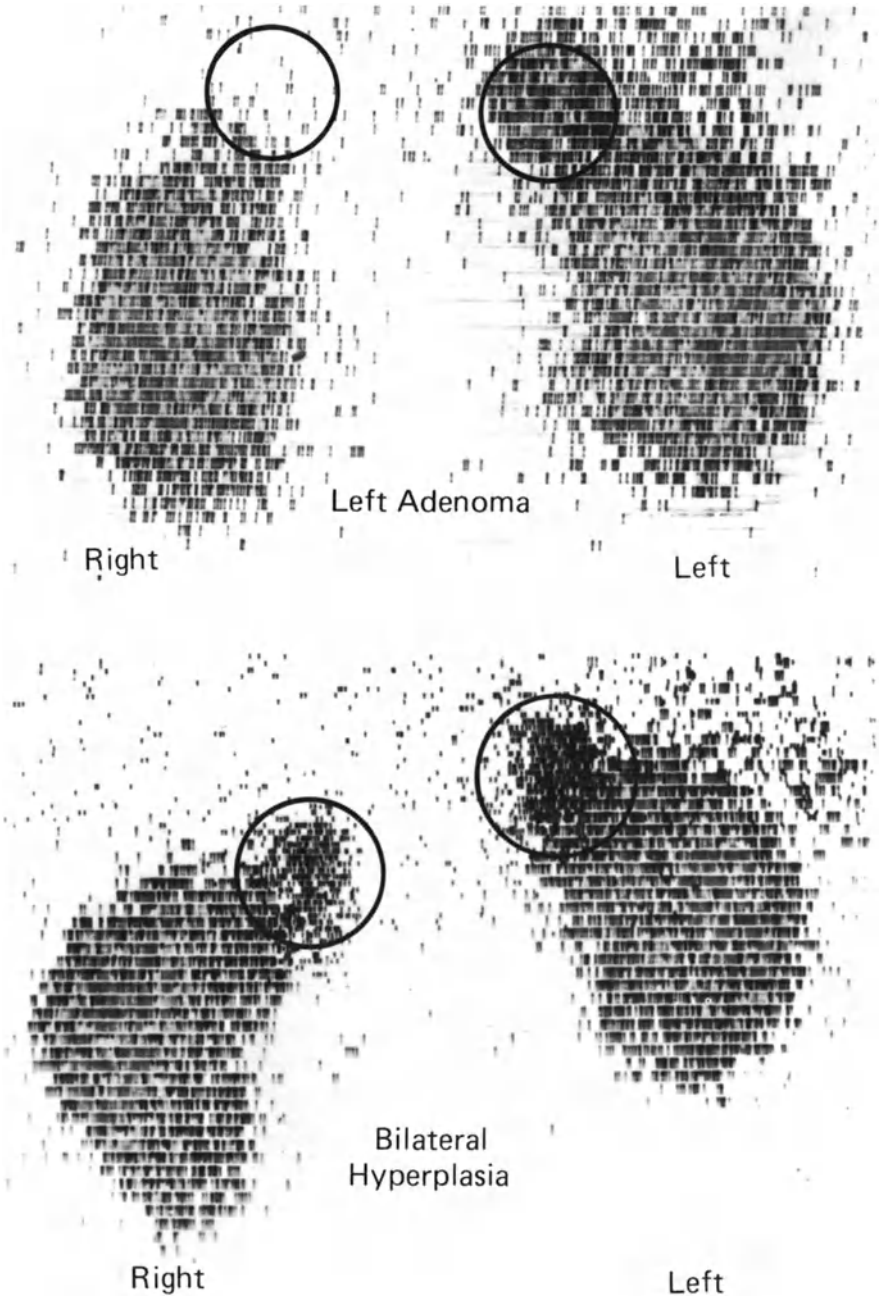


**Figure 3.** $^{131}$I-iodocholesterol scintiscan in adrenal (left adenoma) as well as hypothalamic-pituitary Cushing's syndrome (bilateral hyperplasia). The findings in the adrenal glands are circled for emphasis.

A number of different medications have been used in the treatment of Cushing's syndrome. These are either substances with a direct effect on the adrenal production of cortisol (metyrapone, aminoglutethimide, *o,p'*-DDD) or drugs acting on the central nervous system and hypothalamus (reserpine, cyproheptadine, bromocriptine). Simultaneous administration of these medications has been described.[25] High doses of reserpine have been combined with irradiation of the pituitary with relatively good results.[97] It must be noted that treatment with aminoglutethimide or *o,p'*-DDD may require simultaneous cortisol replacement therapy to avoid an adrenal crisis. In the treatment of inoperable or

metastasizing adrenal cortical carcinoma, *o,p'*-DDD is primarily used at present.[67]

The first neurotransmission-inhibiting substances to be used in the treatment of the hypothalamic-pituitary form of Cushing's syndrome were the serotonin antagonist, cyproheptadine, and the prolactin inhibitor, bromocriptine.[83] Treatment failure has also been described, however.[142]

In ectopic Cushing's syndrome due to paraneoplastic production of ACTH, metyrapone influences the metabolic disorder (hypokalemic alkalosis) without altering the course of the primary disease.[111]

## Primary Aldosteronism

### Historical review

In 1955, Conn[27] first described a patient with hypokalemic hypertension due to an aldosterone-producing adenoma of the adrenal cortex (Conn's syndrome). A few years later, other investigators discovered that the same symptoms can be caused by idiopathic bilateral adrenocortical hyperplasia.[4,39,43,78]

### Frequency and severity of the hypertension

The disease is much less common than Conn originally assumed.[28] Later investigations showed an incidence of primary aldosteronism in a total group of all hypertensive patients of less than 1% as compared to the 7.5% estimated by Conn.[49,58,77]

Contrary to earlier opinion,[31] the hypertension is not benign. Vascular complications have been observed in a very high percentage of cases.[9,37] Malignant hypertension has been repeatedly described.[9,40,75]

### Forms of the disease

***Aldosterone-Producing Adenoma and Carcinoma.*** Primary aldosteronism is caused by an adenoma of the adrenal cortex, usually solitary, in 70% to 80% of the cases. The adenomas are often small and weigh less than 6 g;[100] hyperplasia of both the surrounding adrenal tissue and the contralateral adrenal has been described.[100,123] Left-sided adenomas appear to be more common than right-sided ones. Multiple adenomas in one adrenal gland or bilateral adenomas are rare.[100] The degree of hormone secretion often shows no relationship to the size of the tumor.[95] Thus, very small adenomas may be accompanied by very high aldosterone secretion and relatively large adenomas by low hormone release. Aldosterone-producing carcinomas are extremely rare.

***Idiopathic Bilateral Adrenocortical Hyperplasia.*** In 20% to 30% of the patients, idiopathic bilateral adrenocortical hyperplasia is the cause of the primary aldosteronism. Differentiation is made between macronodular, micronodular, and diffuse (microscopic) hyperplasia. The pathogenesis of hyperplasia of the adrenal cortex is not known; however, there are indications that an extra-adrenal factor contributes to the pathogenesis of hypertension in adrenocortical hyperplasia.[102]

***Glucocorticoid-Curable Form.*** There is another form of primary aldosteronism with adrenocortical hyperplasia that can be cured with glucocorticoids, i.e., in which the blood pressure can be normalized by administration of glucocorticoids.[125]

***Tertiary Aldosteronism.*** The existence of a "tertiary aldosteronism" is disputed. In this form of aldosteronism, stimulation of the renin-angiotensin system is supposed to cause an initial increase in aldosterone secretion. Later, autonomy of the adrenal secretion of aldosterone is said to occur, which then leads to a suppression of renal renin production. This theory is based on the observation that renal artery stenosis was also present in some cases of primary aldosteronism.[9,31,65,84] However, this may involve the coincidental concurrence of two different syndromes.

***Extra-Adrenal Production of Aldosterone.*** Production of aldosterone by extra-adrenal tumors has been described in only a few cases. An ovarian tumor was found in two patients,[45,133] and in one other patient there was an adrenal adenoma at the lower pole of a kidney.[50]

### Diagnosis

***Clinical Symptoms.*** The clinical symptoms, as well as the laboratory abnormalities, are a result of the abnormally increased production of aldosterone and its influence on the metabolism of water and electrolytes. In addition to the elevated blood pressure demonstrable in all patients, in a considerable percentage of the patients there is muscular weakness, fatigue, and, more rarely, transient paralysis, intermittent tetany, and paresthesias.

#### *Laboratory Findings*

*Serum Potassium and Alkalosis.* As discussed earlier, the primary effect of aldosterone is the exchange of potassium and hydrogen ions with sodium ions in the distal renal tubule. An abnormal increase in this process due to an adrenal overproduction of

aldosterone is the principal symptom of the disease, hypokalemic alkalosis. Hypokalemia is observed in practically all cases (Table 2). In those patients in whom hypokalemia is not demonstrable, it can usually be induced by salt loading. Because of the danger of hypokalemia developing rapidly, serum potassium levels should always be closely monitored during salt loading (> 200 mEq sodium/day). In addition, there are other less elaborate procedures available today to confirm the diagnosis of primary aldosteronism.

Likewise, if abnormally low serum potassium levels persist even though diuretics have been discontinued for several weeks, primary aldosteronism should be suspected; normokalemia is uncommon in this disease.[18,30,56]

Since aldosterone-induced potassium loss is limited under salt deprivation by the decreased amount of sodium in the distal tubule, sodium deprivation in patients with primary aldosteronism often leads to a rise of the serum potassium.[56,138] Consequently, a reduction in sodium intake can possibly be held responsible for the occurrence of a normokalemic primary aldosteronism.

*Potassium Excretion.* In primary aldosteronism, the potassium loss occurs primarily through the kidneys. The determination of urinary excretion of potassium is, therefore, a valuable screening test. In most patients, the daily renal excretion of potassium is above 40 mEq/day (Table 2).

*Special Laboratory Diagnostic Procedures.* Diagnosis is confirmed by the simultaneous determination of renin activity or renin concentration and the plasma aldosterone level in peripheral venous blood. Owing to the relationship between aldosterone production and renal renin release already mentioned, the typical feature seen in primary aldosteronism is that of low, or immeasurable, renin

**Table 2.** Clinical and Laboratory Data of 25 Patients with Primary Aldosteronism[a]

| Form of Disease | Patient No. | Age (years) | Sex | BP (mm Hg) | Serum Potassium (mEq/liter) (normal 3.5–4.5) | Urine Potassium (mEq/24 h) (normal 35–90) | Aldosterone-18-glucuronide (μg/24 h) (normal 4–13) |
|---|---|---|---|---|---|---|---|
| Aldosterone-producing adenoma | 1 | 44 | F | 230/130 | 2.3 | 72 | 180 |
| | 2 | 52 | F | 250/120 | 2.6 | 121 | 14 |
| | 3 | 32 | F | 180/120 | 3.1 | 75 | 32 |
| | 4 | 45 | F | 170/110 | 2.6 | 33 | 8 |
| | 5 | 29 | F | 170/110 | 3.2 | 85 | 22 |
| | 6 | 51 | M | 200/120 | 2.1 | 85 | 19 |
| | 7 | 38 | F | 170/110 | 2.8 | 86 | 26 |
| | 8 | 31 | M | 180/120 | 3.0 | 116 | 440 |
| | 9 | 39 | F | 190/100 | 2.7 | 75 | 36 |
| | 10 | 60 | M | 235/105 | 3.5 | 79 | 8 |
| | 11 | 41 | F | 190/125 | 2.5 | 47 | 110 |
| | 12 | 48 | M | 220/130 | 2.6 | 85 | 29 |
| | 13 | 45 | F | 250/120 | 3.1 | 75 | 18 |
| | 14 | 60 | M | 200/120 | 3.0 | 43 | 29 |
| | 15 | 56 | M | 200/120 | 2.0 | 94 | 19 |
| | 16 | 38 | F | 170/125 | 2.5 | 80 | 32 |
| Adrenal carcinoma | 17 | 59 | F | 170/100 | 2.7 | 125 | 97 |
| Adrenal hyperplasia | 18 | 40 | F | 220/140 | 3.0 | 85 | 31 |
| | 19 | 39 | M | 230/125 | 2.2 | 81 | 8 |
| | 20 | 57 | M | 190/120 | 3.2 | 76 | 14 |
| | 21 | 47 | M | 190/130 | 2.3 | 105 | 24 |
| | 22 | 42 | M | 170/120 | 3.1 | 125 | 53 |
| | 23 | 50 | M | 180/120 | 3.0 | 85 | 61 |
| | 24 | 65 | M | 220/130 | 2.9 | 43 | 10 |
| | 25 | 25 | F | 170/125 | 2.8 | 80 | 21 |

[a]16 patients with an aldosterone producing adenoma, 1 patient with an adrenal carcinoma, and 8 patients with bilateral adrenal hyperplasia. In each case diagnosis was confirmed by surgery.

activity with abnormally elevated plasma aldosterone (Fig. 4). Patients with hyperplasia often show a low but measurable renin activity at rest, which usually increases slightly upon standing. In contrast, immeasurable renin activity both at rest and on standing is often observed in patients with adenoma (Fig. 4).

In the diagnosis of primary aldosteronism, determination of the urinary excretion of the acid-labile aldosterone-18-glucuronide can also be used. As a rule, the excretion rate of aldosterone-18-glucuronide is abnormally increased. However, at times normal values can also occur (Table 2).

In patients with primary aldosteronism, the urinary excretion rate of aldosterone or plasma aldosterone levels are scarcely influenced by various suppressive measures. Among such measures mentioned in the literature are sodium infusion,[79] infusion or oral ingestion of hydrocortisone,[106] high (oral) salt intake for several days,[23] intramuscular

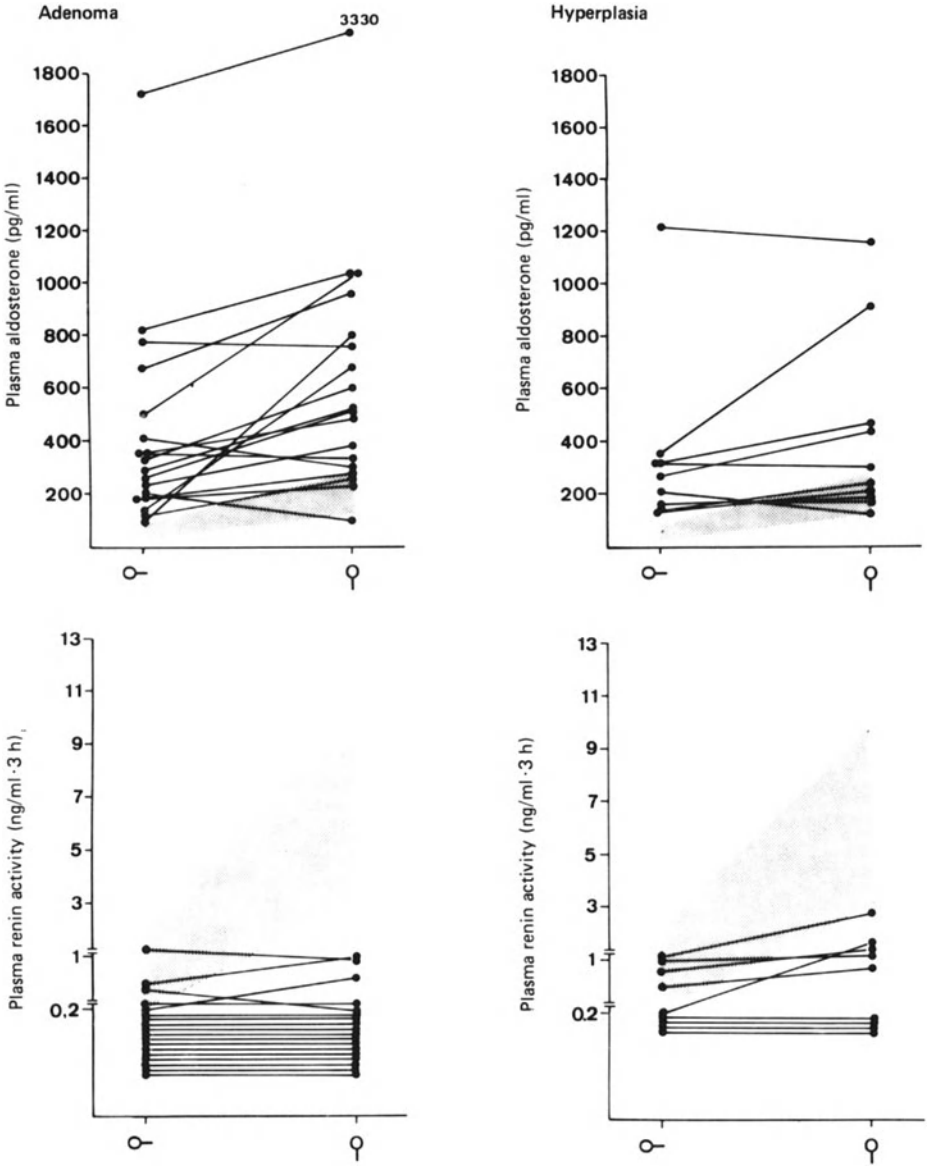


**Figure 4.** Plasma aldosterone (pg/ml) and plasma renin activity (ng/ml·3 h) at 8 AM after overnight bed rest (♂—) as well as after subsequent 2-h ambulation (♀) in patients with primary aldosteronism (aldosterone-producing adrenocortical adenoma, n = 18; bilateral idiopathic adrenocortical hyperplasia, n = 10). Normal ranges are indicated by shaded grids.

injection of 10 mg DOCA every 12 h for 3 days,[127] and oral administration of fludrocortisone every 12 h for 3 days.[13]

However, it must be noted that suppression of the urinary excretion rate of aldosterone demonstrable, for example, under the administration of glucocorticoids does not exclude an aldosterone-producing adenoma of the adrenal cortex in every case.[106] Likewise, in some cases, a marked fall of plasma aldosterone under fludrocortisone can be observed in patients with adenoma as well as in those with hyperplasia.[112] The same is true, according to our experience, for the effect of oral salt loading on the plasma aldosterone level in patients with primary aldosteronism. Consequently, the diagnostic value of these investigations is limited.

### Differentiation between adenoma and hyperplasia

Distinguishing between adenoma and hyperplasia is important, because only patients with an adenoma should undergo adrenalectomy, whereas total or subtotal bilateral adrenalectomy in patients with idiopathic hyperplasia influences the blood pressure only slightly or not at all.[46]

Ferris and co-workers[47] and, in the same group, Aitchison and co-workers[1] (in a retrospective study) used multidimensional analysis of clinical and laboratory data to differentiate between patients with adenoma and those with idiopathic hyperplasia.

Ganguly and co-workers were the first to attempt to distinguish cases of adenoma from those with hyperplasia on the basis of the response of plasma aldosterone following upright posture.[55] Patients with an aldosterone-producing adenoma always exhibited a fall in the plasma aldosterone concentration, whereas an increase was consistently observed in patients with hyperplasia. Later investigations either confirmed these results[11,119] or partially refuted them,[138] although different durations of the upright posture maneuver were chosen by the individual investigators (Fig. 4).

Biglieri and co-workers[11] used the level of the resting plasma renin and the aldosterone values determined after the administration of DOC to differentiate between the two forms of the disease. Other investigators were not able to confirm this.[89] It appears that, under various suppressive maneuvers, no fundamentally different response can be observed between cases of adenoma and hyperplasia.[23]

In the differential diagnosis of the two forms of the disease, the level of the resting plasma aldosterone has also been used.[11] The plasma aldosterone concentration in cases of adenoma was always above 195 pg/ml, whereas it was below this level in hyperplasia. Research in our group has not been able to confirm these findings (Fig. 4). Although the resting plasma aldosterone concentration is higher on an average in patients with adenoma than in those with hyperplasia, a considerable overlapping of individual values in both groups can be observed.

Finally, another method that has been used to differentiate between adenoma and hyperplasia is the response of daily temporal fluctuations of plasma aldosterone to simultaneous changes in the cortisol level.[136] Patients with adrenocortical adenoma showed a significant correlation between aldosterone and cortisol, while no such correlation was demonstrable in cases of adrenocortical hyperplasia.[138,139] Later, other investigators also demonstrated significant correlations between cortisol and aldosterone in some cases of hyperplasia.[80,119]

In summary, it seems that reliable differentiation between aldosterone-producing adenoma and hyperplasia is not possible on the basis of peripheral criteria. Other procedures must be used for this purpose.

***Adrenal Venography.*** This method was first used by Bucht[21,22] and later by Starer[130] to demonstrate adenoma of the adrenal cortex. The method was improved in the following years by modifying the technique for catheterization of the right adrenal vein.[116] It must be emphasized, however, that catheterization of the right adrenal vein is difficult and often unsuccessful. In some cases, radiographic visualization of the right adrenal gland is achieved by venography, but it is not possible to obtain a blood sample for simultaneous determination of aldosterone concentration.

According to Kahn and co-workers, the procedure is capable of revealing adenomas as small as 1 cm in diameter.[73] Other investigators were able to identify adenomas with a diameter of 0.7 cm, provided that the tumor was marginal.[148] Since the contrast material is injected into the adrenal vein under relatively strong pressure, injury of the adrenal tissue, with remission of the aldosteronism[48] and simultaneous adrenocortical insufficiency,[44,132] can occur. However, the number of these cases appears to be negligibly small when compared to the total number of patients with primary aldosteronism in whom venography has been performed up to now. Relatively more often, the patients complain of flank pain that generally disappears within 24 h.

In cases of adenoma, the adrenal veins are usually dislocated in a typical manner (Fig. 5). In adrenocortical hyperplasia, markedly enlarged adrenal glands can be demonstrated in some cases. Normal venographic findings, however, exclude neither a small adenoma nor hyperplasia.

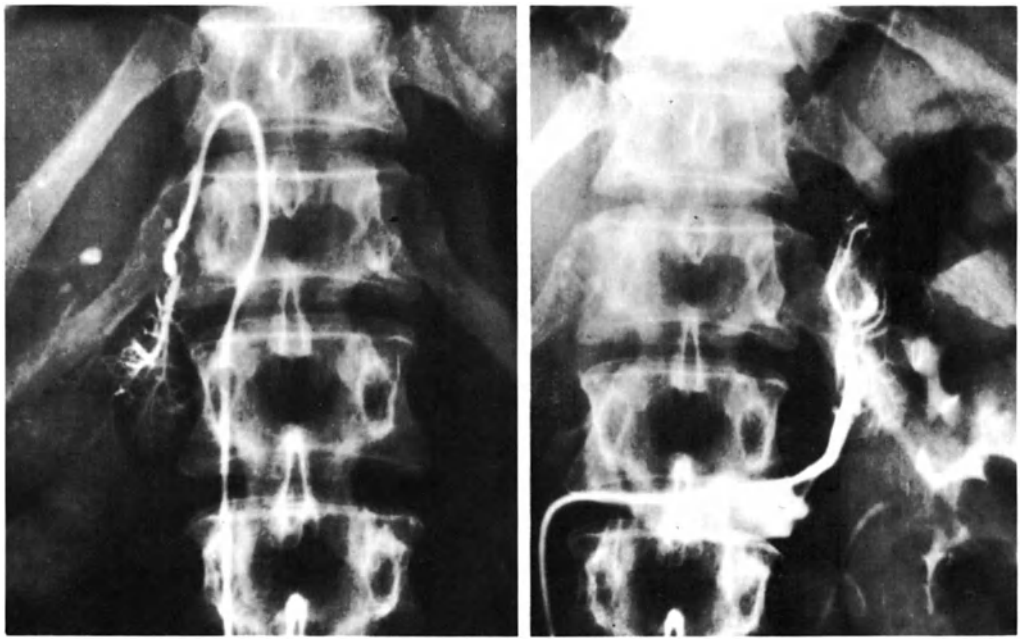

**Figure 5.** Adrenal venography in a 53-year-old woman with primary aldosteronism, showing a small adenoma in the left adrenal gland which is characterized by the arched displacement of the adrenal veins. Normal venographic visualization of the right adrenal gland. A small adenoma of the left adrenal gland was found at surgery.

***Aldosterone in Adrenal Venous Blood.*** In the opinion of most authors, this is the most reliable method of localizing a unilateral tumor that is overproducing aldosterone.[73,95,103] Blood is taken from both adrenal veins for determination of aldosterone before adrenal venography is performed. To assure that adrenal venous blood has actually been obtained, the simultaneous determination of cortisol concentration is absolutely essential. The cortisol value determined in an adrenal vein should be at least two to three times greater than a value measured in the vena cava (below the junction of the renal veins). If this criterion is not met, then the determination must be rejected in case of doubt.

However, it must be noted that the episodic secretion of steroid hormones may lead to considerable fluctuations of cortisol and aldosterone within a few minutes in both normal persons[104,128] and in patients with primary aldosteronism.[140] This can make the interpretation of values considerably more difficult.

Spark and co-workers were able to observe a difference of up to four-fold between concentrations of cortisol on the right and left sides when blood was not taken from both adrenal veins simultaneously.[128] This is consistent with our experience in patients with primary aldosteronism, which showed that when blood was not taken simultaneously from both adrenal veins the demonstration of a significantly different adrenal vein aldosterone concentration did not allow the diagnosis of a unilateral adenoma. Significant differences in the plasma aldosterone concentration in both adrenal veins can also be observed in idiopathic bilateral hyperplasia.

The diagnosis of unilateral adenoma can be made with some certainty, according to our experience, if one or both of the following criteria are met:

1. Low aldosterone ($<$ 1000 pg/ml) on one side indicates a contralateral adenoma
2. High aldosterone ($>$ 40,000 pg/ml) on one side indicates a hormonally active tumor on the same side

The value of the method is limited by the fact that in some cases catheterization of the right adrenal vein is unsuccessful or that, after catheterization, withdrawal of blood is not possible. Since an aldosterone value determined unilaterally (on the left side) does not permit differentiation between adenoma and hyperplasia, additional venographic visualization of one or both adrenal glands should always be performed.

Some authors have described procedures which are supposed to permit localization of an adenoma by comparing the aldosterone level in the left adrenal vein with peripheral aldosterone values[121] or by comparing the values measured in the renal veins

with those measured in the vena cava (above the junction of the right adrenal vein).[54]

***Adrenal Scintiscan.*** This method utilizes the uptake by adrenal tissue of a radiolabeled precursor of the steroid hormone $^{131}$I-iodocholesterol.[16,87] Unilateral adenomas are registered as high concentrations of radioactivity at the respective kidney pole, whereas in typical cases, there is little or no visualization of the healthy contralateral side. In cases of idiopathic adrenocortical hyperplasia, increased radioactivity is measured over both adrenals.

Some authors have drawn attention to the fact that when the standard method is performed, asymmetric concentrations of radioactivity can be demonstrated relatively frequently in bilateral hyperplasia.[29,123] This falsely positive result is supposedly not observed when a "suppression scintiscan" is used.[29,123] In the suppression scintiscan the investigation is done after dexamethasone is given to inhibit ACTH secretion. There is no uptake of radioactivity by aldosterone-producing adrenal carcinomas.[66]

***Computed Tomography.*** This method has recently been introduced as a means of diagnosing and localizing adrenal diseases. In our experience with the method in patients with a unilateral aldosterone-secreting adrenocortical adenoma ($n$ = 7), small adenomas less than 1 cm in diameter could not be detected by computed tomography ($n$ = 2).

### Treatment

Unilateral aldosterone-producing adenomas or carcinomas are usually surgically removed. The extent of the postoperative fall of blood pressure after resection correlates with the preoperative response to spironolactone.[19]

In patients with bilateral adrenocortical hyperplasia, unilateral or bilateral adrenalectomy does not influence or only temporarily influences the hypertension in the vast majority of patients.[46] Hence, these patients should receive antihypertensive therapy. Clinical experience shows that spironolactone is only inadequately effective in some patients with bilateral hyperplasia. In these cases, a combination of an aldosterone antagonist with a thiazide diuretic may have a good blood pressure lowering effect.

## Congenital Adrenocortical Hyperplasia

Some of the enzymatic defects in the synthesis of cortisol lead to the production of relatively large amounts of steroid hormones with a mineralocorticoid effect. The excessive production of these mineralocorticoids causes increased sodium and water retention and, thus, hypertension. Two different forms are distinguished, both of which are accompanied by hypokalemia and hypertension.

### 11-Hydroxylase deficiency

In this disorder, cortisol cannot be formed from the precursor 11-desoxycortisol. The conversion of desoxycorticosterone to corticosterone is also impaired. The increased production of 11-desoxycorticosterone is the primary cause of the hypokalemia and hypertension because of the strong mineralocorticoid effect of this steroid hormone. In 11-hydroxylase deficiency syndrome, the decreased synthesis of cortisol induces increased ACTH secretion. The increased production of ACTH stimulates the synthesis of androgens, thus causing virilization in children. The diagnosis is made in children by the demonstration of virilization combined with high secretion rates of 11-desoxycortisol and desoxycorticosterone.

### 17-Hydroxylase deficiency

Virilization is absent in this syndrome, since 17-hydroxylase deficiency impairs not only the synthesis of cortisol but also that of androgens. The production of estrogens is likewise impaired.[10] As a rule, diagnosis is made during puberty or in early adulthood on the basis of a combination of hypertension, hypokalemia, primary amenorrhea or male pseudohermaphroditism.[105]

In this syndrome also, the lack of cortisol synthesis leads to an increase in the production of ACTH, which in turn induces increased production of mineralocorticoids (primarily desoxycorticosterone, corticosterone, and 18-hydroxycorticosterone).

### Treatment

In both 11-hydroxylase deficiency and 17-hydroxylase deficiency, treatment is with glucocorticoids. Even small amounts of dexamethasone (0.5–1.0 mg/day) or cortisol (5–30 mg/day) produce sodium diuresis and normalization of blood pressure.

In patients with low production of aldosterone, close supervision is recommended during the first phase of therapy, since a hypovolemic crisis can occur as a result of the delayed normalization of aldosterone synthesis. In these cases, a reduced dose of the respective glucocorticoid and increased sodium intake is recommended.

Patients with no production of cortisol show increased sensitivity to exogenous administration of glucocorticoids. Thus, development of a cushingoid aspect has been observed at a daily dexamethasone dose of only 0.25 mg.

### Hypertension Due to Other Steroid Hormones

There is evidence that unknown mineralocorticoids are responsible for the hypertension in some patients with reduced activity of the renin-angiotensin system and low or normal aldosterone values. Thus, Woods and co-workers were able to achieve a reduction in blood pressure in such patients by treatment with aminoglutethimide, an inhibitor of adrenal steroid synthesis.[147] Melby and co-workers observed an overproduction of 18-hydroxydesoxycorticosterone (18-OH-DOC) in some patients with reduced renin activity.[94]

### Liddle's Syndrome

This familial syndrome, clinically similar to primary aldosteronism, is accompanied by lowered secretion of aldosterone.[86] The disease is possibly caused by a defect in the area of the distal renal tubule in which sodium retention and potassium loss can occur independent of aldosterone. This explains why the disease is cured by triamterene, a potassium-retaining diuretic whose effect is independent of aldosterone.[86]

### Hypertension Due to Exogenous Steroid Hormones or Related Substances

#### Iatrogenic Cushing's syndrome

Iatrogenic Cushing's syndrome is often distinguished from the endogenous form by its different clinical symptoms.[26,114] Some of the differences are possibly due to the fact that the exogenous administration of glucocorticoids suppresses the pituitary secretion of ACTH, whereas the majority of patients with Cushing's syndrome, i.e., with a hypothalamic-pituitary disorder, show increased production of ACTH. It is known that increased secretion of ACTH increases the adrenal release of androgens[41,68,69] as well as of mineralocorticoids.[12,94,120] The increased effect of androgens possibly explains the higher incidence of hirsutism, acne, and menstrual disorders in endogenous Cushing's syndrome with excess ACTH. Conversely, the more frequent demonstration of hypertension in true Cushing's syndrome would be a result of increased mineralocorticoid production.

Some of the complications of long-term steroid therapy, such as pseudotumor cerebri,[143] cataract,[38] and aseptic osteonecrosis,[62,135] are found almost exclusively in iatrogenic and not in true Cushing's syndrome.

Numerous papers provide evidence that the administration of steroids every other day (alternate-day therapy) leads to regression of cushingoid symptoms or prevents their development.[51,59,61,90,91,115,126,129] This is also true for drug-induced hypertension. Thus, a fall of blood pressure values and a reduction in antihypertensive therapy could be achieved after daily administration of steroid medication was replaced by administration on alternate days.[115,126,129]

#### Pseudoaldosteronism

The principal symptom of primary aldosteronism, hypokalemic hypertension, can be caused by licorice abuse,[32] ingestion of carbenoxolone,[6,146] or chronic abuse of medications containing mineralocorticoids.[3]

In cases of licorice abuse and in hypertension induced by carbenoxolone, the observed clinical and laboratory changes can be attributed to the aldosterone-like effect of glycyrrhizic acid (licorice) or glycyrrhetinic acid (carbenoxolone). Contrary to primary aldosteronism, however, these syndromes show inhibition of the adrenal production of aldosterone[3,6,32,146] which is reversible after abuse of the medication has been discontinued.[3] The sodium and water retention caused by these substances leads to a suppression of renin secretion similar to that in primary aldosteronism.

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# Pheochromocytoma

# 9

K. A. Meurer

## Definition

Pheochromocytomas are catecholamine-producing tumors arising in the chromaffin cells which are of neural crest origin. They can therefore be located in the adrenal medulla as well as in the sympathetic ganglia. In the latter case, they are also called paragangliomas. The paragangliomas have been classified further by various authors according to their anatomic location and microscopic structure.[43] In general, however, every catecholamine-producing tumor is classified as a pheochromocytoma, regardless of its location.

Pheochromocytomas and paragangliomas are usually benign tumors; only about 10% are malignant. Determination of malignancy is difficult, because in these cases the multiple occurrence of tumors, or even the invasion of the tumor capsule, are not clear-cut criteria for malignancy. The tumor cannot be considered malignant with certainty until chromaffin cells that synthesize catecholamines are found in places in which this type of cell does not usually occur, i.e., when metastasis has occurred in the lungs, skeletal system (including bone marrow), liver, etc., or significant invasion of adjacent tissue is evident.

## History

The name pheochromocytoma is derived from the gray-black appearance of the tumors (*phaios* means gray) due to their affinity for chromium salts on staining, whereby the tumors acquire a brown to yellow-brown appearance.[85a] The pheochromocytoma was first described in 1886 by F. Fraenkel, who found tumors in both adrenal glands at autopsy of a girl who had died suddenly in collapse. Possibly the first case of familial pheochromocytoma was described by Marchetti in 1904; however, the first documented case was not reported until 1943, by Hyman and Mencher.[55a] In 1910, Suzuki reported on the concurrence of pheochromocytoma and neurofibromatosis. In 1953, Glushien described the concurrence of pheochromocytoma with Hipple's disease, angiomatosis retinae. The frequent incidence of carcinoma of the thyroid with pheochromocytoma was reported on in 1952 by DeCourcy and DeCourcy[21a] and, in 1961, by Sipple.[103a] Cushman[19] described in 1962 the concurrence of parathyroid adenomas and pheochromocytoma, while Manning et al. described the concurrence of parathyroid adenomas, thyroid carcinomas, and pheochromocytoma.[71] With respect to the problems and details of the so-called multiple endocrine neoplasms (MEN, types 2 and 3) and the associated APUD-cell system (amine and amine precursor uptake and decarboxylation), refer to Bolande,[9] Metz and Levine,[72] and Pearse.[81]

The characteristic clinical picture of pheochromocytoma presenting with hypertensive crisis was described by Volhard in 1907, by Helly in 1913, and by L'abbé; pheochromocytoma with persistent hypertension was first reported by Binger and by Palmer in 1938. The first successful operation in a patient with pheochromocytoma presenting with hypertensive crisis was performed by Roux in 1926.[70a]

Kendall isolated epinephrine in crystalline form from a pheochromocytoma in 1936, while the second pressor substance, norepinephrine, was first identified in 1946 by von Euler and Holtz et al., and was demonstrated in pheochromocytomas by Holton in

1949. Finally, von Euler et al.[33] found that patients with pheochromocytoma occasionally also excreted increased amounts of dopamine in the urine, and Weil-Malherbe[120] found that excessive dopa was also excreted in the urine of pheochromocytoma patients.

Based on these discoveries, rapid progress was made in the diagnosis of pheochromocytoma. Diagnosis was simplified when Armstrong et al. were able to show, in 1957, that patients with pheochromocytoma excreted increased amounts of vanillylmandelic acid (VMA), the primary metabolite of epinephrine and norepinephrine, in the urine.[2a]

## Incidence

Pheochromocytomas are uncommon tumors. Their incidence in unselected autopsy material is reported at 0.09%[76,101] to 0.25%.[5] In patients with hypertension who had undergone sympathectomy, the percentages were 0.47%[46] and 0.5%.[107] In an unselected group of hypertensive patients, the frequency of pheochromocytoma is probably 0.1% to 0.2%.

Based on statistical calculations, it is presumed that in the United States there are 600 to 1000 deaths annually due to pheochromocytoma.[20,45] Schaefer reported in 1959 that in the Federal Republic of Germany approximately 100 patients die of pheochromocytoma each year.[99] According to Harrison, 1 of every 10 patients with pheochromocytoma who have undergone successful surgery dies as a result of hypertensive crisis. On the whole, pheochromocytoma discovered at autopsy appears to be twice as frequent as that diagnosed during life.[4]

## Occurrence

Pheochromocytomas can occur at any age; however, a peak in frequency is observed in the fourth and fifth decades. A 1-month-old infant can surely be considered the youngest patient;[66a] the oldest patient was 82 years of age.[25] Cone et al. found only 11 patients under 10 years of age among the cases of pheochromocytoma reported in the literature up to 1957.[12] Stackpole and Melikow reported on 100 children 15 years old or younger with pheochromocytoma, two-thirds of whom were boys.[108] In this group 35 patients were under 10 years of age.

In adult patients with pheochromocytoma, there is no clear-cut sex predilection; the reported differences are probably coincidental.

Familial pheochromocytoma is described in from 3%[122] to 10%[71] of cases; autosomal dominant inheritance with high penetration is presumed.[109] Based on investigations by Steiner et al., familial pheochromocytoma was known in 26 families up to 1968, including the family they studied.[109] In familial pheochromocytoma, the coexistence of carcinoma of the thyroid, Sipple's syndrome, and/or parathyroid adenoma must be borne in mind (MEN, type 2). In MEN, type 3, mucous membrane neurinoma, pheochromocytoma (frequently bilateral with familial aggregation), medullary carcinoma of the thyroid, Marfanoid appearance, thickening of corneal nerves, and ganglioneuromatosis of the gastrointestinal tract are found together. In addition, there is a significant association of pheochromocytomas with neurofibromatosis (Recklinghausen's disease), angiomatosis retinae (Hippel's disease), cerebral hemangiomatosis (Lindau's disease), acromegaly, Cushing's syndrome, and Addison's disease. Furthermore, pheochromocytomas have been found in patients with carcinoid syndrome, hypernephroma, hamartoma of the liver, neurolemmoma, hemangioma of the liver, neuroblastoma, ependymoma, astrocytoma, meningioma, spongioblastoma, chemodectoma, Down's syndrome, and in one patient with megacolon.[70a] Pheochromocytomas located near the renal hilus occasionally cause a compression of the renal artery, so that renovascular hypertension may also be present.

A unifying concept of the diseases arising from a maldevelopment of the neural crest was proposed by Bolande in 1974.[9] Pearse's concept of the APUD-cell system strengthened this theory.[81,82]

## Location

The developmental origin of pheochromocytoma from the neural crest cells is responsible for the fact that these tumors occur everywhere that chromaffin tissue is found. Over 95% of the pheochromocytomas are located in the abdominal area, and between 85% and 90% are located in the adrenal glands, with predilection of the right side.[46,88,111] Bilateral renal tumors can be expected in 10% of adults, but in about 25% of cases in children and youth.[54,108] Moreover, in patients with familial pheochromocytoma and in children, more frequently bilateral adrenal tumors or multiple extra-adrenal tumors occur.[12,103,108]

The sites of occurrence of extra-adrenal pheochromocytomas were compiled by Fries and Chamberlain on the basis of over 205 cases reported in the literature.[38] Most of the tumors were located in the

abdomen, above the kidneys, followed in frequency by infrarenal tumors in the periaortic area, and in the organ of Zuckerkandl. Pheochromocytomas were found in the bladder 20 times, in the anal area once, in the vaginal area twice, and once in the sacral area. Pheochromocytomas were located in the chest 24 times and 5 times in the neck area. To date, one patient with a pheochromocytoma in the pericardium has been described.[6] A few cases of intraspinal pheochromocytoma have been reported.[14,85,89]

The weight of the tumors varies considerably from 70 g (70%) to over 3000 g. In 5% of cases the pheochromocytomas are so small that, under certain circumstances, they cannot even be located surgically.[65]

## Biochemistry and Physiology of Catecholamines

The clinical symptoms of pheochromocytoma are based upon the production of excessive quantities of epinephrine, norepinephrine, and, in a few cases, dopamine. Norepinephrine and epinephrine are synthesized in the adrenal medulla, in some chromaffin tissue, in the brain and the paraganglia; norepinephrine is additionally synthesized in the postganglionic sympathetic neurons. In the adrenal medulla, epinephrine accounts for 85% of the catecholamines.[32] Both hormones affect the circulation and metabolism, while norepinephrine also acts as a peripheral neurotransmitter. Dopamine, the precursor of norepinephrine, is considered to be a central sympathetic transmitter substance; it also causes vasodilatation of the renal artery.[43a]

The amino acid tyrosine is the starting point for the synthesis of epinephrine and norepinephrine (Fig. 1; for details, see Perlman and Chalfie[84] and Kopin[63]). The initial reaction in the biosynthesis of the catecholamines, the conversion of tyrosine to dihydroxyphenylalanine (dopa), is catalyzed by tyrosine-3-monoxygenase (TH; formerly tyrosine hydroxylase), with tetrahydrobiopterine as cofactor. Thus, TH is the enzyme that determines the rate of catecholamine synthesis. At the same time, TH can be inhibited by catecholamines, so that catecholamine biosynthesis is influenced by a feedback mechanism. The next step, the conversion of dopa to dopamine, is catalyzed by the aromatic L-amino acid decarboxylase (AADC). Norepinephrine is derived from dopamine through the action of the dopamine beta-monoxygenase (DBH), a glycoprotein containing copper. Cells producing epinephrine contain another enzyme, phenylethanolamine-*N*-methyltransferase (PNMT), which causes the conversion of norepinephrine to epinephrine.

Inhibition of the synthesis of the catecholamines is possible at every step; thus, alpha-methyltyrosine inhibits TH. AADC is influenced by alpha-methyl-

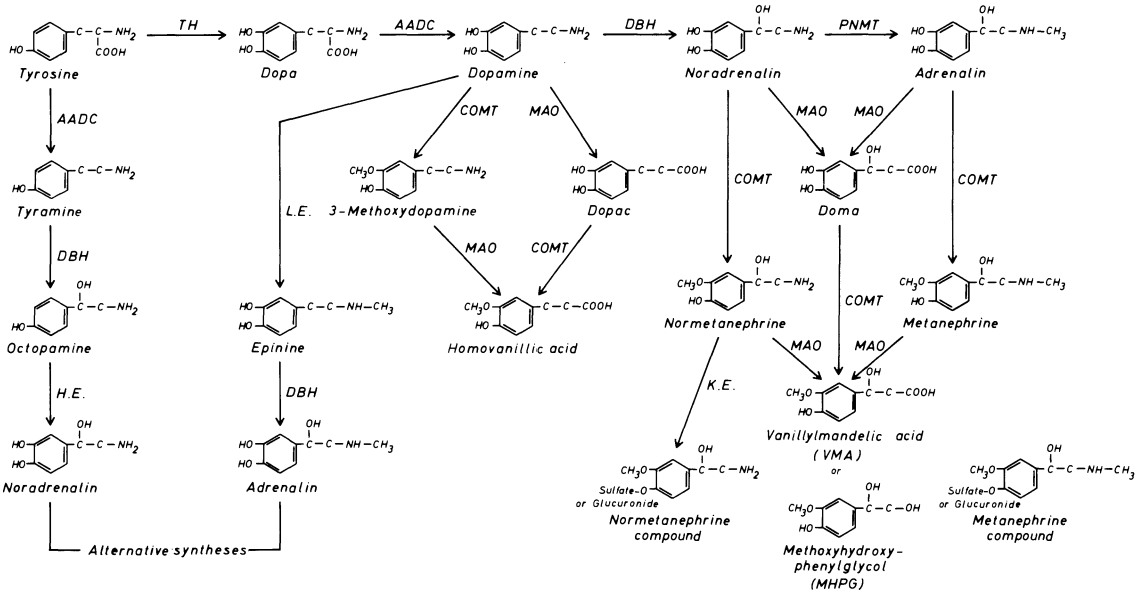


**Figure 1.** Synthesis and metabolism of catecholamines. AADC, aromatic L-amino acid decarboxylase; TH, tyrosine-3-monoxygenase; DBH, dopamine-$\beta$-monoxygenase; PNMT, phenylethanolamine-*N*-methyltransferase; COMT, catechol-*O*-methyltransferase; MAO, monoaminooxidase; H.E., hepatic enzyme; L.E., pulmonary enzyme; K.E., conjugating enzyme. From Manning PC Jr et al., ref 71

*m*-tyrosine and 3-hydroxybenzylhydrazine, among others. The effect of DBH can be inhibited by various aromatic phenylethylamine isomers and copper chelate-forming substances. Finally, PNMT is inhibited by both epinephrine and norepinephrine.

The inactivation of catecholamines from both the adrenal medulla and the nerve endings results from reuptake into the specific storage granules in the sympathetic nerve endings and also from metabolism in the liver or effector cells by catechol-*o*-methyltransferase (COMT).[3] Normetanephrine and metanephrine are the metabolic products; they are broken down by monoaminooxidase (MAO) into vanillylmandelic acid (VMA) and methoxy-4-hydroxyphenylglycol (MHPG)[3] (Fig. 1). The circulating catecholamines are converted by COMT to normetanephrine and metanephrine.

Metabolism of the catecholamines in the organism is largely complete, so that only small quantities (3%–7%) are excreted unchanged in the urine. In normal subjects about 8%, and in pheochromocytoma patients about 25% of the catecholamines are excreted as metanephrines. Of total VMA (which was discovered in 1957 by Armstrong et al.[2a] as a common catabolite of catecholamines), 90% is found in the urine of normal subjects, but only 70% in pheochromocytoma patients.[17a] Homovanillic acid and methoxytyramine are excreted as the principal metabolites of dopamine.

The regulation of catecholamine biosynthesis will not be discussed in detail here, since in pheochromocytoma there is considerable variance in the rate of synthesis and release of catecholamines from the chromaffin cells or tumor. To be sure, the synthesis of catecholamines in the pheochromocytoma functions normally; however, the relationship of epinephrine to norepinephrine deviates considerably from normal under certain circumstances. Therefore, only limited conclusions regarding the site of the tumor can be drawn from the relationship of epinephrine to norepinephrine. Tumors secreting epinephrine are almost always located in the adrenal glands, whereas only two-thirds of the tumors primarily or exclusively producing norepinephrine occur in the adrenal glands.[16] Only on very rare occasions does an extra-adrenal pheochromocytoma also secrete epinephrine. According to investigations by von Euler and Ström[34] and Goodall and Stone,[45] two-thirds of the tumors secrete epinephrine and norepinephrine, and one-third secrete norepinephrine. Tumors secreting only epinephrine are very rare. Manger and Gifford reported that both catecholamines were found to be increased in 84.6% of the patients with pheochromocytoma with persistent hypertension and in all patients with paroxysmal hypertension.[70a]

**Table 1.** Normal Range of Catecholamine and Metabolite Concentrations in Urine and Plasma

| | Upper Limit of Normal |
|---|---|
| Urine | |
| Norepinephrine | 60 μg/24 h |
| Epinephrine | ≤15 μg/24 h |
| Dopamine, total | 800 μg/24 h |
| Metanephrine, total | ≤1.0 mg/24 h |
| Vanillylmandelic acid | 7 mg/24 h |
| Plasma | |
| Norepinephrine | ≤0.3 μg/100 ml |
| Epinephrine | ≤0.1 μg/100 ml |
| Dopamine | 1.5 ng/ml |

In malignant pheochromocytoma the synthesis of catecholamines is impaired; apart from epinephrine and norepinephrine, these tumors secrete dopamine, dopa, and homovanillic acid which, except for the latter metabolite, can also be found in patients with benign tumors.

There is no close correlation between the size of the tumor or its catecholamine content and the clinical features. Generally, however, especially in the case of small tumors, catecholamine metabolism is increased and the excess hormones are released directly into the circulation, so that usually a severe clinical picture results.[16] Large tumors usually demonstrate a lower sustained secretion and often milder symptoms.

The release of catecholamines from the tumor is enhanced by histamine, nicotine, acetylcholine, tyramine, 5-hydroxytryptamine, glucagon, reserpine, and guanethidine, as well as conditions of stress, exercise, shock, and hypoxia. In patients with pheochromocytoma, compression of the tumor leads to increased hormone secretion and thus to precipitation of an attack.

The normal catecholamine and metabolite concentrations in the urine are given in Table 1. In addition to pheochromocytoma, concentrations of these substances can also be elevated in neurodystonia, stress situations, myocardial infarction, heart failure, uremia, delirium tremens, thallium poisoning, lymphoma, and after administration of various drugs such as beta-receptor blockers, sympathomimetics, reserpine, guanethidine, tetracyclines, erythromycins, and after clonidine withdrawal.

## Pharmacologic Effects of Catecholamines

Catecholamines exert manifold effects on the body, and a knowledge of them is very useful in under-

standing the clinical findings in pheochromocytoma. These substances not only influence central and peripheral hemodynamics but also exert various effects on the metabolism, autonomic central nervous activity, and gastrointestinal functions (see Table 2).

Since norepinephrine mainly affects the alpha receptors, epinephrine the beta-adrenergic receptors, and dopamine the dopaminergic receptors[56] in the brain and kidney as well as the alpha receptors and to some extent the beta receptors, the clinical manifestations of pheochromocytoma may be quite varied, depending on which catecholamine is secreted in the largest amounts. On the whole, however, it is difficult to assign hormone-induced symptoms specifically to epinephrine, norepinephrine, or even dopamine, since in cases of such exaggerated hormone secretion the effects of the hormones tend to overlap.

## Clinical Symptoms

The clinical symptoms of pheochromocytoma present a broad spectrum of subjective signs and objective findings. The typical clinical pictures in pheochromocytoma are (1) paroxysmal hypertension in about 45% of cases; (2) persistent hypertension (with or without hypertensive crises) in about 50% of cases; (3) relatively asymptomatic cases, in which the metabolic symptoms—elevated basal metabolism, hyperglycemia, or manifest diabetes mellitus—are more pronounced, but with little or no increase in blood pressure; (4) very rarely hypotensive episodes (sometimes alternative with hypertensive episodes); and (5) signs and symptoms of metastatic lesions may be present with malignant tumors.

The symptoms associated with increased catecholamine secretion that were reported by patients with pheochromocytoma have been compiled in Table 3. The compilation is based on investigations by Gifford et al.[40] in patients with paroxysmal hypertension, studies by Rosenberg and Varco[92] in patients with persistent hypertension, and investigations by Hume[54] in children with both persistent and paroxysmal hypertension.

Especially characteristic of pheochromocytoma are headache, excessive sweating, palpitations, tachycardia, bradycardia, pallor, anxiety, nausea, constipation, vomiting, chest pain, flank pain, weight loss, and epileptic seizures. As a result of the strong effect of norepinephrine, both intermittent claudication and Raynaud's phenomenon can occur. Fever is not uncommon.

The objective findings that are suggestive of pheochromocytoma are listed in Table 4 (after Kirkendall et al.[60]). Special attention is drawn to cases with extremely labile hypertension or with postural hypotension, to the presence of polycythemia[31,64,119] attributable to the simultaneous rise of erythropoietin production, as well as to the frequent occurrence of gallstones, the cause of which is unknown.[70a]

The clinical picture in children with pheochromocytoma can vary somewhat from that in adults, according to various reviews on the subject.[36,54,70a,108] Children have persistent hypertension in more than 90% of the cases, and outbreaks of sweating and visual disturbances are particularly common.[54] Furthermore, dizziness, vomiting, weight loss, polydip-

**Table 2.** Physiological Effects of Catecholamines

| | Norepinephrine | Epinephrine |
|---|---|---|
| Heart rate | Decrease or increase | Increase |
| Mean arterial pressure | Slight increase | Slight increase or decrease |
| Blood pressure | | |
| systolic | Marked increase | Slight increase |
| diastolic | Marked increase | Decrease |
| Cardiac output | No change | Marked increase |
| Peripheral resistance | Marked increase | Decrease |
| Muscle vessels | Vasoconstriction | Vasodilatation |
| Skin vessels | Vasoconstriction | Vasoconstriction |
| Kidney vessels | Vasoconstriction | Vasoconstriction |
| Sweat glands | Activation | Activation |
| Bronchial system | No change | Relaxation |
| Smooth muscles | Relaxation | Relaxation |
| Basal metabolic rate | Increase | Marked increase |
| Blood glucose | Increase | Marked increase |
| Free fatty acids | Increase | Marked increase |

**Table 3.** Prevalence of Symptoms in Pheochromocytoma in Adults with Paroxysmal and Persistent Hypertension and in Children

| Symptom | Paroxysmal (%) | Persistent (%) | In Children (%) |
|---|---|---|---|
| Headache | 91.9 | 71.8 | 81.0 |
| Perspiration | 64.9 | 62.2 | 62.0 |
| Palpitation | 73.0 | 51.3 | 34.0 |
| Pallor | 59.5 | 28.2 | 27.0 |
| Anxiety | 59.5 | 28.2 | |
| Tremor | 51.4 | 25.6 | |
| Nausea, vomiting | 43.2 | 25.6 | |
| Weakness | 37.8 | 15.4 | 27.0 |
| Chest pain | 32.4 | 12.8 | |
| Flank pain | 16.2 | 15.4 | 35.0 |
| Visual disturbances | 2.7 | 20.5 | 44.0 |
| Weight loss | 13.5 | 15.4 | 44.0 |
| Dyspnea | 10.8 | 17.9 | 16.0 |
| Convulsions | 5.4 | 2.6 | 23.0 |
| Bradycardia | 8.1 | 2.6 | |
| Dizziness | 10.8 | 2.6 | 56.0 |
| Paresthesia (arms) | 10.8 | | |
| Intolerance of warmth | 13.0 | 15.0 | |
| Polydipsia | | | 25.0 |
| Polyuria | | | 25.0 |

From Gifford RW Jr, Kvale WF, Maher FT, Roth GM, ref 40, and Rosenberg JC, Varco RL, ref 92 (data on adults); Hume DM, ref 54 (data on children).

sia, and polyuria occur more frequently than in adults (see Table 3). Children with pheochromocytoma may show retarded growth in very rare cases.

The occurrence of a pheochromocytoma during pregnancy poses a serious threat to the life of the mother as well as the child, especially since toxemia of pregnancy is more likely to be suspected in this situation than pheochromocytoma. Yet, the symptoms are the same in most cases as in nonpregnant patients. According to various summaries,[21,37,54] the maternal mortality is 50% and the infant mortality is 30%. Complaints usually begin in the last trimester of pregnancy, probably owing to pressure exerted on the tumor by the uterus. In one-third of the patients described by Gemmell,[39] the onset of symptoms did not occur until immediately before delivery or up to 24 h thereafter. Pochedly[86] and Voute et al.[118] reported on six women with the clinical symptoms of pheochromocytoma in whose children a neuroblastoma was later discovered. Apparently, the secretion of catecholamines from the neuroblastoma was responsible for the symptoms in these patients.

**Table 4.** Objective Findings in Patients with Pheochromocytoma

| Signs | % |
|---|---|
| Slender build | 89 |
| Persistent hypertension | 50 |
| Hypertensive crises | 44 |
| Hemoglobin, >15 g/100 ml | 50 |
| Proteinuria | 44 |
| Glucosuria | 39 |
| Fasting blood glucose, >100 mg/100 ml | 33 |
| Glucose intolerance | 28 |
| Cholelithiasis | 17 |
| Postural hypotension | 11 |
| Neurofibromatosis | 6 |

From Kirkendall WM, Liechty RD, Culp DA, ref 60.

The paroxysmal hypertensive crises in pheochromocytoma usually occur dramatically and explosively and may be provoked by a physical maneuver causing an increase of abdominal pressure; urination, defecation, and sexual intercourse; physical exertion; sudden, vigorous rotation; sneezing; pressure on the carotid body; nicotine and alcohol abuse; fatty and flatulating meals; hypoglycemia; excitement; pain; hyperventilation; changes in body temperature; or administration of certain medications such as circulatory drugs containing catecholamines, glucagon, histamine, tyramine, Mecholyl, ACTH, nitroglycerin, and saralasin. Further, radiologic procedures used to diagnose pheochromocytoma (angiography, retroperitoneal gas insufflation) may provoke an attack. Occasionally, however, the attacks also occur during sleep. Rarely, the attack is preceded by premonitory scotodinia, nausea, and pain in the limbs. The attacks generally occur at ir-

regular intervals, varying from hours to months; the duration of each attack also fluctuates within a broad range. In the course of time, the paroxysmal attacks generally occur more frequently, without necessarily becoming more severe; however, the danger of complications usually increases.

The paroxysmal rises in blood pressure are usually very pronounced and affect both the systolic and diastolic pressures, which can rise to over 300 mm Hg and 200 mm Hg, respectively. Furthermore, cases have been described in which there was a transient fall of blood pressure during the attack and then a renewed increase. An increase in the systolic blood pressure with a simultaneous fall in the diastolic pressure is a very rare occurrence. The blood pressure values in patients with persistent hypertension often fluctuate within a wide range. In one patient with a pheochromocytoma secreting epinephrine, there was pronounced hypotension with tachycardia during the attacks.[90]

Postural hypotension is also observed in some patients with pheochromocytoma and appears to be due to functional autonomic blockade of the sympathetic circulatory reflexes involved in the maintenance of blood pressure in an erect posture. The physiologic reduction of blood volume is also blamed for this finding.[28]

The blood pressure usually returns to normal quite rapidly after a pheochromocytoma attack; however, the profuse sweating continues and, characteristically, a drastically increased diuresis occurs. Conversely, inhibition of diuresis and even anuria have also been observed during the attack. After an attack, the patients feel tired and exhausted for an extended period of time.

The persistent hypertension in patients with pheochromocytoma can resemble that of essential or renal hypertension and occasionally that of renovascular hypertension; however, in addition, abrupt intermittent rises in blood pressure are often superimposed. A transition from paroxysmal hypertension to persistent hypertension occasionally occurs. Additional findings, which in these cases suggest the presence of pheochromocytoma as being responsible for the hypertension, are summarized in Table 5. The presence of pheochromocytoma should especially be considered in children and young persons with hypertension, as well as in all patients with autonomic disorders or attacks.

The course of pheochromocytomas may be asymptomatic if the tumor tissue does not produce catecholamines that significantly affect hemodynamics and metabolism. On the other hand, a few cases have been described in which increased catecholamine or VMA excretion was accidentally discovered in asymptomatic patients.[93,113] Finally, cases have been reported in which, after a series of typical attacks, the symptoms of pheochromocytoma disappeared, whereupon surgery demonstrated bleeding in the tumor that had apparently destroyed the hormone-producing tissue and thus promoted spontaneous healing.[65]

After surgical excision of the pheochromocytoma, a recurrence with specific symptoms can develop in rare instances. The incidence of recurrence is probably about 10%.[88] However, the occurrence of more frequent relapses is noteworthy. On the average, these occur after a period of over 8 years, though considerably shorter intervals have been reported.[64] The identification of a recurrence may be difficult, since small pheochromocytomas might have been overlooked at the first operation. A recurrence is considered highly probable if an asymptomatic interval with normal catecholamine excretion has been documented.

## Complications

Owing to misinterpretations of the changeable and polymorphic symptoms of pheochromocytoma,

**Table 5.** Suggestive Signs of Pheochromocytoma in Patients with Persistent Hypertension

1. Attacks of headache, palpitations, nervousness, chest and abdominal pain, tremor, and, particularly, persistent or excessive perspiration
2. Patient is underweight
3. Age less than 35 years
4. Impaired glucose tolerance and/or rise of basal metabolic rate with no demonstrable hyperthyroidism
5. Short duration of hypertension
6. Severe funduscopic abnormalities
7. Rise of blood pressure in response to ganglionic blocking drugs or guanethidine
8. Rise in blood pressure during induction of anesthesia
9. Postural hypotension and striking fluctuations in blood pressure and/or labile pulse
10. Hypertension with neurofibromatosis, cholelithiasis, etc.

From Meurer KA, Lang R, Kaufmann W, ref 74, and Sack H, Koll FJ, ref 95.

there is often a rather long interval of time between diagnosis and surgery during which serious cerebral, cardiorenovascular, and ocular complications due to the hypertension can develop. However, cases have been described in which the first pheochromocytoma attack led to death.

According to a report by Graham on 72 nonoperated patients, massive cerebral hemorrhages and infarctions head the list of causes of death, followed by acute cardiac decompensation, hyperpyrexia, pneumonia, and myocardial infarction.[46] Circulatory shock as a result of hemorrhage and necrosis in the presence of large pheochromocytomas has also been reported.[55] Circulatory shock can also develop in conjunction with a severe hypertensive crisis. Severe retinopathy is not infrequent in patients with persistent hypertension. High concentrations of catecholamines can cause development of intestinal obstruction with megacolon and constipation or ischemic enterocolitis. "Catecholamine myocarditis" is frequently found at autopsy and can be considered a cause of congestive heart failure and perhaps cardiac arrhythmias. Large pheochromocytomas are capable of compromising the function of neighboring organs (e.g., by compression of the renal arteries or ureter).

## Diagnosis

In the search for a pheochromocytoma, with its polymorphic symptoms, careful history taking with direct questioning in regard to typical symptoms is essential. As presented in Tables 3–5 and in the depiction of the clinical picture, the presence of pheochromocytoma should be suspected in symptomatic patients with persistent or paroxysmal hypertension and in cases of unclear attacks suggesting excess circulating catecholamines. It is especially important that pheochromocytoma be ruled out in pregnancy and when surgery is planned in hypertensive patients. Furthermore, pheochromocytoma must be considered if certain behavior or activity leads to hypertension or hypotension (exertion, excitement, palpation of an area where the tumor is located, ingestion of food containing tyramine, administration of certain drugs, nicotine abuse, etc.), if diseases are present that are significantly associated with pheochromocytoma, or in the presence of familial pheochromocytoma.

By considering these factors, it should be possible to single out almost all patients with pheochromocytoma; determination of catecholamines or their metabolites does not appear to be necessary in every hypertensive patient.

## Laboratory Tests

### General Findings

Changes in the red blood cell picture are only rarely found; patients have been described with anemia as well as with polycythemia, and, in the latter cases, increased erythropoietin activity was demonstrable in the tumors or serum. Anemia is especially frequent in patients with metastasizing pheochromocytoma. The leukocyte count is usually normal, though leukocytosis can reportedly occur during attacks. The erythrocyte sedimentation rate is normal in uncomplicated pheochromocytoma.

As a rule, blood and plasma volume are reduced in patients with pheochromocytoma.[22,30,57,102,112] This accounts for the postoperative shock encountered in patients that have not received prior treatment for normalization of blood volume.

Creatinine and urea are normal in uncomplicated pheochromocytoma. Slight proteinuria is frequently demonstrated, especially if nephrosclerosis has developed. Owing to the release of catecholamines, hypokalemia is sometimes found.

Increased plasma renin activity and aldosterone excretion have sometimes been found without there having been a distinct relationship to the main catecholamine excreted.[53,61,67,73,115,122,123] The hypovolemia, renal vasoconstriction, concurrent renal arteriostenosis, or the stimulation of intrarenal beta receptors could be considered the cause of this finding.[53,61]

Sometimes there are substantial alterations in the carbohydrate and lipid metabolism. Besides increased fasting blood glucose and glucosuria in a large portion of patients with persistent and paroxysmal hypertension, subclinical diabetes or manifest diabetes mellitus can frequently be demonstrated. A parallel response of blood glucose and blood pressure is often found. There is virtually no development of ketoacidosis in patients with pheochromocytoma. Basal metabolism is increased primarily in patients with persistent hypertension.[40] Increased cholesterol concentrations are only rarely found in patients with pheochromocytoma. However, there are no extensive investigations available on lipid metabolism in patients with pheochromocytoma.

### Electrocardiographic Abnormalities

Abnormalities in the ECG are recorded very frequently in patients with pheochromocytoma and include arrhythmias of various natures as well as impaired repolarization. The features of a myocardial infarction are often simulated.[62,62a,70a,97,98]

The pathogenesis of the ECG abnormalities are considered by Sayer et al. to be a complex interaction between the relative amounts of epinephrine and norepinephrine secreted, the duration of the secretion, and the net effect of the catecholamines on the heart rate, rhythm, stroke volume, oxygen supply and demand, as well as on coronary perfusion, pulmonary and peripheral vascular resistance, and the electrolyte distribution.[98] Arrhythmias are especially likely to occur during hypertensive crises and regress after resection of the tumor or treatment with alpha- or beta-receptor blocking drugs. Concomitant arteriosclerotic changes in long-standing hypertension also contribute to the ECG abnormalities and, as is the case in abnormalities due to catecholamine myocarditis, they rarely regress.[62,116] The ECG abnormalities often change very rapidly and, in this case as well as in cases of otherwise unexplained ECG findings, they should prompt the search for a pheochromocytoma.

### Pharmacologic Tests

Since the determination of catecholamines and their metabolites became possible, provocative drug tests and lysis tests that were used earlier have been largely discarded, especially since they posed a danger to the patient and gave both false-positive and false-negative results. At most, the glucagon test should be performed in doubtful cases where catecholamine excretion is only slightly above normal but symptomatology is positive, since this procedure cannot provoke a dangerous rise in blood pressure. The patient should receive preliminary treatment with phenoxybenzamine, and the recommendations of Mühlhoff et al.[77] should be followed. A modification of the phentolamine test was reported by Spergel et al.[107a] Blood samples for catecholamine analysis should be obtained before and during a hypertensive crisis caused by a provocative test. Refer to the literature for details on the conduct of the test.[23,70a,107a,122]

### Biochemical Tests

Demonstration of elevated concentrations and/or excretion of catecholamines or their metabolites is prerequisite to preoperative diagnosis of pheochromocytoma, except in emergency situations. Various methods developed for this purpose in recent years are available. Diagnostic procedures include the following determinations: in urine and plasma, assay of epinephrine, norepinephrine, dopamine, and dopa; in urine only, the assay of metanephrine, normetanephrine, and VMA (see Table 1). The urinary assay requires either a 24-h urine specimen or the urine passed during an attack. Concurrently measured creatinine excretion, or creatinine clearance, can be used as a reference value to check for errors in collection.

The determination of metanephrine, as well as VMA, in the urine has proved highly reliable according to the literature.[16,23,40,40a,70a,88] Diagnosis can be confirmed in almost every case by determination of total metanephrine, and in about 97% of cases by the determination of VMA. Dopamine has been demonstrated in only a few patients with pheochromocytoma. In two patients, dopa could also be found in the urine.[120] The determination of plasma catecholamines is important in diagnostic procedures to localize the pheochromocytoma and in the rare cases of only intermittently increased or borderline catecholamine secretion when determinations are done in conjunction with a provocative test.[1,16,29,33,35,49,65,67,69,70a,74,79,83,125]

In spite of the specific assays used today, some substances can influence the results, especially sympathomimetic drugs and medications that interfere with catecholamine biosynthesis or catecholamine metabolism, e.g., antihypertensive drugs that inhibit sympathetic activity, monoamine oxidase inhibitors, dehydrogenase inhibitors, and alcohol. In addition, the fluorimetric methods are affected by tetracycline, erythromycin, chinidin, chinin, and chlorpromazine. Chromatographic analysis of the urinary catecholamines is influenced by increased bilirubin concentrations. Various radiologic contrast media interfere with the assay of metanephrine in urine by the method of Pisano. The determination of metanephrine should therefore be done immediately before or 3 days after the administration of a contrast medium. Various less specific methods for the determination of VMA are affected by citrus fruits, coffee, tea, cocoa, bananas, and vanilla; however, in general, the values are not altered enough to give false-positive or false-negative results. However, the influence on catecholamine release of the drugs mentioned should be borne in mind, and they should be discontinued, if possible, approximately 8 days prior to the planned investigation.

It is only in fluorimetric determinations that alpha-methyldopa is concurrently measured, so that the resultant excessively high values can thus be recognized as a false-positive result. Preliminary treatment of the patients with phentolamine or phenoxybenzamine, on the other hand, does not usually influence catecholamine determination.

Further consideration must be given to the fact that various pathological and physiological conditions can lead to an increase or decrease in cate-

cholamine excretion (see ref. 70a). In addition, the presence of other neuroectodermal tumors (ganglioneuroma, neuroblastoma, and ganglioneuroblastoma) must be considered.

Decreased excretion is found in familial dysautonomia (Riley-Day syndrome), in asympathicotonic postural hypotension, in malnutrition, and in some patients with renal insufficiency and/or oliguria if the catecholamine excretion is not compared with the creatinine excretion.

For the laboratory tests, a portion of the 24-h urine specimen is used. This batch must be acidified with hydrochloric or sulfuric acid if norepinephrine, epinephrine, normetanephrine, or metanephrine is to be determined. This procedure is not necessary for the determination of VMA; in case of borderline findings, however, a sample of acidified urine would then be available to serve as control for determination of other metabolites.

## Differential Diagnosis

Owing to the extreme variability of symptoms in patients with pheochromocytoma, numerous differential diagnoses must be considered. Above all, it is important to always bear in mind that the patient's complaints might be due to pheochromocytoma.

First of all, the presence of a pheochromocytoma must be considered in every case of arterial hypertension, whether persistent or paroxysmal, and a search made for other characteristic symptoms, which, no matter how slight, should prompt investigation to exclude pheochromocytoma. In addition, it should be borne in mind that a pheochromocytoma can also be the real cause of the complaints in patients with marked symptoms suggesting sympathetic overactivity, nervousness, anxiety, hyperthyroidism, paroxysmal tachycardia, hyperkinetic heart syndrome, menopause, migraine, coronary ischemia, diabetes mellitus, hypertensive encephalopathy, toxemia of pregnancy, hypertensive crises induced by the interaction of MAO-inhibitors with food or drinks containing tyramine, carcinoid syndrome, spontaneous hypoglycemia, familial dysautonomia (Riley-Day syndrome), acute infectious diseases, acute intermittent porphyria, lead poisoning, tabetic crises, encephalitis, after abrupt clonidine withdrawal, and in Wernicke and Guillain-Barré syndrome.[70a] Moreover, it must be considered that the latter syndromes are often accompanied by elevated catecholamine excretion.[70a] Furthermore, a thorough examination should be conducted in hypertensive patients in whom it is suspected that abnormal laboratory results are based on increased circulating catecholamines, as well as in those patients whose blood pressure is difficult to control with antihypertensive medication.

The diseases that most frequently accompany pheochromocytoma and the pathophysiologic changes that can induce a crisis have already been mentioned in detail earlier in this chapter. The differential diagnosis must also include consideration of other tumors of neuroectodermal origin, such as neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Neuroblastoma is one of the most common malignant tumors of childhood. Its location and symptoms may correspond to those of pheochromocytoma. In most cases, the urinary excretion of dopa, dopamine, norepinephrine, normetanephrine, VMA, and homovanillic acid (HVA) is increased.[117] Ganglioneuroblastoma—also a malignant tumor—usually differs from pheochromocytoma and neuroblastoma in its symptoms, although the cells are capable of producing dopamine and norepinephrine. In addition to occasional hypertensive crises and episodes of sweating, diarrhea with hypokalemia, flatulence, erythema, and impaired growth are most prominent. These patients excrete catecholamines and their metabolites in the same manner as patients with neuroblastoma.[117] Ganglioneuromas occur in older children and adults and develop in the lumbar and thoracic regions of the sympathetic chain. They are benign tumors. The clinical picture can also be characterized by chronic diarrhea and occasional hypertensive crises, episodes of sweating, polyuria, and polydipsia. Increased amounts of dopamine, norepinephrine, VMA, and HVA are excreted in the urine. During differential diagnosis, attention must also be given to the fact that some patients wish to simulate the presence of a pheochromocytoma by taking sympathomimetic drugs (see under pseudopheochromocytoma, ref. 70a.

## Localization Procedures

Even though 98% of pheochromocytomas are located in the abdominal area, precise preoperative localization is indicated in order to be able to better determine the number of tumors present, to obtain indications for postoperative therapy in cases of bilateral adrenal involvement, and to obtain information on the vascularization of the tumors, which enables the surgeon to proceed rapidly and carefully by selecting the best approach.

The initial step in the localization of the pheochromocytoma is to obtain chest x-rays (sagittal, lateral, and oblique views) in order to detect an in-

trathoracic tumor. This should be followed by an intravenous urogram with tomography of the kidneys, since the tumor sometimes presents a recognizable low-density shadow even in plain films. Occasionally, calcifications in the tumor, a sign of tissue degeneration, are also demonstrated.[75] Depending on their size, pheochromocytomas cause depression or flattening of the kidneys, as well as displacement of the ureter or extinction of the marginal shadow of the psoas. The fundus of the stomach, spleen, or tail of the pancreas can occasionally give the impression of a left-sided tumor and lead to misinterpretation. The frequency of a positive urogram has been reported to vary from 30% to 90%.[40,47,88,124] The combination of intravenous urogram and retroperitoneal gas insufflation has been all but discarded because of the danger to the patient and the availability of improved radiographic techniques.

As an aid to localization, selective blood sampling from various parts of the vena cava, as reported by von Euler et al. in 1955,[32] has provided very good results in our investigations[65,74] and has proved to be low in risk and easy to carry out. In the meantime, this method has been successfully employed by numerous investigators.[1,16,32,35,49,65,66,68,69,70a,79,83,124] Particular emphasis should be placed on the great accuracy and low risk of this procedure. The sites for blood sampling from the vena cava are selected (Fig. 2) to include all areas of influx to the vena cava, including the lower extremities; the pelvic, head, and neck areas; and, of course, the kidney and adrenal areas. The junction of the tumor vein and, hence, the approximate site of the pheochromocytoma can usually be located on the basis of the marked difference in catecholamine concentration in comparison to the other sampling sites. In particular, small and multiple tumors can be detected and the duration of surgery can be shortened; this can be especially important in seriously ill patients. If necessary, phlebography can subsequently be carried out.

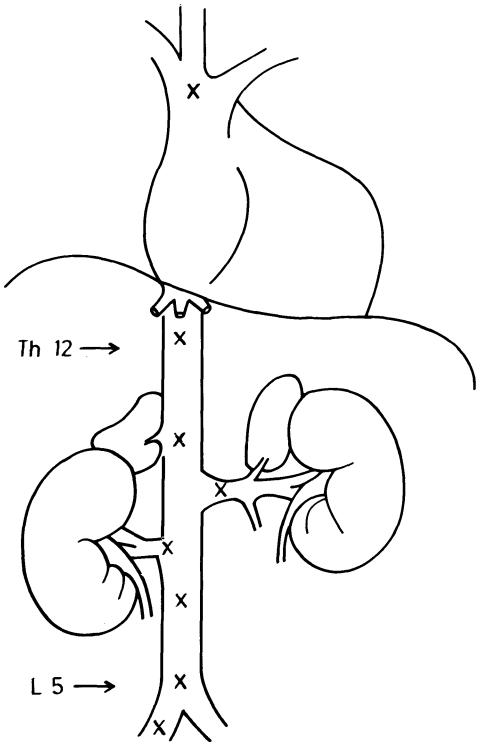


**Figure 2.** Sites of blood sampling in the vena iliaca, vena cava, and renal veins for the localization of pheochromocytomas.

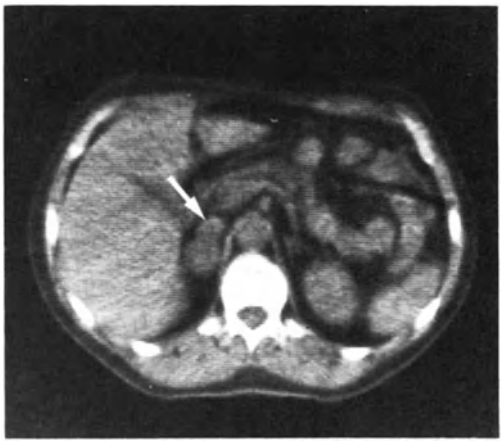

**Figure 3.** Computed tomogram of a right adrenal pheochromocytoma. Relative density: 30 Housefield units. Courtesy of the Department of Radiology, Cologne University; Professor Dr. G. Friedmann, director

Since a pheochromocytoma can be localized to a great extent by selective determination of catecholamines in the blood of the vena cava, and arteriography is associated with higher risk to the patient, computerized axial tomography can be carried out when feasible as a means of localizing the tumor in its topographic relationship to the surrounding organs (Fig. 3).[23a,65] Radiation exposure is comparable to that of an intravenous urogram. Computerized tomography should not be done to search for tumors of unknown location; however, under the conditions stated, it apparently can replace arteriography in suitable cases or make it possible to direct and thus limit angiography to the area or areas of suspected location, especially since routine general abdominal aortography includes only the direct renal and perirenal areas, and thus other ectopic pheochromocytomas could escape detection.[65]

In arteriography, the pheochromocytoma can usually be readily distinguished by its fine, rich network

of blood vessels and resultant hypertrophy of the adrenal artery, as well as by the visualization of capsule vessels. If the pheochromocytoma is not highly vascularized, selective or superselective angiography is often indicated in order to identify the tumor and demonstrate its vascularity.[65] Under the same conditions, it is sometimes necessary to attempt visualization of the tumor by phlebography, since especially smaller and weakly vascularized—and thus already necrotic—tumors can be demonstrated by this procedure.[1,70a,78] If excessive injection pressure is employed during adrenal arteriography or phlebography, necrosis of the tumor can occur and lead to spontaneous healing. Furthermore, a pheochromocytoma attack can be induced by any type of angiography, so that the patients should be pretreated with alpha- and beta-receptor blocking agents; phentolamine or sodium nitroprusside should also be readily available. Without these precautionary measures, arteriography in patients with pheochromocytoma is associated with a high mortality risk.[1,99] During angiography, ECG, blood pressure, and heart rate must be continuously monitored. On the whole, approximately 80% of pheochromocytomas can be demonstrated by angiographic procedures.[8,22,124] As an additional procedure to detect small tumors, sonography should also be mentioned.

Furthermore, very recently Sisson et al.[103b] reported a procedure for scintigraphic imaging of pheochromocytomas by means of $^{131}$*meta*-iodobenzylguanidine. Also, in cases of pheochromocytoma located in the adrenal gland, adrenal scans with $^{131}$I-iodocholesterol permit lateralization of the tumor, since the pheochromocytoma causes scintigraphic storage defects with resultant displacement of the $^{131}$I-iodocholesterol–storing adrenal rest and, consequently, displacement of the adrenal gland from the renal pole.[52,65,110]

Cystoscopy should be mentioned as a further procedure for localization in cases with symptoms suggesting a pheochromocytoma of the bladder. Cystoscopy should be performed only after $\alpha$-blockade. Furthermore, cholecystography/cholangiography should always be done to exclude cholelithiasis.

## Therapy

The therapy of choice in patients with pheochromocytoma is without doubt the surgical excision of the tumor, which leads to an arrest of the clinical symptoms and causes normalization of blood pressure in about 75% of cases.[70a] Medical treatment with alpha- and beta-receptor blocking agents is reserved for patients whose condition does not allow surgery and those patients with metastasizing pheochromocytoma.

The patient should be carefully prepared for surgery, barring an emergency situation, in order to keep the operative risk at a minimum. In recent years preoperative treatment with a combination of alpha- and beta-receptor blocking drugs has been generally successful and has been accepted by many,[24,49,57,58,80,87,88,96,100,103,105,114] although a few other groups have obtained excellent surgical results without such preparation.[22,40] In particular, with this medical preparation it has become possible to prevent hypertensive crises and arrhythmias before and during surgery and to avoid the hypotensive crises after excision of the tumor that were often severe, long-lasting, and difficult to control. Of course, such medication prevents the intraoperative induction of hypertensive crisis as an aid to diagnosis, but the preoperative localization of the tumor makes this disadvantage slight. On the other hand, it is felt by some that only a partial $\alpha$-blockade should be used because some response of blood pressure can be a great value to the surgeon.[70a]

For therapy with alpha-receptor blocking agents, phenoxybenzamine (Dibenzyline) is well-suited because of its longer duration of action (half-life for iv injection approximately 24 h); furthermore, it can also be administered intravenously (dosage 1 mg/kg body weight). This therapy should be started 1–3 weeks before surgery is scheduled with an initial dose of 10 mg p.o.; the dosage can be increased to 100 mg to control clinical events. In addition to phenoxybenzamine, phentolamine is also available as an alpha-receptor blocking agent, but it has only a short duration of action; however, it is suitable for control of hypertensive crises because of its rapid onset of action after intravenous administration. Experience with prazosin (Minipress) in pheochromocytoma therapy is not yet available.

A further advantage of phenoxybenzamine therapy is considered to be that, by blocking the vasoconstricting effect of norepinephrine, the blood volume is restored prior to surgery in patients with hypovolemia, which is often demonstrated in the presence of pheochromocytoma.[22,27,29,112] In this way a postoperative hypotensive reaction can be avoided. Engelman attributes this hypotension in part to a functional autonomic insufficiency of the vessels, so that even the postoperative administration of norepinephrine cannot elicit an adequate response.[28,30] In addition, to avoid a fall in blood pressure, an infusion of 1000 ml of blood, a plasma expander, or an albumin solution on the evening prior to surgery is recommended, as well as intraoperative infusions with volumes which exceed the intraoperative blood loss.[10,22,44,100,105] Besides volume

replacement and alpha-receptor blockade, therapy with beta-receptor blockers, introduced by Prichard and Ross, has proved useful in patients with pheochromocytoma.[87,93] With beta blockers, it is not only possible to largely control tachycardias and cardiac arrhythmias that frequently occur, but tachycardias that may occur after alpha-receptor blockade in patients with pheochromocytoma primarily excreting epinephrine can also be avoided. *Treatment with beta-receptor blockers must not be started until after therapy with alpha-receptor blocking agents, since, otherwise, marked rises in blood pressure can occur.* In certain circumstances, it is necessary to increase phenoxybenzamine medication. Therapy with beta-receptor blockers also should be started at a low dosage, i.e., initially one tablet of one of the commercial drugs, paying attention to any contraindications that may exist (heart failure, conduction disturbances, airway obstruction).

Should it be necessary to digitalize the patient, special care must be taken, since, owing to the so-called catecholamine myocardiopathy, there is increased irritability of the myocardium with increased danger of inducing arrhythmias.

If preoperative evaluation has shown the presence of bilateral pheochromocytoma, MEN, type 2 or 3, or the coexistence of Cushing's syndrome, so that both adrenal glands must be removed, hydrocortisone replacement therapy should be started prior to induction of anesthesia and continued postoperatively (for details see ref. 70a). Prior to the induction of anesthesia, the monitoring of blood pressure, ECG, and central venous pressure must be assured. Halothane or enflurane together with $N_2O$ are accepted anesthetics.[7,13,44,59,70a,91,92]

Despite improved procedures for localization, either a large epigastric transverse incision or a paramedian incision is mandatory to permit a thorough explorative operation after excision of the main tumor.[24,70a,100] With this exposure it is also possible to perform a cholecystectomy at the same time if necessary.

The treatment of pheochromocytoma during pregnancy involves some special considerations. If a pheochromocytoma becomes manifest before the fifth month, treatment with phenoxybenzamine should first be undertaken and the plasma volume restored so that surgery can subsequently be performed.[37] If the pheochromocytoma is discovered after the fifth month, medical treatment can be continued up to the delivery date, if symptoms of the pheochromocytoma can be adequately controlled so that it does not pose a serious threat to the patient or fetus.[26] At that time delivery should be performed by cesarean section, with simultaneous excision of the pheochromocytoma.[37,48,106] On the whole, very careful supervision of the woman is necessary in order to reduce or avoid the considerable danger to mother and child of hypertensive crises or falls in blood pressure. In children with pheochromocytoma, it is important to recall that bilateral and multiple tumors are more frequent than in adults.

### Medical Treatment

As already mentioned, medical treatment of pheochromocytoma is indicated in patients who are not in an operable condition—perhaps until surgery is possible, in cases where complete extirpation of the tumor is not feasible, and in patients with metastatic pheochromocytoma.

Allen et al. were first able to successfully control the manifestations of a pheochromoblastoma for an extended period of time with phenoxybenzamine.[2] Furthermore, Engelman and Sjoerdsma reported long-term therapy in four patients with malignant pheochromocytoma or pheochromocytoma that was initially inoperable.[27] The dosage of phenoxybenzamine must be individualized according to the therapeutic response. Medical treatment normalizes both blood pressure and the metabolic effects of excessive catecholamine secretion; however, the growth of the pheochromocytoma is not influenced.[27] Cytostatic therapy or radiotherapy of the malignant pheochromocytoma has proved ineffective.[70a] In addition to phenoxybenzamine, the administration of beta-receptor blockers is often necessary to control tachycardia and arrhythmia. Phentolamine and other antihypertensive drugs are not suitable for the long-term treatment of pheochromocytoma.

## Prognosis

Surgical excision of a pheochromocytoma leads to normalization of blood pressure in 75% of the cases. A failure of blood pressure response may be due to an overlooked pheochromocytoma, inadvertent ligature of a renal artery, or the manifestation of hypertension due to arteriosclerosis of the renal vessels in long-standing undetected pheochromocytoma.

If an immediate postoperative fall in blood pressure fails to occur for reasons other than those mentioned, preoperative or intraoperative overtransfusion may be responsible. In these cases, diuretic therapy rapidly leads to normalization of blood pressure.[30] Incomplete excision of pheochromocytoma tissue can be diagnosed by a fall of blood pressure in response to phentolamine. Furthermore, in

cases where a residual pheochromocytoma is suspected, catecholamine excretion should be determined 4 to 5 days after surgery, since after complete excision of the pheochromocytoma, catecholamine excretion will have returned to normal by the second or third postoperative day.

Surgical mortality has been reduced from 40% to 50% in earlier cases and in cases in which pheochromocytoma was incidentally discovered during surgery to approximately 5%[44,108] as a result of accurate localization and preparation for surgery with adrenergic-receptor blocking agents and infusions.[100,13,18,22] Manger and Gifford have stressed the importance of an expert team in the management of a patient with pheochromocytoma; with proper expertise, they state the operative mortality should not exceed 3%, whether or not preoperative adrenergic blockade is employed.[70a] In patients with malignant pheochromocytoma, the 5-year survival rate is 44%; the longest survival reported thus far is 21 years.[88]

## Postoperative Follow-up

In all operated patients with pheochromocytoma, urinary catecholamine excretion should be checked before release from the hospital; furthermore, the patients should be examined at regular intervals for some years so that a recurrence is not overlooked. Family members with hypertension or symptoms that indicate pheochromocytoma or diseases which frequently occur in conjunction with pheochromocytoma should also be examined.

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# Hematologic Aspects of Arterial Hypertension

10

A. B. Gould

Various hematologic disorders are associated with hypertension. These include the anemia of malignant hypertension; polycythemia associated with nonneoplastic renal disease such as hydronephrosis, polycystic kidney disease, renal artery stenosis; and relative or benign polycythemia, sometimes called Gaisböck syndrome. This chapter will describe these conditions and the methods which are used to treat them.

## Hemolytic Anemia of Malignant Hypertension

Hemolytic anemia with red blood cell fragmentation and intravascular coagulation is associated with a group of disorders which includes malignant hypertension.[8,11,16,27,28,41] Because morphological changes of the red blood cells may be secondary to the disease of small blood vessels, Brain et al. applied the term *microangiopathic hemolytic anemia* (MHA) to describe this condition.[8] The two principal components of MHA are red blood cell fragmentation and intravascular coagulation. In patients with malignant hypertension, it is not certain whether intravascular coagulation precedes hemolysis[28,60] or hemolysis, secondary to vascular damage, precedes coagulation.[7,8] Experimentally, red blood cells were fragmented by fibrin strands while moving through a clot at the velocity of arterial blood flow.[10] Similarly, hemolysis of red blood cells may occur by fibrin within the microcirculation.[7,51,52]

Evidence of intravascular coagulation is not found in patients with benign hypertension,[28] chronic renal failure (excluding malignant hypertension),[8] or pregnancy-induced hypertension.[15,22] Hematologic aberrations and hypertension associated with these diseases may in part be caused by abnormalities of vascular endothelium caused by severe vasospasm.[15,22,34]

Microangiopathy occurring in other disease states such as hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, Sanarelli-Schwartzman reaction, and renal cortical ischemia is characterized by changes in the intima that are similar to those of malignant hypertension.[34,35] From this observation it was theorized that localized coagulation caused by increased permeability of small blood vessels to fibrinogen as a result of high arterial pressure initiates or at least contributes toward the transition of hypertension from the benign to the malignant phase.[27,28,41] The condition is exacerbated when red blood cells fragmented by fibrin deposits are hemolyzed, leading to further deposits of fibrin. Although patients with benign hypertension[28] or chronic renal failure[8,28] are relatively free of intravascular coagulation, increased clotting capacity of the blood is found in patients with arterial hypertension, which may lead to the development of intravascular thrombi.[17,45,58,60,63] Vascular thromboses are said to be found in most cases of death from arterial hypertension and atherosclerosis.[45]

One objection to the theory that malignant hypertension is triggered by microangiopathic hemolytic anemia is that MHA is not always found in patients with malignant hypertension,[2,27,28,41] possibly because the clinical symptoms of intravascular coagulation do not persist[41] or perhaps the anemia of malignant hypertension is not always "microangiopathic" in origin. In a series of 24 patients with severe renal failure, Stewart has shown the fragmentation of red

blood cells to be equally severe in malignant hypertensive patients having extensive lesions of small blood vessels[56] as in patients with renal tubular necrosis in which microangiopathy is reported to be absent or minimal.[8] Failure to demonstrate a correlation between red blood cell fragmentation and fibrinogen metabolism also suggests that red blood cells are not damaged by intravascular coagulation in malignant hypertensive patients.[54] Hemolysis might occur if the metabolism of the erythrocyte was affected by uremia. However, neither erythrocyte life-span nor degree of erythrocyte fragmentation in patients with malignant hypertension is related to serum urea.[56] The presence of other toxic substances normally excreted or metabolized may damage red blood cells or interfere with erythropoiesis. Formation of "burr cells" was observed when normal red blood cells were incubated in serum from uremic patients. The red blood cells were apparently damaged by a heat-labile, nondialyzable factor in uremic serum.[13] As suggested by Erslev, it seems reasonable "to relate premature destruction of red cells in uremia to mechanical disruption of metabolically impaired cells."[20]

The enzyme renin or components of the renin system are sometimes considered responsible for intravascular coagulation and the transition of benign to malignant phase hypertension.[61] (See Giesa[29] for review.) However, in four patients entering the malignant phase a fall in the hematocrit level occurred concomitantly with a marked increase in blood urea nitrogen (Table 1). These changes were apparently not caused by abnormal amounts of renin inasmuch as they occurred in three of the patients prior to any increase of renin. The possible role of other vasoactive substances in precipitating vascular lesions has been reviewed by Giesa[29] and Wardle.[60]

Many patients with chronic renal failure have erythropoietin levels that are inappropriately low for the degree of anemia.[21,25,43,59] (See Erslev[20] for review.) In contrast to this group, malignant hypertensive patients with high renin and substrate levels usually have high erythropoietin titers.[3] Shown in Table 2 are values for serum renin, renin substrate, erythropoietin, and hematocrit for two groups of patients undergoing hemodialysis for end-stage kidney failure. One group (seven patients) exhibited high serum renin and accelerated hypertension. The other group (five patients) was characterized by low serum renin and normal blood pressure. Six of the seven patients with accelerated hypertension had abnormally high renin and erythropoietin values. Although the hematocrit values were significantly lower in the normotensive group ($p < 0.001$), erythropoietin was stimulated in only one patient. Renin substrate was high in 7 of the 12 patients studied; furthermore, only those with elevated renin substrate in either study had detectable levels of erythropoietin.

In a study of 33 hypertensive patients, Bourgoignie et al. showed an association of high renin and erythropoietin in patients with renovascular hypertension.[6] However, in patients with accelerated hypertension, only renin activity was significantly elevated, and they concluded that the two activities were dissociated. It should be pointed out that none of the patients in their study had more than minimal azotemia. It has been our experience that patients with accelerated hypertension have renin values within the normal range until there are definite

**Table 1.** Blood Pressure, Serum Renin, Blood Urea Nitrogen, and Hematocrit Percentage in Four Patients Entering the Malignant Phase of Hypertension

| Patient | Age, Sex | Date | Etiology of Hypertension | BP | Renin (IRU/ml × $10^4$)* | BUN (mg/100 ml) | Hematocrit (%) |
|---|---|---|---|---|---|---|---|
| CA | 41,F | 2/2/68 | Essential | 220/150 | 0.15 | 20 | 50 |
| | | 10/30/69 | Malignant | 230/170 | 1.45 | 28 | 43 .5 |
| | | 12/9/69 | Malignant | 210/120 | 2.18 | 110 | 30 |
| | | 12/30/69 | Malignant | 230/170 | 4.02 | 144 | 27.5 |
| BG | 42,F | 3/4/70 | Malignant | 220/128 | 0.23 | 40 | |
| | | 4/15/70 | Malignant | 230/130 | 0.23 | 42 | 41.5 |
| | | 12/16/70 | Malignant | 230/120 | 1.76 | 86 | 27.5 |
| HE | 41,F | 6/7/71 | Essential | 180/160 | | 26 | 46 |
| | | 6/5/72 | Essential | 220/130 | 0.33 | 18 | 46 |
| | | 6/13/72 | Essential | | 0.45 | | 39 |
| | | 1/5/73 | Malignant | 220/130 | 3.10 | 108 | 34 |
| DS | 49,M | 5/20/71 | Chronic renal failure | | 0.81 | 23 | 44 |
| | | 8/25/72 | Chronic renal failure | 230/130 | 0.69 | 85 | 30 |
| | | 10/16/72 | Malignant | 200/120 | 1.77 | 134 | 19.5 |

*IRU = international renin units; normal range: trace–1.20.

**Table 2.** Serum Renin, Renin Substrate, Erythropoietin, and Hematocrit Percentage in Chronic Renal Failure

| Patient | Age, Sex | Renin (IRU/ml × $10^4$)* | Renin Substrate (pmol/ml)† | Erythropoietin (IRU/ml)‡ | Hematocrit (%) |
|---|---|---|---|---|---|
| *Hypertensive Patients* | | | | | |
| HS | 40,M | 35.5 | 4800 | 0.35 | 29.5 |
| HG | 52,M | 3.2 | 1200 | 0.22 | 24.5 |
| LL | 46,M | 1.6 | 1385 | 0.10 | 32.5 |
| FT | 47,M | 11.8 | 2455 | 0.075 | 27 |
| EG | 36,F | 37.5 | 6000 | 0.050 | 27 |
| RS | 57,F | 12.4 | 5400 | 0.035 | 32 |
| LM | 57,M | 10.4 | 643 | ND | 20 |
| *Normotensive Patients* | | | | | |
| BB | 39,F | ND | 1262 | 0.09 | 16 |
| MS | 30,F | ND | 750 | ND | 16 |
| LC | 20,F | ND | 960 | ND | 16 |
| MF | 37,F | ND | 927 | ND | 16 |
| ME | 53,M | 0.18 | 857 | ND | 16 |

IRU = international renin units.
*Normal value: trace–1.25.
†Normal value: 691–924.
‡Normal value: ND.

signs of azotemia (Table 1). Perhaps the lack of agreement between the studies of Bourgoignie and ours centers on the definition of "high renin."

In any event, it seems reasonable to assume that anemia in dialysis patients with chronic renal disease and malignant hypertension is not caused by an insufficient production of erythropoietin. Some evidence suggests that the formation of new red blood cells may be inhibited by toxic substances in the serum of uremic patients.[23,44,59]

Hemodialysis has been used effectively in treating both the anemia[21,40,46] and high blood pressure[62] of patients with chronic renal disease. Increased dialysis time has been recommended to remove middle-sized molecules thought to be toxic.[1] Hemodialysis[4,18] and peritoneal dialysis[50] improve the prognosis of severe hemolytic-uremic syndrome. Ekberg et al. found that early treatment with hemodialysis given almost daily to a group of six children with a severe form of hemolytic-uremic syndrome was essential in saving the lives of all six and normalizing the blood pressure in the four who were hypertensive.[18] Heparin was either not used between the dialyses or given in small amounts.

Blood transfusions to most patients with renal disease anemia are considered unnecessary[40] and even dangerous.[47,48] For many patients hemodialysis treatment on a thrice weekly schedule was successful in removing substances which inhibit erythrocyte production and shorten red blood cell life-span, making transfusions unnecessary.[40] In addition, as stated by Mitchell, oxygen delivery to the tissues is adequate unless heart failure supervenes.[47] Uremic hypertensive patients have high cardiac output and a normal to slight increase in peripheral vascular resistance. (See Neff et al.[48] for review.) Although transfusion with packed red blood cells decreased cardiac output to normal values, diastolic blood pressure was increased on the average 20 mm Hg.[48] Apparently, severe anemia causes hypoxic vasodilation and may, as suggested by Neff, "serve to protect patients from the effect of an otherwise devastating hypertension."

## Hypertension and High Hematocrit

Hypertension associated with a high hematocrit has been reported in two types of patients characterized by the absence or presence of renal disease. The first group, described by Gaisböck[24] and others,[5,9,12,19,30,33,38,53,55] consists predominantly of white, middle-aged men, who are often described as being anxious or tense, of stocky build and ruddy complexion, moderately hypertensive, and overweight. They have a benign form of polycythemia which is more apparent than real inasmuch as the

high hematocrit percentage is caused by a red blood cell mass near the upper limit of normal[36] and a reduced plasma volume.[12,19,30,33,36,38,53,55]

Ferrokinetic studies and erythropoietin determinations show no evidence of an increased rate of erythropoiesis.[12,36,55] Blood viscosity, plasma proteins, serum cholesterol, triglycerides, uric acid, plasma renin, and sodium excretion are higher than normal.[55] This group can readily be separated from patients with polycythemia vera because the bone marrow is normal, white blood cell and platelet counts are normal, the spleen and liver are not enlarged, and granulocyte alkaline phosphatase activity is not increased.[53] The relationship between high hematocrit and some of the other characteristics of this syndrome is not understood but may be familial.[30,53,55] More recent studies suggest that a contracted plasma volume and high hematocrit percentage in some patients are caused by systemic hypertension.[12,19,55] Treatment of the hypertension[12,19] and loss of weight[55] causes a reduction in the hematocrit level and an expansion of the plasma volume.

In contrast with the first group of patients in which the hypertension and high hematocrit may be related through some form of a "stress factor," polycythemia and hypertension in the second group are associated with nonneoplastic renal disease such as hydronephrosis, polycystic kidney disease, and renal artery stenosis. Hypertension is common in patients with coexistent polycythemia and nonneoplastic renal disease. Of the first 10 cases reported all had blood pressures higher than 140/90 mm Hg.[32] Sometimes the hypertension is observed prior to the onset of polycythemia;[14,37] more often polycythemia and hypertension are reported together.[26,31,32,39,42,57] Remission of the polycythemia and lowering of the blood pressure often occur following nephrectomy[14,26,31,42] or excision of the renal cysts.[49]

Perhaps a common factor is responsible for both hypertension and polycythemia in patients with renal disease. A decrease in perfusion pressure caused by the renal disease may limit the oxygen delivery to a vital site, thus interfering with normal renal metabolism and initiating hypertension. In severe cases, the oxygen supply may be limited to such an extent that erythropoietin is stimulated[32,49] and polycythemia develops.

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# Hypertension and Hyperthyroidism

# 11

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The cardiovascular manifestations of hyperthyroidism, such as tachycardia, tachyarrhythmia, atrial fibrillation, and systolic hypertension, often represent the focal point of both the objective and subjective clinical symptoms of hyperthyroidism.[35,37,43] They are an important aid not only in the diagnosis of thyroid dysfunction but also in the assessment of therapeutic results. The hemodynamic changes observed in hyperthyroidism, such as elevated cardiac output, increased blood volume, and decreased peripheral vascular resistance, lead in severe cases to a rise of systolic blood pressure and a fall of diastolic pressure, and thus to the typical water-hammer pulse of the "hyperkinetic circulatory syndrome."

In a study of 458 hyperthyroid patients, Hurxthal found a systolic blood pressure of 150 mm Hg or higher in 26% of the patients overall, and in 42% of those with severe hyperthyroidism.[22] The average blood pressures in this study were 137/70 mm Hg before operative treatment and 129/77 mm Hg 3 months after subtotal thyroidectomy. A fall of systolic pressure and rise of diastolic pressure following attainment of a euthyroid state were observed in about half the patients studied. However, the overall prevalence of hypertension was no higher among the hyperthyroid patients than in a euthyroid control population. According to Thompson et al., diastolic readings of 100 mm Hg or more are a certain sign, and systolic readings above 190 mm Hg a probable sign, that hypertension will persist even after thyroidectomy.[41] About 10% of all normotensive hyperthyroid patients display hypertensive blood pressures only after normalization of their metabolism. This tendency is particularly marked in hyperthyroid patients with cardiac arrhythmias and signs of cardiac decompensation.

From a pathophysiologic standpoint, the cardiovascular changes in hyperthyroidism are the result, first, of the hemodynamic demands of the peripheral hypermetabolic state and, second, of the direct cardiotropic effect of thyroid hormone.

## Peripheral Circulation

Typically, the circulation of the hyperthyroid patient is accelerated, and tissue perfusion is increased owing to dilatation of the arterioles and opening of the capillary bed.[13,24] The latter leads to an increase in the circulating blood volume.[10] The decrease in systemic vascular resistance, which sometimes leads to a fall of the diastolic blood pressure, plays a central role in the pathogenesis of the hyperkinetic circulatory state. Presumably the peripheral vasodilation results from an increase in peripheral tissue oxygen consumption associated with the thyroxine-induced rise of metabolic rate, as well as from the need for greater heat dissipation through the skin due to increased thermogenesis.

The degree to which peripheral tissue hemodynamics are influenced by the metabolic changes of hyperthyroidism remains unclear. Under physiologic conditions the rise of metabolic rate is accompanied by a proportionate increase in tissue perfusion.[16] This phenomenon of active hyperemia is observed in isolated skeletal muscle in which contraction is evoked by electrical stimulation[36] and is independent of nervous control. It has been postulated that the observed local vasodilation is mediated by the buildup of metabolites such as lactate, adenosine, adenosine nucleotides, and $CO_2$, the re-

lease of histamine, or pH changes in metabolically active tissues. However, this mechanism remains unproved despite extensive animal studies.[8,32] It is generally assumed that the dilatation of the mesarteriolar and precapillary vessels is mainly the result of a regional oxygen lack caused by the increased oxygen demand of the metabolically active tissue.[16]

Although the hypermetabolic state is obviously a causative factor in the peripheral vasomotor changes of hyperthyroidism, the increase in tissue perfusion is considerably greater than that required to meet the excessive oxygen demand.[13,24] By contrast, the cardiac output and peripheral blood flow increase little when a comparable oxygen demand is induced in humans by salicylic acid[25] or in animals by dinitrophenol.[20] This disproportionate increase of tissue perfusion in hyperthyroid patients remains unexplained.

The calorigenic effect of thyroxine leads to a temperature rise which, like exogenous heat application,[18] causes cutaneous vasodilation through autonomic mechanisms. Opening of the cutaneous capillary bed leads to a more than threefold increase in cutaneous blood flow[24] and is considered an essential mechanism for heat dissipation. Capillary dilatation is responsible for the typical warm, moist, red skin of the hyperthyroid patient.

The increase in peripheral blood flow causes a greater volume load to be placed on the heart and thus increases the stroke volume via the Frank-Starling mechanism.[16] Through this mechanism of peripheral autoregulation, each tissue controls its own blood flow in accordance with metabolic demands. The fact that the augmented stroke volume in hyperthyroidism is at least partly the result of peripheral vasodilation is demonstrated by the decrease in cardiac stroke volume caused by the administration of the vasoconstrictor phenylephrine to hyperthyroid patients.[40]

## The Heart

Tachycardia, arrhythmias, and high cardiac output with the possible consequences of congestive heart failure are the cardinal symptoms of hyperthyroidism.[13,21,24] The elevated cardiac output is due to the aforementioned autoregulative increase in peripheral blood flow as well as to a direct effect of thyroid hormone on myocardial contractility.[1,4,14]

The cardiotropic action of thyroxine is documented by in vitro studies of homogenates from the cat heart, in which the production of cyclic adenosine monophosphate (cAMP) was stimulated by the administration of thyroxine.[27] Thyroxine may lead to a change in excitation-contraction coupling and an increase in myosin-ATPase activity.[12] The utilization of chemical energy in the form of creatine phosphate and ATP in the papillary muscle of hyperthyroid cats is disproportionately high relative to the muscular output, indicating reduced efficiency in the conversion of chemical energy to mechanical work.[31] Accordingly, the excessively high myocardial oxygen consumption seen in animals with experimentally induced hyperthyroidism[34] cannot be attributed to the uncoupling of oxidative phosphorylation postulated earlier.

Goodkind et al. found that the papillary muscle of guinea pigs treated with thyroxine showed an increase in both the force and rate of isometric contraction as compared to normal animals.[12] In similar experiments on hyperthyroid cat hearts, Taylor,[38] Buccino et al.,[4] and Skelton et al.[34] observed an increase in the maximum velocity of muscle fiber shortening during isotonic contraction, as well as a higher rate of tension development and maximal attainable tension during isometric contraction. The total contraction time and the time required to achieve maximum tension were shortened. This increase of myocardial contractility is not a product of tachycardia and is unaffected by the administration of beta-blocking agents or the depletion of catecholamine storage sites by reserpine.[1,4,12,14]

Amidi et al. found an elevation of the cardiac index, stroke volume index, and left ventricular systolic ejection rate in their studies of hyperthyroid patients.[1] Compared with the elevated heart rate, the low-grade augmentation of stroke volume contributes little to the high cardiac output state.[1,21] The rise of cardiac output is accompanied by a systolic pressure increase in the right ventricle and pulmonary artery.[21] The hemodynamic changes during exercise are, in the absence of heart failure, similar to those in healthy persons. However, the cardiac output of hyperthyroid individuals increases considerably more during strenuous exercise than the higher oxygen demand would account for.[30]

Noninvasive studies, such as the simultaneous recording of the carotid pulse curve, electrocardiogram, and phonocardiogram, make it possible to determine the systolic time interval. The latter correlates with the rate of left ventricular pressure rise and cardiac stroke volume and thus serves as a means of assessing myocardial contractility. A shortening of electromechanical systole, determined by the interval between the Q wave in the ECG and the second heart sound, can be demonstrated in patients with hyperthyroidism.[42] The rate-adjusted isovolumic period (interval between the onset of ventricular excitation and the rise of the carotid pulse curve) and the systolic ejection time are short-

ened in hyperthyroidism, while, conversely, they are prolonged in hypothyroidism. In accordance with the increased pulse rate, the time between the start of ventricular excitation and the diastolic Korotkoff sound over a peripheral artery is shortened.[48] These findings in humans are interpreted as indirect evidence of a direct inotropic effect of thyroxine and confirm the data from animal studies.[4,34,38] The change in hemodynamic patterns, finally, is responsible for the systolic hypertension observed in at least a portion of hyperthyroid patients.

The clinically known fact that the inotropic effect of digitalis glycosides is diminished in patients with thyrotoxicosis is explained on the one hand by the decreased glycoside sensitivity of the myocardium[4] and on the other by the low serum digitalis level resulting from accelerated glycoside removal via the circulation.[9] Three to four times the normal glycoside dose is often needed, therefore, to achieve a therapeutic effect.

Besides its positive inotropic effect on the myocardium, thyroxine also exerts a positive chronotropic effect. Thus, isolated atrial muscle from rats treated with triiodothyronine and thyroxine shows an increased rate of spontaneous contraction.[19] In rats with hypothyroidism, by contrast, this rate is markedly lower than normal. Not surprisingly, the heart rate of hyperthyroid patients remains elevated even after functional denervation by pharmacologic adrenergic and cholinergic blockade, owing to the direct chronotropic action of thyroxine.[23] Conversely, thyroxine replacement in hypothyroid patients raises the heart rate into the normal range.[48] The tachycardia of hyperthyroidism represents the most important determinant of the high cardiac output state.

## The Sympathoadrenal System

Clinical experience has long pointed to reciprocal influences between thyroid function and the sympathoadrenal system.[17] The observations that the symptoms of hyperthyroidism are similar in many respects to those induced by the administration of epinephrine and that sympatholytic drugs are able to lower the heart rate and cardiac output have suggested the possibility that the observed cardiovascular effects of thyroid hormone are mediated by an increase in sympathetic outflow or a heightened sensitivity of the effector organs to adrenergic stimuli.[3] According to modern opinion, however, the cardiovascular effects of the two systems are independent and additive, rather than synergistic.[2,26]

The favorable effect of beta-blocking drugs on the symptoms of hyperthyroidism suggests that the adrenergic system plays an important role in the genesis of the associated hyperdynamic circulatory syndrome. The blockade of beta-adrenergic receptors with propranolol or sympatholysis with reserpine and guanethidine lowers the heart rate, cardiac output, and pulse pressure and prolongs the circulation time.[2,4,14,44] Tremor of the fingers, hyperkinesia, sweating, nervousness, and lid retraction—signs of increased adrenergic activity—can also be reduced by beta-receptor blockade.[39] However, complete normalization of cardiac and circulatory parameters does not occur, owing to the direct inotropic and chronotropic effect of thyroxine.[39,44,45] Clinically, it must be noted that the negative inotropic effect of beta-blocking drugs may precipitate congestive heart failure in patients with severe thyrotoxicosis.

On the other hand, beta-receptor stimulation in pharmacologically induced hyperthyroidism leads to a similar absolute rise of heart rate and cardiac output and fall of mean arterial pressure as in the euthyroid state.[2,29,33,45] In experimental studies of papillary muscle in hyperthyroid cats, a decrease rather than increase of myocardial contractility was found after administration of norepinephrine.[4] These findings of an absence of myocardial sensitization to catecholamines are supported by in vitro studies showing similar increases of cAMP levels in the cardiac homogenates of hyper- and euthyroid cats following the administration of norepinephrine.[27,28] Opposing this is the finding of increased cAMP production in response to adequate stimuli (epinephrine, glucagon, and parathyroid hormone) in hyperthyroid patients.[15]

It would be natural to suppose that the clinically presumed increase in adrenergic activity is the result of an oversecretion of catecholamines in the hyperthyroid organism. However, it has been shown that the plasma levels[5–7] as well as the secretory and excretory rates of epinephrine[5] and norepinephrine[7] are unchanged in hyperthyroid patients. The degradation rates of epinephrine and norepinephrine[5,7] and their excretory products, metanephrine and vanillylmandelic acid,[46] are apparently unaffected by thyroid hormone. Thus, there is no evidence that thyroid hormone has a significant influence on medulloadrenal secretion, norepinephrine release from sympathetic nerve endings in response to adequate stimuli, or catecholamine metabolism. The degree to which elevated catecholamine levels are present in the myocardia of hyperthyroid individuals is unclear. The levels appear to vary among different species. For example, the norepinephrine level and norepinephrine uptake are elevated in the thyrotoxic guinea pig heart,[11,47] while normal levels are found in the heart of thyrotoxic cats.[4]

On the whole, then, one gains the impression that the activity level of the sympathoadrenal system is

increased in experimentally induced or spontaneous hyperthyroidism, although so far no such increase has been demonstrated biochemically.[26]

In summary, the cardiovascular changes observed in the hyperthyroid state are in part the result of a direct effect of thyroid hormone on the myocardium and the impulse formation and conduction system. In addition, peripheral vascular resistance is lowered as a consequence of an increase in peripheral tissue metabolism. Aggravated by increased adrenergic activity, the hyperkinetic circulatory syndrome represents one of the most important manifestations of hyperthyroidism.

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# Influence of Calcium Balance and Rarer Ions in Hypertension

12

R. Ziegler

## Calcium

### The Clinical Challenge: Hypertension in Primary Hyperparathyroidism

Studies on the effects of certain blood constituents such as electrolytes, metabolic substrates, and hormones on pathophysiologic phenomena such as hypertension are prompted on the one hand by the theoretical possibility of such effects and on the other by epidemiologic observations which point to correlations.

The question of calcium and hypertension has been approached in both ways. Clinical experience first suggested a connection, while abundant data on the influence of calcium on hormone secretion at the cellular level later suggested a possible mechanism for the simultaneous occurrence of hypercalcemia and high blood pressure.

In 1958 Hellström et al. first reported on the phenomenon of hypertension in hyperparathyroidism in an article from a series dealing with the problem of primary hyperparathyroidism from the standpoint of its renal manifestations (stone formation, renal calcification).[25] Their study population consisted of 105 patients observed during the period from 1940 to 1957 at the Karolinska Hospital in Stockholm. During that time 70% of the patients had at least periods of hypertension, 50% had continuous hypertension, 20% became normotensive after successful removal of the hyperactive parathyroid tissue (adenoma or hyperplasia), while 30% (preoperatively normotensive or periodically hypertensive) developed hypertension following parathyroidectomy.

Hellström et al. attempted to correlate their blood pressure observations with renal function and pathology.[25] Their normotensive patients generally had normal renal function (GFR) or at most a moderate functional impairment.

On the basis of their finding of impaired renal function in the absence of hypertension, they concluded that the hypertension was secondary to a renal lesion. This conclusion was supported by the correlation between the extent of renal damage and the severity of the hypertension. Secondary infections of kidneys damaged by hyperparathyroidism had no apparent effect on the development of hypertension.

The fact that patients with advanced renal damage showed more frequent radiologic signs of osteitis fibrosa as an osseous manifestation of parathyroid hyperfunction suggested an increase of multiple organic disorders in such severe forms or late stages of the disease.

The conclusion of the Hellström study that the mechanism of hypertension in hyperparathyroidism is unexplained and requires further study was heeded with some hesitancy. Aside from incidental remarks on the discovery of elevated blood pressures in hyperparathyroid patients,[21] it was not until 1972 that systematic research was done: Rosenthal and Roy found 13 cases of hypertension in a group of 40 patients with primary hyperparathyroidism.[51] Since only two of the hypertensive patients had impaired renal function, it became apparent that hypertension could develop even in the absence of renal damage. Rosenthal and Roy also pointed out the value of routine serum calcium determinations in hypertensive patients.

Again from Scandinavia came the interesting ob-

servation of Christensson et al. that hypercalcemia is discovered more frequently in hypertensives treated with thiazides (1.9% of cases) than in a general cross-section of hypertensive patients (0.6%).[10,11] Following discontinuance of thiazides in the 20 patients concerned, the serum calcium remained elevated in many, and parathyroid adenomas were surgically removed from 14. Thus, antihypertensive therapy provided a means of detecting primary hyperparathyroidism in these patients. The mechanism involved an "unmasking" of the latent hypercalcemia by the thiazides, which decrease the urinary excretion of calcium.[12] In the next section we shall examine findings which suggest possible etiologic mechanisms of hypertension in cases of parathyroid hyperfunction. The hypertension is probably the result of a multifactorial process in which different factors can become predominant, depending on the circumstances.

## Systems Involved

### Vascular muscle

It is well known that the presence of calcium ions is essential for many biochemical processes. But beyond this, it is now believed that calcium ions are not restricted to a mute presence but apparently perform the role of second or third messengers within the cell.[50] These intracellular shifts of calcium ions are controlled via multilevel systems and aid in the performance of the cell's specific function: The release of material from exocrine and endocrine cells (cf. following sections) and excitation and movement in contractile cells. The latter mechanism is of particular interest with regard to the vascular smooth muscle.

Tobian and Chesley reported in 1966 that the calcium content of the mesenteric artery walls of rats made hypertensive by renal artery stenosis was 13% higher than in normotensive control animals.[60] They suggested that, in view of the importance of calcium ions in actomyosin contraction, such a calcium enrichment could be partly responsible for the reduction of the arteriolar lumen.

The source of the calcium may be extracellular and intracellular. The enrichment takes place intracellularly and, by increasing the free ion concentration, elicits contraction of the contractile proteins (troponin-actomyosin-ATPase system).[56,57] The increase in calcium permeability produced by excitatory drugs is consistent with this concept. Possible intracellular sources of the cytosolic calcium ions are the mitochondria and microsomes; calcium release from a membrane pool corresponding to a primitive sarcoplasmic reticulum has also been proposed.[50]

The process whereby cytosolic calcium enrichment is induced by hormones or other specific agents, such as vasoactive drugs, may involve several mechanisms, as indicated by studies in various models. Species differences complicate the picture: Subcellular fractions of sarcolemma and reticulum from the rat myometrium bound more calcium from weak calcium ion solutions and less calcium from concentrated ion solutions than did the mitochondrial fractions of this tissue. By contrast, mitochondrial fractions from human myometrium absorbed more calcium from weak solutions than the vesicular fractions,[26] and the activity of the mitochondrial uptake of calcium varied, depending on the type of smooth-muscle cell investigated. It has been shown that ionophores, which mediate the transport of calcium through biologic membranes, can produce tensions in guinea pig blood vessel preparations which are equal to one-third to one-half the maximum tension produced by norepinephrine.[32]

The physiologic stimuli of vascular contraction also show varying degrees of dependence on the calcium ion milieu. In a calcium-free milieu, the contraction of strips of rabbit aorta under maximal norepinephrine stimulation decreases by only 7%, while contraction induced by angiotension II decreases by 40%. In each case the original strength of contraction can be restored by the addition of calcium.[44] Thus, the effect of angiotensin II apparently depends on an external or labile calcium pool which norepinephrine does not utilize.

It is presumed that the smooth-muscle tone of the resistance vessels is maintained by a sodium-ion–mediated mechanism which keeps the intracellular calcium ion concentration above the threshold of contraction.[3] The transport system (i.e., Na-Ca exchange mechanism) in the sarcolemma must function in such a way that the calcium ion concentration is maintained; changes in the sodium gradient cause an intracellular calcium shift, with a resulting change of tension. Even if it is accepted that intracellular calcium ion enrichment is one link in the chain of events leading to hypertension, it remains unclear whether a rise in the serum calcium level can produce such an increase in the $Ca^{2+}$ concentration within the cell, thus leading to a tension increase and rise of blood pressure. In vitro models, such as the stimulation of contraction by sodium-poor, calcium-rich incubation media,[3] are of limited use in explaining in vivo phenomena, because chronic hypercalcemia (e.g., in primary hyperparathyroidism) follows entirely different laws and never exhibits acute changes in the levels of the involved ions, i.e., changes measured on a scale of minutes. It is true that arterial constriction and rises of vascular resistance have been shown to accompany an increase in

the serum calcium level.[14,23] But the fluid, sodium, and potassium losses that occur in hypercalcemia undoubtedly also have effects on vascular smooth muscle, thereby complicating the pathogenic mechanism. Thus, the direct effect of hypercalcemia on vascular muscle tone can be considered at best a contributing factor in the development of hypertension or a causative factor under certain circumstances; it cannot be considered causative as a general rule.

Recent experiments in rats stress the importance of magnesium ions for contractile tension of portal venous blood vessels.[80] Hypomagnesemia leads to increased, and hypermagnesia to decreased, vascular tension. In alloxan diabetic rats revealing a higher basal contractile tension, the reactivity to magnesium changes is lost. The absence of magnesium is also accompanied by decreased responsiveness to prostaglandins.[66]

### Catecholamines

Earlier studies on essential hypertension showed no evidence of an overproduction of catecholamines. However, these negative findings were probably the result of a lack of accuracy or specificity in the determination methods employed. Moreover, the measurement of only the urinary excretion of catecholamines or their metabolites poorly reflects the situation actually present in the circulation. When reliable techniques were developed for measuring the concentrations of catecholamines in the bloodstream, it became possible to demonstrate a correlation between catecholamine levels and blood pressure in patients with essential hypertension, although the hormone levels were not as high as those associated with pheochromocytoma.[31,48] It is unclear whether the high levels are due to an overproduction of norepinephrine or a disturbance in the breakdown of circulating catecholamines.[33] De Champlain et al. not only confirmed elevated serum catecholamine levels in the essential hypertensive patient but also measured them in experimental rats which had been rendered hypertensive by treatment with desoxycorticosterone acetate (DOCA).[8] The broad scatter of values measured in these studies, and consequent overlapping of groups, remain unexplained.

An important reason for the interest in the connection between calcium and catecholamines is that the adrenal medulla was one of the first endocrine organs in which calcium was shown to exert an influence on hormone secretion.[13] Physiologic stimuli cause the release of epinephrine or norepinephrine in chromaffin tissue and the sympathetic postganglionic fiber in the following manner: Nerve stimuli trigger the release of acetylcholine, which increases the permeability of the nerve fiber membrane to calcium ions; these ions then enter the fibers and release the catecholamines from their storage sites.[7]

Whether an elevation of catecholamines is present in the hypertension that accompanies hypercalcemia is still unknown. The clinical studies reporting an increased incidence of hypertension among patients with primary hyperparathyroidism (see p. 160) contain no data on measurements of catecholamines or their metabolites.

### The kidney and the renin-angiotensin system

While earlier observations suggested that hypertension was secondary to hypercalcemic nephropathy owing to the correlation between the extent of renal damage and the severity of the hypertension,[25] Rosenthal and Roy found signs of impaired renal function in only 2 of 13 hypertensive hyperparathyroid patients studied.[51] Interest then shifted toward the kidney's own system of blood pressure control, the renin-angiotensin axis, to determine how it is influenced by changes in the calcium level in order to differentiate such humoral effects from the etiology of hypertension in late-stage renal disease. Inasmuch as parathyroid hormone inhibits sodium reabsorption in the proximal renal tubule, activation of the renin-angiotensin-aldosterone system would be expected on theoretical grounds.

A calcium dependence of renin release from renal tissue was indeed demonstrated in vitro; however, an increase in the calcium concentration of the incubation medium did not provoke a significant increase in renin release.[39] In spite of numerous additional experiments, the situation is still controversial. Several investigators reported on powerful stimulation of renin secretion by lowering extracellular calcium.[70,73,78] Raising calcium led to diminished renin secretion.[75,76] Calcium ionophores that induce calcium influx into cells also inhibit renin secretion.[67,71] Thus, it could be speculated that renin might be a second hormone that is stimulated by hypocalcemia,[69] in addition to parathyroid hormone. The latter itself stimulates renin secretion,[79] but the individual effects of the several agents present at the same time cannot be clearly differentiated. The net significance of calcium movements in the contributing systems warrants further elucidation. In 1972, Weidmann et al. performed calcium infusion tests in 7 subjects with healthy kidneys and 50 subjects with varying degrees of renal insufficiency.[64] After the infusion, blood pressure readings were taken, and, in a portion of the subjects, plasma renin activity was measured. The rise of serum calcium was paralleled by systolic blood pressure increases of 20 mm Hg or more in 45 of the 56 subjects tested, and diastolic increases of 10 mm Hg or more

in 41 subjects. Of the seven normotensive subjects with normal renal function, only one responded to the induced hypercalcemia with a rise of blood pressure, whereas the subjects with renal insufficiency showed a tendency toward greater increases according to the degree of renal function impairment. In the subjects with renal insufficiency and a hypertensive response to calcium, the plasma renin determinations showed an increase in one of seven cases. Thus, no conclusion could be drawn from this study with respect to the involvement of the renin-angiotensin system in hypercalcemic hypertension.

In a more recent study plasma renin activity was measured in 12 patients with primary hyperparathyroidism, 6 patients with hypercalcemia of other etiologies, and 5 patients with secondary hyperparathyroidism and was compared with values for healthy subjects.[5] While the renin activity was normal in all five normotensive patients with primary hyperparathyroidism, it was elevated in four of the seven hypertensives of this group. In all four of these patients the calcium and renin values normalized after parathyroidectomy. The hypercalcemic cases unrelated to parathyroid hormone showed no renin elevation, nor did the patients with secondary hyperparathyroidism. Calcium-infusion–induced hypercalcemia in the healthy controls resulted in a slight but statistically insignificant rise of renin levels. From these findings the authors conclude that elevated levels of parathyroid hormone in themselves do not lead to hyperreninism, while the hypertension in some hypercalcemic patients with primary hyperparathyroidism may well be based on stimulation of the renin-angiotensin system.

In contrast to many in vitro and animal experiments documenting increased release of renin at low extracellular calcium concentrations, acute or chronic hypocalcemia in humans did not affect renin secretion.[77] Furthermore, stimulated plasma renin activity was found to be low in untreated, hypocalcemic hypoparathyroidism and rose after normalization of serum calcium was achieved by means of vitamin $D_2$ treatment.[72]

Thus, the question of the significance of this system remains unanswered. In particular, we do not know the contributory circumstances and mechanisms whereby hypercalcemia from overproduction of parathyroid hormone can lead to renin-induced hypertension. Again, the multifactorial etiology of the complex phenomenon of hypertension requires that more than a single factor be considered.

### Parathyroid function, parathyroid hormone

The relationships between the function of the parathyroid gland and the blood-pressure–regulating systems are not yet represented in a satisfactory theory. As mentioned above, it has been shown that parathyroid hormone (PTH) promotes the renal excretion of sodium in both the rat[35] and dog.[59] The result is a secondary hyperaldosteronism, which raises the question of the conditions encountered in chronic hyperparathyroidism. This disease does not automatically produce hypertension, as shown by the studies described previously.[5]

On the other hand, DOCA-induced hypertension in the rat is apparently dependent on intact parathyroid glands, since the usual blood pressure increase with DOCA is completely or partially absent in parathyroidectomized animals.[40] The same researchers described an increase of calciuria in the DOCA model of hypertension[41] and, using the latest methods of analyzing the calcium balance, found a rise in the serum PTH level of the treated rats as well as an (independent) increase in the renal excretion of cyclic adenosine monophosphate.[2] The slight (statistically insignificant) fall of serum calcium resulting from hypercalciuria was suggested as the cause of this parathyroid activation, but stimulation of PTH secretion by the catecholamines must also be considered. As evidence of this, it has been shown that beta-adrenergic stimulators such as norepinephrine and isoproterenol cause a rise of serum PTH in humans when administered in therapeutic doses,[29] suggesting that endogenous overproduction of catecholamines may lead initially to secondary hyperparathyroidism.[8] Such a process could terminate in the hyperparathyroidism of the Sipple syndrome, which has previously been regarded as primary.

The adrenomedullary hormones not only play a possible role as physiologic stimuli of PTH secretion (besides the classic hypercalcemic stimulus), but are also involved in the effects of PTH on the skeletal and renal end organs in some circumstances. Marnay-Gulat et al. found in the medulloadrenalectomized guinea pig a decrease in the hypercalcemic activity of exogenously administered PTH, which could be restored with norepinephrine but not with epinephrine.[34] The PTH-induced excretion of cyclic AMP was also decreased in medulloadrenalectomized animals; this decrease was not prevented by norepinephrine. It remains unclear how these differentiated permissive catecholamine effects on PTH activity are to be categorized and whether they also play a role in other species, particularly humans.

Finally, the inhibitory effect of PTH on renal sodium reabsorption may relate to redistributions of renal blood flow. While no hemodynamic effects could be found in the dog kidney following acute administration of PTH, chronically thyroparathyroidectomized dogs (with thyroid hormone replacement) showed an alteration of renal blood flow in favor of

the inner cortex. The effects of this await further study.[17] With respect to uremic arterial disease, histopathologic studies were performed in rats.[68] Uremia was induced by five-sixths kidney resection and the animals developed typical arterial lesions. Parathyroidectomy largely prevented the changes. But there were no significant intergroup differences of mean systolic blood pressure.

Thus, we are faced with an abundance of data which point to effects of individual blood-pressure–regulating factors on the secretion and action of PTH in certain mammals and, to some extent, humans, as well as effects of PTH on the systems controlling the blood pressure. However, we still lack the important links necessary for a complete pathophysiologic concept, or at least a basis for determining which of the findings are pharmacodynamically useful but irrelevant in physiologic terms.

### Phosphorus

The high incidence of hypertension in primary hyperparathyroidism prompted Ljunghall and Hedstrand to investigate the connections between blood pressure and serum phosphate levels.[30] In the 1768 men studied, no relationship was found between the measured blood pressure and serum calcium values, whereas the phosphate levels and blood pressure showed a highly significant correlation. The authors assume that the hypertension is a primary event accompanied by an increased excretion of ions (sodium and calcium) in the urine. The calcium ions, in turn, could stimulate PTH secretion leading to phosphaturia and hypophosphatemia.

### Conclusions

In view of the high incidence of hypertension in patients with primary hyperparathyroidism, there can be no doubt of a connection between the two disorders. Data on the prevalence of hypertension in cases of parathyroid hyperfunction range from 10% to 70%.[10]

In a portion of these cases the "renal manifestation" of parathyroid hyperfunction, i.e., impaired renal function, with subsequent activation of the renin-angiotensin system may play the principal role. The more severe cases described in earlier studies[25] lend particular support to this view. Accordingly, the prognosis of patients with advanced renal disease is poor even after successful removal of the hyperactive parathyroid tissue, i.e., after the hyperparathyroidism is "cured": The renal failure becomes progressively worse and is accompanied by hypertension.[6,9]

On the other hand, broader clinical experience combined with improved diagnostic techniques have enabled the detection of hyperparathyroidism before any renal function impairment has developed. The hypertension in these cases must obey different laws, and its functional character is demonstrated by its regression following the successful treatment of parathyroid hyperfunction.[4,62] It is unclear why some hypertension cases persist despite normal renal function following correction of the hyperparathyroidism.[52] The implications with regard to future work are both practical and theoretical.

On the practical side, the possibility that hypertension may be associated with unrecognized primary hyperparathyroidism merits greater attention. For example, in a group of 900 patients with diastolic hypertension, Rosenthal and Roy discovered 7 cases of hypercalcemia, i.e., 1 case of primary hyperparathyroidism per 130 hypertension cases.[51] Christensson et al. point out that unrecognized cases of hyperparathyroidism among hypertensive patients can be "unmasked" by antihypertensive treatment with thiazides, which decrease the urinary excretion of calcium, thereby raising borderline calcium levels into the more blatant hypercalcemic range.[11] With regard to the question of whether "asymptomatic" primary hyperparathyroidism should be surgically treated or not, the demonstration of hypertension probably represents a sufficient indication for operative intervention.[52]

In view of our ignorance concerning the connections between primary hyperparathyroidism and the hypertension that may or may not accompany it, synchronous studies of PTH levels, renal function, catecholamine levels, renin activities, etc., would be desirable. Of course the complexity of the method arsenal and the problem of patient stress impose limits on such procedures which cannot be entirely overcome by animal studies.

## Lithium

The widespread use of lithium salts in the treatment of cyclothymia and their frequent use in hyperthyroidism raises the question of how lithium might affect systems which are susceptible to its influence or are the target organs of lithium therapy. Clinical observations of reduced blood pressure in cases of lithium poisoning indicate possible disturbances.[20,36]

One known side effect of lithium therapy is the development of a picture resembling nephrogenic diabetes insipidus: The patient develops polyuria and polydipsia owing to an impairment of renal concentrating ability, which is restored poorly or not at all by vasopressin injection.[49] The reported inci-

dence of polydipsia in lithium-treated patients is 40%; that of polyuria, 32%.[19]

The interference of lithium with the adenyl cyclase system has been demonstrated in rats, in which the lithium-induced, vasopressin-resistant polyuria could be attributed to a hyporesponsiveness of adenyl cyclase in the kidney to vasopressin.[65]

Martinez-Maldonado et al. conducted more extensive studies in rats and found that lithium not only inhibits the activation of adenyl cyclase by vasopressin, but also depresses the renal response to cyclic adenosine monophosphate (dibutyryl cAMP.)[37] Thus, lithium apparently also produces a block beyond the stage of cAMP formation. The authors expand the discussion of lithium effects by suggesting that besides producing these peripherorenal disturbances, lithium also interferes with the release mechanism of endogenous antidiuretic hormone and stimulates thirst.

Reports vary as to the extent and frequency of electrolyte shifts with lithium. Vendsborg et al. found no significant changes in the serum sodium, potassium, calcium, magnesium, or plasma glucose in humans after an acute lithium load, but detected a marked fall of the serum phosphate level.[63] This observation was confirmed during the monitoring of diurnal phosphate variations in patients treated with lithium: The levels were lower than in untreated controls, particularly at night.[38] Since there was no attendant change in phosphaturia, while the in vitro phosphate uptake of isolated muscles is increased by lithium only in the presence of glucose,[47] the authors relate the changes in phosphate level secondarily to events in the carbohydrate balance of the muscles.

On the other hand, Arruda et al. report a lithium-induced decrease of phosphaturia in dogs if the phosphate excretion was produced by drugs or by mechanisms which act via the adenyl cyclase system: PTH, bicarbonate, or cAMP itself.[1] Thus, the site of action is again located beyond the stage of cAMP formation. PTH administration in humans had no inhibitory effect on either the subsequent increase in cAMP excretion or phosphaturia.[58] This not only casts doubt on the importance and transferability of animal responses to disease pictures in humans, but also weakens the theory that lithium is suitable for use in hyperparathyroidism, as it is in other states of endocrine hyperfunction involving the adenyl cyclase system (e.g., hyperthyroidism). The same investigators found that the usual rise of serum calcium following exogenous PTH did not occur in lithium-treated patients.[22] This could be attributed either to an inhibition of cAMP formation in the skeleton, which then offsets the absence of inhibition in the kidney, or to the fact that lithium is capable of exerting a PTH-independent effect on the calcium level in other biologic compartments.

Since the adenyl cyclase system plays a role at a variety of sites involved in blood pressure regulation, several researchers have been prompted to investigate the effects of lithium at these locations.

In view of the rise of cyclic AMP in the plasma following the administration of beta-adrenergic agents, Ebstein et al. investigated this rise following the injection of epinephrine: It was abolished following acute and chronic administration of lithium.[15] This observation is at odds with the very weak effects of lithium therapy on the peripheral cardiovascular system,[61] implying that the considerably higher intracellular cAMP concentrations may remain unaffected by the lithium-induced changes in the bloodstream, thereby ensuring the maintenance of the blood pressure. In any event, Fann et al. observed a 22% decline in the pressor response to norepinephrine infusion during lithium therapy.[16]

The fact that lithium increases the renal excretion of sodium raises the question of whether this also activates the renin-angiotensin system. However, Fleischer et al. found no significant increase in plasma renin activity in human subjects under these conditions.[18] There was a decrease in the pressor response to angiotensin, but only in a portion of the subjects and much less consistently than in experimental animals. A depletion of norepinephrine in the sympathetic postganglionic fibers or a lithium-induced depletion of sodium from the smooth-muscle cells has been suggested.

Finally, decreased cortisone levels were found when diurnal variations were tracked during lithium therapy.[24] The response of the adrenal cortex to exogenous ACTH was undiminished, however, suggesting that lithium does not directly inhibit cortisol secretion, but rather exerts its influence at the level of the hypothalamic-pituitary axis.

On the whole, despite alterations in many responses of the systems involved in blood pressure regulation, no grave side effects have been associated with lithium therapy. This may be attributable to processes resulting in a mutual cancellation of effects, adaptation to chronic dosing, or the reduction of system stresses associated with the sedating effects of lithium therapy.

## Cadmium

Unlike many trace elements considered essential to health, such as iodine, iron, zinc, copper, manganese, and cobalt,[43] cadmium has no known biological functions. However, the chronic administration of cad-

mium has adverse consequences, particularly in the kidney.

It has been shown in experimental rats that small doses of cadmium administered parenterally cause an elevation of the blood pressure.[46] The addition of cadmium to the animals' drinking water in concentrations of 1–5 ppm has similar effects.[54] In one study, the cadmium levels found in the kidneys of animals with cadmium-induced hypertension were comparable to those found in inhabitants of North America who had no apparent exposure to cadmium.[53] Other studies comparing the cadmium content of incinerated renal tissue showed higher levels in formerly hypertensive persons;[45] no marked differences in blood levels were found. Analyses of urinary cadmium excretion also showed no clear correlations with blood pressure, although some studies showed a tendency toward increased cadmium excretion in the urine.[45] The salutary effects of chelating agents with a preference for cadmium in the treatment of hypertension were too slight or short-lasting to permit reliable conclusions to be drawn.[45] Regarding the relation between parathyroid hormone and blood pressure or renin secretion, respectively (see above), the effects of cadmium on the parathyroid glands were of interest. In mice, cadmium treatment induced ultrastructural changes indicating increased functional activity.[74] However, data on parathyroid hormone levels and secretion are lacking.

No data are availble on the possible mechanism of the moderate hypertension caused by cadmium. However, epidemiologic studies from cadmium-polluted regions in Japan show that exposed segments of the population developed tubular proteinuria accompanied by a parallel increase in cadmium excretion (7.5 μg/liter vs. 2 μg/liter in a control population).[27] These renal function impairments also included tubular glucosuria and aminoaciduria in many cases.[42] This indicates that the disturbances may be sufficiently far-reaching in some circumstances to produce hypertension due to renal disease.

According to recent reports in West German newspapers, wild common table mushrooms have been found to contain high levels of cadmium, and the consumption of an additional 100 to 150 g of these mushrooms exceeds the tolerance limit for this element. Due attention should be given to possible blood pressure changes in individuals so exposed.

## Water Hardness

Various reports indicate an inverse correlation between cardiovascular mortality and the hardness of the drinking water; i.e., the softer the water, the higher the mortality rate.[55] It remains to be determined whether soft drinking water leads to increased mortality independent of the cardiovascular system.

In one study by the Social Medicine Unit of the Medical Research Council, comparative investigations were conducted in 12 cities in England and Wales, half of which had a soft water supply and half a hard water supply. The soft water regions exhibited higher numbers of cases of sudden death, suggesting an increased vascular risk. The notes of the attending physicians seemed to indicate an increased prevalence of hypertension, though the reliability of such notes is questionable. Relevant clinical differences with respect to body, weight, size, etc., were not apparent, while a tendency toward higher pulse rates and cholesterol levels was noted in the soft water population.[55] Complicating factors include the fact that smoking habits were found to vary among different cities, and that biochemical urine and serum analyses indicated various disparities, e.g., that men from hard water cities tended to have higher serum albumin and phosphate levels. Due to the multifactorial relationships involved, the connections between blood pressure and water hardness cannot be clarified on the basis of the data available. It is hoped that prospective studies in this area will shed additional light on the problem.

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# Kallikrein-Kinin and Prostaglandin Systems in Hypertension

13

J. M. Sullivan, J. C. McGiff

Initiation of some forms of hypertension, as well as the development of the accelerated phase of essential hypertension, reflects the operation of one or more hormonal pressor factors, such as overactivity of the renin-angiotensin system or mineralocorticoid excess. Of no less importance to the regulation of blood pressure is a failure of countervailing forces that normally act to lower blood pressure. The kallikrein-kinin system possesses the properties requisite to mediate this function, particularly when considered in terms of its interactions with prostaglandins.[1] Absence of the normal countervailing function may cause sustained hypertension without an increase in the activity of any pressor factor. Thus, if one assumes tonic activity of the opposing blood-pressure–regulating systems, a deficiency of the vasodepressor system may lead to hypertension without an increase in the basal activity of the blood-pressure–elevating system.

Within the kidney, and probably within extrarenal blood vessels as well, prostaglandins interact with the principal blood-pressure–regulating systems, the kallikrein-kinin and the adrenergic nervous-renin-angiotensin, reinforcing the former and buffering the latter.[2] Prostaglandins, thereby, contribute to the blood-pressure–lowering effects of kinins and nullify the blood-pressure–elevating effects of angiotensins. Decreased responsiveness of the renal kallikrein-kinin system has been shown in some forms of both human and experimental hypertension.[3,4] Moreover, kallikrein excretion is decreased in the children of hypertensive parents.[5] Can this observation signify the means whereby the prehypertensive subject can be identified? If so, the importance to all aspects of the disease, its pathogenesis, therapy (and prophylaxis), and epidemiology, seems great. As there is evidence linking the basal release of renal prostaglandins to the level of activity of the renal kallikrein-kinin system,[6] and as prostaglandins can be shown to oppose the actions of pressor hormones[7] and adrenergic nervous activity,[8] the following hypothesis is suggested: A deficiency in the renal kallikrein-kinin system may contribute to the development of hypertension by decreasing the production of one or more prostaglandins having antihypertensive activity. A direct effect of kinins as antihypertensive agents, one independent of a prostaglandin mechanism, must also be considered. The demonstration that inhibition of prostaglandin synthesis by nonsteroidal anti-inflammatory drugs can result in hypertension in animals[9] and humans[10] urges consideration of the contribution of vasodepressor systems to hypertensive disease in humans.

To understand the functional consequences, including blood pressure regulation, of the interactions of prostaglandins and kinins, it is necessary to consider the effects of kinins on prostaglandin synthesis and metabolism, and also to recognize the sphere of activity of these hormones.

1. Release of prostaglandins from tissues in response to kinins, as well as other stimuli, usually denotes increased prostaglandin synthesis within that tissue (Fig. 1). This results in the immediate entry of the newly synthesized prostaglandin into the extracellular compartment. Kinins increase prostaglandin synthesis primarily by enhancing delivery of substrate, arachidonic acid, to the prostaglandin-synthesizing complex.[11] This action of the kinin results from activation of a phos-

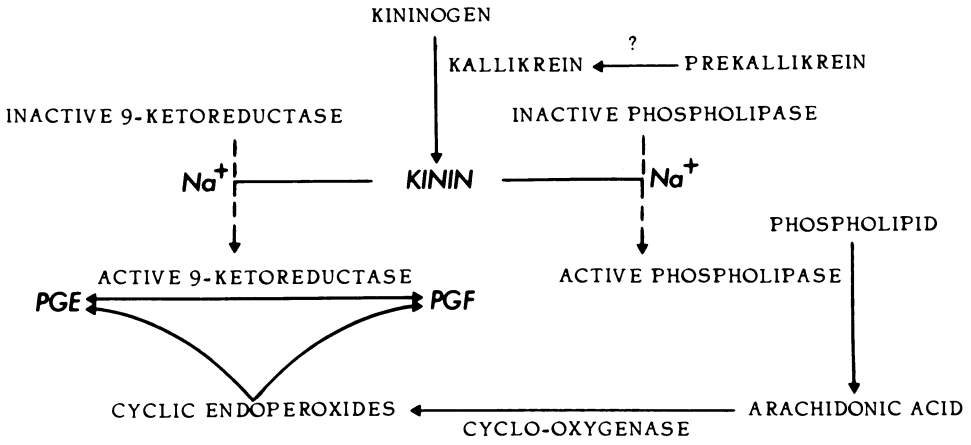


**Figure 1.** Kinin-prostaglandin interactions. Kinin increases prostaglandin synthesis by making more substrate available to the synthetase complex. Kinins also may regulate production of the major end product, a PGE or PGF, by activating the enzyme PGE-9-ketoreductase. These two steps, activation of phospholipase and 9-ketoreductase by kinins, are possibly sensitive to either sodium or other ions. Reprinted with permission of the Federation of American Societies for Experimental Biology; from Fed Proc 35:176, 1976

pholipase which liberates arachidonic acid from phospholipids.[12]

2. Kinins may also affect the activity of prostaglandin-metabolizing enzymes (Fig. 1). Kinins, through their ability to increase the activity of PGE-9-ketoreductase,[13] can determine the major products of enhanced prostaglandin synthesis. This action of the kinin, which may result from an antecedent effect of the kinin on guanyl cyclase,[14] favors the production of $PGF_{2\alpha}$ by converting $PGE_2$, arising from enchanced prostaglandin synthesis, to $PGF_{2\alpha}$. Thus, the dual effects of kinin on prostaglandin synthesis and PGE-9-ketoreductase in bovine mesenteric veins result in increased release of $PGF_{2\alpha}$.[15] The latter may mediate the venoconstrictor effect of the kinin. In addition, an effect of kinins on those enzymes responsible for the transformation of the prostacyclin endoperoxides to thromboxane, prostacyclin, or the primary prostaglandins cannot be excluded (Fig. 2).
3. Prostaglandins and kinins function primarily as tissue or local hormones; i.e., their activity is restricted to the tissue in which they are formed.[16]

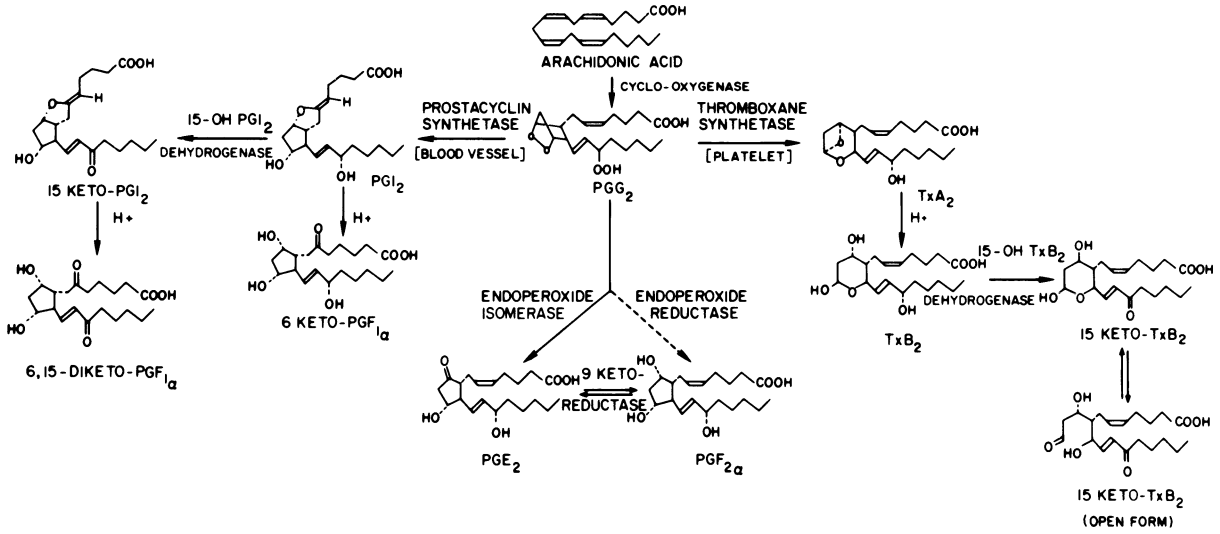


**Figure 2.** Metabolism of arachidonic acid by the prostaglandin synthetase complex. A major product of vascular tissues is prostacyclin ($PGI_2$), and a major product of blood platelets is thromboxane $A_2$ ($TxA_2$).

The functional effects of their interactions are primarily registered within an organ or tissue. Thus, altered vascular reactivity and changes in salt and water excretion occur as a result of prostaglandin-kinin interactions within the vascular wall and the renal distal tubule, respectively; their interactions contribute to the regulation of vascular tone and extracellular fluid volume and, thereby, the regulation of blood pressure.[1]

Interactions of prostaglandins and kinins can also be described in terms of the contribution of prostaglandins to the biological effects of kinins. The functional consequences of prostaglandin-kinin interactions may be considered in terms of three categories:

1. *Modulation.* Prostaglandins may amplify the action of kinins, e.g., vasodilation evoked by bradykinin in skeletal muscle.[17]
2. *Mediation.* The release of one or more prostaglandins by the kinin may be responsible for the effect of the kinin. This type of interaction has been suggested for the actions of kinins on the urinary-concentrating mechanism[18] and their venoconstrictor effect on bovine mesenteric veins.[15]
3. *Maintenance.* Continuous release of a prostaglandin may contribute to maintaining normal blood flow to the kidney[9,19] and gravid uterus.[20] This basal generation of prostaglandins within these tissues may depend upon the level of activity of the kallikrein-kinin system.

## Interaction of the Kallikrein-Kinin and Renin-Angiotensin Systems

Parallel increases in the activities of the kallikrein-kinin and renin-angiotensin systems have been demonstrated in several clinical studies.[21,22] Elevated plasma kinin levels may prevent the pressor effects of angiotensin II under these conditions and in other hyperreninemic states. The rise in plasma kinin and angiotensin II evoked by sodium depletion could be rapidly suppressed by infusion of saline.[21] Assumption of the upright posture, an effective stimulus to renin release, also results in elevated kinin levels in peripheral venous blood.[22] Indeed, a form of orthostatic hypotension may be caused by exaggerated release of kinins in response to standing.[22] It should be recalled that kinin levels in venous plasma probably indicate local generation of kinins resulting from activation of kallikrein.[21] In the resting state, the activity of plasma kallikrein is low. Therefore, under physiological conditions, when kinins are found in the venous blood of an organ, they arise primarily from that organ, as the lung destroys all but a small fraction of the kinins which enter the pulmonary circulation.[23] Further, those kinins which survive pulmonary passage, or which are generated by plasma kallikrein, are destroyed rapidly by plasma or tissue kininases.[24] Thus, 90% of bradykinin infused into the renal artery is destroyed on passage across the renal vascular bed.[25]

The absence of elevated blood pressure in patients with Bartter's syndrome, despite greatly increased activity of the renin-angiotensin and aldosterone systems, has been ascribed to enhanced activity of the kallikrein-kinin system,[26] as well as to increased release of renal prostaglandins.[27] The possible interactions within the kidney of these systems, the kallikrein-kinin and renin-angiotensin, may be appreciated on comparison of their components and activities (Fig. 3).[28]

Despite the fact that the kallikrein-kinin and renin-angiotensin systems have opposing effects on the arterial circulation and salt and water excretion (specifically, kinins dilate resistance blood vessels and promote salt and water excretion, while angiotensin II is a vasoconstrictor-antinatriuretic hormone), they have many similarities. The enzymes renin and kallikrein are formed and stored within the kidney, may be released by autonomic nervous signals, and when released act on plasma globulins to liberate decapeptides, angiotensin I, and lysyl-bradykinin, respectively. The activity of each decapeptide is affected by an enzyme that cleaves the terminal dipeptide, thereby generating octapeptides, either angiotensin II or the inactive metabolite of the kinin.[29] This enzyme may be considered, depending on the substrate, angiotensin-converting enzyme or kinin-catabolizing enzyme; the latter activity designates a kininase. Erdös has marshaled impressive evidence which supports the proposal that angiotensin-converting enzyme and kininase II are identical.[30]

In addition, angiotensins and kinins release prostaglandins from all tissues thus far examined (Fig. 3). Release denotes, as indicated previously, enhancement of prostaglandin synthesis, consequent to the effects of the polypeptides on the activity of one or more tissue acylhydrolases.[31] Either bradykinin or angiotensin II can evoke peak increases in prostaglandin levels in renal venous blood of ten- to fiftyfold above control values.[32,33] Increased levels of kinins in the blood of patients with Bartter's syndrome may contribute to the reduced vascular responsiveness to infused angiotensin II;[26] the latter was noted by Bartter et al. in their original report.[34]

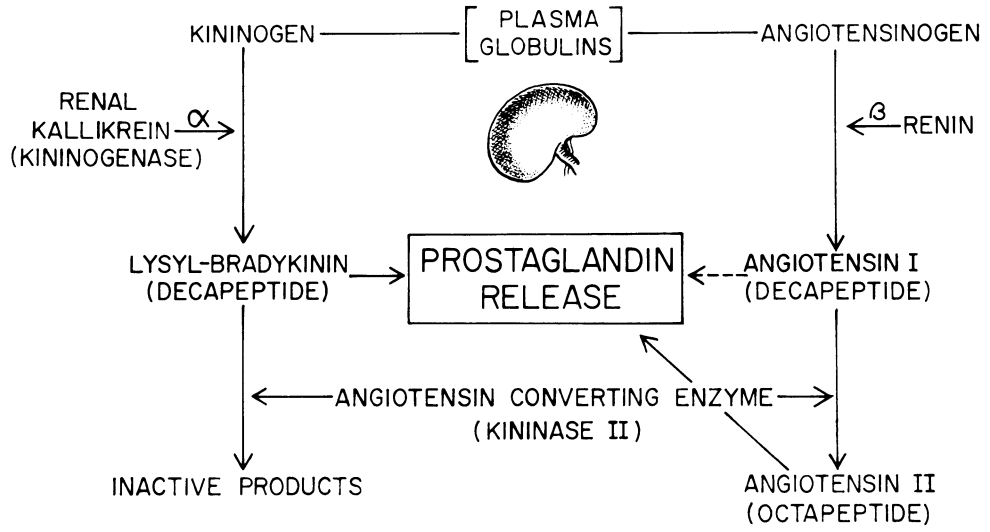


**Figure 3.** Comparison of the renal kallikrein-kinin and renin-angiotensin systems. The symbols $\alpha$ and $\beta$ above the arrows proceeding from kallikrein and renin, respectively, refer to adrenergic mechanisms which participate in the regulation of kallikrein ($\alpha$) and renin ($\beta$) release. The major products of each system are capable of releasing prostaglandins. Angiotensin-converting enzyme, which increases the activity of the renin-angiotensin system by conversion of angiotensin I to the more active form, angiotensin II, correspondingly reduces the activity of the kallikrein-kinin system by degrading lysylbradykinin to inactive products.

## Kallikrein Excretion in Hypertension

Excretion of kallikrein is decreased in human and experimental forms of hypertension. This association was first recognized by Elliot and Nuzum more than 40 years ago[35] and has been confirmed by Margolius et al.[36] The introduction of a radiochemical assay for urinay kallikrein in 1971 by Bevan, Pierce, and Pisano[37] has greatly facilitated studying excretion of urinary kallikrein. This method is based on the measurement of urinary alkaline esterase activity, as kallikrein has been demonstrated to be the principal alkaline esterase of urine. The application of this method to large and diverse populations of hypertensive subjects and their progeny has resulted in important findings on age- and race-dependent differences in excretion of kallikrein.[38,39]

Before reviewing these studies, it is important to recognize that changes in kallikrein excretion are assumed to be an index of changes in the activity of the kallikrein-kinin system intrarenally. This assumption, however, does not take into account the potential importance of kininases as regulators of the levels of kinins, i.e., by affecting the rate of degradation of kinins. Nor does it take into account alterations in the amounts of substrate, kininogen, made available to critical sites in the kidney which can affect salt and water excretion and vascular tone, i.e., the distal convoluted tubules, and the vascular or interstitial compartments. As renal kininase activity is ordinarily high,[25] small decreases in this activity should result in large increases in the levels of kinins within the kidney. In support of this hypothesis, Nasjletti et al. have shown that inhibition of kininase II by the nonapeptide $BPP_{9\alpha}$ resulted in increased renal blood flow and sodium excretion.[25,40] These changes reflect increased intrarenal generation of endogenous kinins and were associated with tenfold and twofold increased levels of kinins in urine and renal venous blood, respectively. One may conclude from this study that there need be no change in kallikrein excretion for major changes in effective intrarenal levels of kinins to occur. This consideration is important to answering questions raised by those studies which are based on changes in excretion of kallikrein in experimental and human forms of hypertension.

In order to resolve some of these questions, it is necessary to measure simultaneously changes in kallikrein and kinin excretion and renal venous kinin levels. Indeed, some of the apparent discrepancies can be resolved in terms of independent variations in kallikrein and kinin levels in the urinary and vascular compartments. Thus, in a recent study of Bartter's syndrome, it has been shown that urinary levels of kallikrein and kinins are affected differently by indomethacin treatment, and that kinins in blood and in urine varied in opposite directions after

indomethacin treatment.[41] Before indomethacin treatment, urinary excretion of kallikrein was high and that of kinin was low, whereas levels of kinin in venous blood obtained from the forearm were high. Indomethacin treatment reduced excretion of kallikrein and elevated that of kinin; the concentration of kinins in brachial venous blood decreased.

Subjects with essential hypertension usually excrete less kallikrein than normotensive subjects and demonstrate decreased responsiveness to stimuli which increase kallikrein excretion.[42] The lowest excretory rates are found in the hypertensive black, although the normotensive black shows decreased kallikrein excretion when compared to normal white subjects matched for age and sex.[38] These differences were not related to variations in salt or water intake,as urinary sodium and potassium excretion and volume are not different among the groups. Urinary kallikrein excretion correlated with renal blood flow in all groups except normotensive blacks on a low-sodium diet. However, when the activity of each system, the renin-angiotensin and the kallikrein-kinin, was considered in terms of their opposing actions on renal blood flow, then significant correlations were found for all groups, black and white, normotensive and hypertensive, irrespective of salt intake. Thus, renal blood flow (per square meter of body surface area) correlated with the log of urinary kallikrein/PRA for all subjects, on either low or unrestricted salt intake. This study supports the hypothesis that one or more renal mechanisms play a decisive role in initiating and in maintaining the hypertensive state.

Examination of the relationships between urinary kallikrein, plasma renin activity, and renal blood flow suggests that a vasodilator system, the kallikrein-kinin-prostaglandin, participates in the regulation of vascular resistance in the kidney, together with the renin-angiotensin system. Studies of nephrogenic forms of hypertension in the dog[43] and rat[44] led to similar conclusions and suggested that a major determinant of renal blood flow is the level of activity of the kallikrein-kinin system within the kidney. Decreased kallikrein excretion in the dog subjected to renal arterial stenosis did not correlate with changes in either urinary volume or excretion of sodium but rather with reduction in renal blood flow.[43] Mills and colleagues have presented evidence that kallikrein excretion and renal perfusion pressure are positively correlated in the dog.[45]

The signal which leads to kallikrein release is presumably related to changes in pressure within a segment of the vasculature of the kidney, as alterations in blood flow will ultimately affect renal perfusion pressure. This site is quite likely located beyond the afferent arteriole and the glomerulus, as both vasoconstrictor and vasodilator agents can release renal kallikrein.[45] More specifically, the signal is probably a change in transmural pressure, as blunting of kallikrein release has been reported after renal compliance was reduced by wrapping the kidney with latex.[45] These studies affirm the complementary nature of the renin-angiotensin and kallikrein-kinin systems; viz., changes in renal perfusion pressure have opposite effects on release of kallikrein and renin from the kidney.

A recent study of hypertensive patients with unilateral renal arterial stenosis provided additional evidence for depressed activity of the kallikrein-kinin system in the ischemic kidney, and an inverse relationship intrarenally between the activities of the renin-angiotensin and kallikrein-kinin systems.[46] In this study, plasma renin activity was elevated and kinin levels were depressed in the venous effluent of the diseased kidney, whereas the reverse was obtained for the contralateral kidney.

A recent study of kallikrein excretion in hypertension has made important contributions to our understanding of the pathogenesis and inheritance of hypertension.[5] Decreased urinary concentration of kallikrein was shown in black children as well as in black adults. As blood pressures in these children were within normal limits, a relationship was sought between urinary kallikrein and the level of blood pressure within these families. Families having the highest and lowest 10% of mean log urinary kallikrein concentration were selected, and mean family blood pressures were compared. Both diastolic and systolic blood pressures in the families with the lowest urinary kallikrein concentrations were significantly higher than in those families showing the highest urinary kallikrein concentrations. Further, this relationship held when the selection was based on blood pressure; the families with the highest 10% of diastolic blood pressures had lower mean urinary kallikrein concentrations than the families with the lowest 10% of diastolic blood pressures. These findings applied to both white and black families and were repeated 3 years later in the same population.[39]

In the later study, rates of kallikrein excretion, rather than concentrations, were measured; this did not modify the earlier conclusion based on urinary kallikrein concentration. A high correlation was noted between urinary concentrations of kallikrein and potassium, although single regression analysis failed to disclose a relationship between urinary concentrations of kallikrein and sodium. An inverse relationship between urinary concentration of kallikrein and sodium could be shown only after removal of the effects of other variables by multiple

regression analyses. The full significance of these studies must await definition of the contributions of the kallikrein-kinin system to blood pressure regulation and the validation of the reliability of urinary kallikrein excretion as an index of the intrarenal activity of the kallikrein-kinin system. Overall, these studies support the hypothesis that a deficiency of the kallikrein-kinin system contributes to the development of high blood pressure in a susceptible population.

The major exception to the conclusion that hypertension is usually associated with deficient kallikrein excretion is the secondary hypertension of increased secretion of mineralocorticoids;[3] aldosteronism is associated with increased excretion of kallikrein. The finding that kallikrein excretion is also elevated in normotensive subjects by enhanced mineralocorticoid activity induced either by administration of sodium-retaining steroids or by sodium restriction[3] suggests that mineralocorticoids participate in the regulation of kallikrein excretion. Further, the demonstration that elevated kallikrein excretion induced by a low-sodium diet can be decreased by the aldosterone antagonist, spironolactone, led to the proposal that the effective concentration of mineralocorticoids determines the rate of kallikrein excretion.[3]

An alternative explanation is that one or more functional consequences of elevated mineralocorticoid activity, such as increased potassium excretion, may play a decisive role in increasing renal kallikrein-kinin activity. In support of this proposal, it should be recalled that urinary kallikrein concentration has been positively correlated with potassium excretion[5] but not with sodium excretion. These relationships point to another possible interaction of the kallikrein-kinin and prostaglandin systems, in this instance operating through potassium. Decreased potassium concentration in one or more body compartments, associated with increased potassium excretion, may result in enhanced renal prostaglandin synthesis; the latter is postulated to augment the activity of the kallikrein-kinin system within the kidney. There is evidence that changes in extracellular potassium concentration can affect renal prostaglandin synthesis.[47,48] Changes in prostaglandin synthesis induced by altered concentrations of potassium may then affect kallikrein release and/or kinin generation, perhaps by operating through a kallikrein-releasing mechanism similar to that prostaglandin mechanism which regulates renin release.[28] It is important to note once again that the kinin levels intrarenally are of paramount consideration, not kallikrein excretion as such. Vinci et al. have shown that over a wide range of excretion of kallikrein, urinary kinin levels were not affected.[49] They also demonstrated that urinary excretion of kinins was independent of the level of mineralocorticoids in normal subjects.

The relationship between sodium excretion and the activity of the renal kallikrein-kinin system is uncertain. In most of the studies which addressed the effects of altered activity of the renal kallikrein-kinin system on salt and water excretion, changes in kinin levels were not measured; rather, changes in kallikrein excretion were measured. An exception is the study of Marin-Grez et al., who measured simultaneously changes in urinary kallikrein excretion and kinin levels in caval blood in response to acute expansion of extracellular fluid volume induced by oral administration of saline in the dog.[50] They demonstrated a positive correlation between changes in blood levels of kinins of renal origin and changes in sodium excretion induced by saline administration. In the anesthetized rat, antibodies to bradykinin have been shown by Marin-Grez to attenuate the enhanced excretion of sodium chloride in response to acute isotonic saline loading.[51] In addition, there are several studies which suggest that the renal kallikrein-kinin system, perhaps in concert with renal prostaglandins, does participate in regulating sodium chloride excretion:

1. Nasjletti et al. have demonstrated a close relationship between the transient decrease of urinary sodium in the conscious rat produced by the kallikrein inhibitor, aprotinin, and the immediate reduction in PGE excretion.[6]
2. In the anesthetized dog, enhancement of the activity of the renal kallikrein-kinin system induced by inhibition of the major degradative enzyme, kininase II, was associated with natriuresis.[25]

As changes in kinin generation have profound effects on prostaglandin levels within the kidney,[52] and as prostaglandins may contribute to or mediate some of the effects of kinins on salt and water excretion,[18] prostaglandins should be measured simultaneously with the components of the kallikrein-kinin system in order to assess the effects of changes in the latter on salt and water excretion. In view of the widespread distribution of prostaglandin-synthesizing enzymes among various cellular elements of the kidney,[53] it is important to recognize that compartmentalization of kinin and prostaglandin metabolism may have important consequences for renal function (Fig. 4). Thus, the functional consequences of interactions of the renal kallikrein-kinin and prostaglandin systems may be restricted primarily

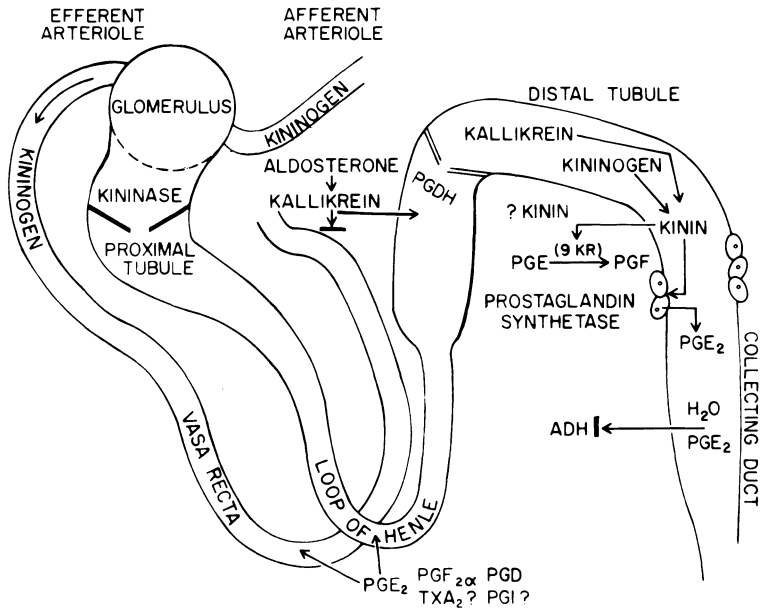


**Figure 4.** Prostaglandin-kinin interaction in the nephron. The generation of kinins in the distal nephron and collecting ducts results in the release of prostaglandins which inhibit the effect of ADH and thereby participate in the excretion of solute-free water: prostaglandin 15-OH-dehydrogenase (PGDH) and PGE-9-ketoreductase (9KR).

to the urinary compartment. Entry of kallikrein into the distal tubules[54] and subsequent formation of kinin, then, may result in kinin-mediated generation of prostaglandins in the distal nephron and collecting ducts; the latter affects the excretion of solute-free water.[18]

A recent study by Weber et al. indicates that a major prostaglandin-metabolizing enzyme, PGE-9-ketoreductase, which converts $PGE_2$ to $PGF_{2\alpha}$, is influenced by the state of sodium chloride balance.[55] Thus, excretion of a water load and conservation of sodium are facilitated by increased activity of this enzyme, which has the effect of lowering levels of $PGE_2$ intrarenally by favoring formation of $PGF_{2\alpha}$. As prostaglandins of the E series inhibit ADH activity,[56] their removal (by conversion to PGF) facilitates reabsorption of water. It should be recalled that kinins are capable of influencing the activity of PGE-9-ketoreductase.[13] Further, this interaction may be crucial to the effects of kinins on free-water generation. When prostaglandins are relased through the actions of kinins, free water is generated if $PGE_2$ is the principal product, whereas when $PGF_{2\alpha}$ is released in response to kinin, water conservation occurs. The activity of PGE-9-ketoreductase, as determined by its susceptibility to activation by kinins, may be a function of the state of sodium chloride balance. It is here that a hypertensive mechanism may be invoked; viz., deficient generation of kinins or prostaglandins intrarenally in response to salt intake may result in inappropriate expansion of extracellular fluid volume, a recognized factor in the pathogenesis of hypertension.[57]

Because of the importance of renal prostaglandins to the actions of kinins, as well as their major effects on renal function independent of an interaction with kinins, renal prostaglandin will now be considered separately. As one or more renal mechanisms are considered to be pivotal in the regulation of blood pressure,[58] it is important to consider possible relationships between renal prostaglandins and the antihypertensive function of the kidney.

## Prostaglandins and the Kidney

There are a number of ways by which the kidney can participate in the regulation of blood pressure; dysfunction of one or more of these might lead to elevated blood pressure. First, the kidney plays a pivotal role in the regulation of extracellular fluid volume. Guyton et al. have postulated that renal inability to excrete fluid appropriately leads to overfilling of the vascular tree, an elevated cardiac output, tissue autoregulation, increased vascular resistance, and finally hypertension.[57] In addition to its role in the excretion of fluid, the kidney is also involved in the regulation of electrolyte balance. Retention of sodium leads to enhanced vascular responsiveness to pressor stimuli such as angiotensin II.[59] Potassium depletion is believed to result in impaired dilatation, which might participate in a chain of events leading to hypertension.[60] The kidney also releases pressor substances which can affect vascular resistance. Angiotensin I may function as a vasocon-

stricting agent within the kidney;[61] it is converted to the potent pressor agent angiotensin II primarily during passage across the pulmonary vascular bed.[16] The kidney may also secrete antihypertensive substances, such as vasodepressor neutral lipids[62] and prostaglandins.[7]

As prostaglandins have been found to be involved in the regulation of renal function, evidence linking prostaglandin synthesis and degradation to the regulation of blood pressure and to hypertension has been avidly sought. Prostaglandins have been shown to play an important role in the regulation of renal blood flow, particularly when renal function is challenged.[19] Prostaglandins also have the ability to modulate the effects of angiotensin. In 1970, McGiff et al. showed that antidiuresis and renal vasoconstriction evoked by angiotensin II were diminished owing to intrarenal release of $PGE_2$.[33] Later, Aiken and Vane showed that indomethacin administration, which inhibits prostaglandin synthesis through inhibition of the enzyme cyclooxygenase, resulted in enhanced vasconstrictor effects of angiotensin II in the kidney but not in the hind limb.[63] $PGE_2$, the principal product of prostaglandin synthesis in the kidney,[64] has been found not only to attenuate the effect of angiotensin but also to modulate the activity of the adrenergic nervous system, diminishing norepinephrine release.[65] Further, as noted previously, $PGE_2$ can attenuate the action of ADH.[56]

Experiments using inhibitors of the prostaglandin cyclooxygenase reaction result in a preparation in which all the products formed downstream from this step are reduced (Fig. 2). Thus, not only is production of the vasodilator and natriuretic agent $PGE_2$ diminished, but also that of the vasoconstrictor $PGF_{2\alpha}$. Additionally, synthesis of $PGI_2$ and thromboxane $A_2$, which have opposing effects on platelet aggregation and vascular tone, is also inhibited.[66] Experiments using either indomethacin, meclofenamate, aspirin, or ibuprofen all result in diminished production of the products of arachidonic acid metabolism, which have markedly different physiological effects. It is not surprising, therefore, that the effects of cyclooxygenase inhibitors on the renal circulation vary widely with experimental conditions.

Terragno et al. have shown that indomethacin does not affect renal blood flow in either the anesthetized or conscious dog.[19] However, when the anesthetized dog is acutely stressed by laparotomy, a large increase in renal prostaglandin release occurs. Under these conditions, administration of indomethacin results in greatly increased renal vascular resistance and a fall in renal venous prostaglandin levels to those observed in the conscious dog. There remains a basal efflux of renal prostaglandins which cannot be suppressed by indomethacin, even in toxic doses. The significance of this component has not been determined. Any stress—hemorrhage or laparotomy, for example—will increase prostaglandin release severalfold. This increase is associated with maintenance of renal blood flow at normal levels. When indomethacin is administered under these conditions, a precipitous decrease in renal blood flow results.

The prostaglandins are involved not only in the regulation of renal blood flow during stress but also in the intrarenal distribution of blood flow,[67] herein providing an example of their generally accepted role as local hormones. In studies using the isolated dog kidney, Itskovitz et al. studied the effect of endogenous $PGE_2$ on the distribution of renal blood flow.[67] They found that blood levels of $PGE_2$ correlated with increased fractional distribution of blood flow to the inner cortex, while administration of indomethacin was followed by a disproportionate reduction of blood flow to the inner cortex, thus resulting in a redistribution of renal blood flow. As the efferent arterioles of the inner cortex extend into the medulla, giving rise to the vasa recta, the inner cortical and medullary circulations are continuous. Thus, changes in blood flow to the inner cortex can reflect primary alterations in medullary blood flow. Further, as the major site of prostaglandin synthesis is the inner medulla and papilla,[68] changes in prostaglandin synthesis will directly influence medullary blood flow and, secondarily, blood flow to the inner cortex.

A possible clinical correlation of these findings is the nephropathy of analgesic abuse. This condition has been suggested to be due to medullary ischemia secondary to reduced synthesis of one or more vasodilator prostaglandins, as $PGE_2$ or $PGI_2$.[69] However, the capacity to synthesize prostaglandins is shared by a number of structures in all zones of the kidney. Thus, Larsson and Änggard have demonstrated synthesis of prostaglandins in the renal cortex.[68] Cyclooxygenase is present in at least three different tissues in the kidney. First, the interstitial cells of the renal medulla were found to have the ability to synthesize prostaglandins.[62] Cyclooxygenase was also identified within the vascular structures of the kidney.[70] Additionally, cyclooxygenase was localized in the cells lining the distal nephron and collecting ducts;[53] this location accords with the known interrelationships between prostaglandins and ADH. It has been found that ADH causes a greater concentration of urinary solute if given after treatment with indomethacin.[71] Thus, a prostaglandin of the E series blunts the effects of ADH[56] and favors the excretion of free water.[71]

There are complex interrelationships of the prostaglandin and the renin-angiotensin-aldosterone

systems. In 1970, it was reported that infusion of angiotensin II results in the release of renal prostaglandins.[33] Several years later, it was noted that administration of arachidonic acid, the precursor of renal prostaglandins, enhanced renin release.[72] Indomethacin decreased plasma renin activity and prevented the aforementioned effects of arachidonic acid. Indomethacin also prevented prostaglandin release in response to infusion of angiotensin. Thus, a prostaglandin mechanism appears to participate in the regulation of renin release; generation of angiotensins following release of renin can in turn stimulate prostaglandin synthesis.

Frölich and his co-workers have studied the possible participation of a prostaglandin mechanism in the regulation of plasma renin activity in humans.[73] They found that indomethacin administration is followed by diminished plasma renin activity, plasma aldosterone concentration, and urinary sodium and prostaglandin excretion in both normal and hypertensive subjects. As angiotensin infusion continues to stimulate aldosterone secretion after the administration of indomethacin, the effect of indomethacin on aldosterone secretion is due presumably to diminished generation of angiotensin. They have also noted that indomethacin prevents the immediate increase in plasma renin activity which ordinarily follows administration of furosemide. Indomethacin has two effects which might explain these observations. First, it interferes with the synthesis of prostaglandins and other products of arachidonic acid metabolism. Second, indomethacin causes sodium and fluid retention. Thus, the relative contribution of inhibition of prostaglandin synthesis and of sodium retention to the fall in plasma renin activity that ordinarily follows indomethacin administration is not evident.

Frölich et al. have found that in patients on a 10-mEq sodium diet, indomethacin had no effect on the elevated plasma renin activity, despite evidence that it did inhibit prostaglandin synthesis under these conditions as indicated by excretion of a major metabolite of PGE.[74] However, in these patients, propranolol lowered plasma renin activity, suggesting that, under conditions of sodium deprivation, activation of the sympathetic nervous system plays an important role in renin release. When patients were studied on a 150-mEq sodium diet, indomethacin administration was again followed by a fall in excretion of prostaglandins, but under these circumstances urinary sodium excretion and basal plasma renin activity also fell, emphasizing the importance of a prostaglandin mechanism in the mediation of renin release under usual conditions of sodium balance. However, other investigators have observed a fall in plasma renin activity after subjects on a 10-mEq sodium diet received indomethacin.[75] Thus, the relative importance of the sympathetic nervous system and a prostaglandin mechanism in regulating renin release during sodium deprivation requires clarification.

Weber and his co-workers have made important contributions to our understanding of these interrelationships.[76] They demonstrated in renal slices that $PGE_2$, the principal product of renal prostaglandin synthesis, did not affect renin release directly. However, a metabolic intermediate in the production of $PGE_2$, the endoperoxide $PGG_2$, was shown to increase renin release from renal slices. The effects of prostacyclin and thromboxane have not been studied. These data suggest that inhibition of $PGE_2$ synthesis does not affect renin release directly; rather, the suppression of prostaglandin endoperoxide synthesis, or one of its breakdown products, may be the determining factor.

Weber and his colleagues have also studied the mechanism of furosemide-induced renin release in humans.[77] They have found that furosemide administration is followed by elevations in plasma levels of arachidonic acid and renin activity, and in urinary excretion of $PGF_{2\alpha}$ and sodium. Studies of the time course of the rise of these factors have demonstrated that arachidonic acid and plasma renin activity rise simultaneously; however, the latter gradually falls while arachidonic acid remains elevated. The administration of indomethacin prevented the rise in plasma renin activity and arachidonic acid and urinary prostaglandin excretion, while sodium excretion was unaltered. The authors conclude that release of arachidonic acid was the primary mechanism of furosemide-induced prostaglandin biosynthesis and, thereby, renin release.

The relationship between prostaglandin synthesis and plasma renin activity has important implications in the treatment of patients with Bartter's syndrome.[34] This syndrome of renal juxtaglomerular hyperplasia is characterized by elevation of plasma renin activity, plasma angiotensin II concentration, and aldosterone secretory rate; hypokalemic alkalosis; normal blood pressure; and resistance to the pressor effects of angiotensin II and norepinephrine. The renal tubular reabsorption of sodium or chloride may be abnormal in these patients, resulting in a greater than normal amount of filtered sodium being delivered to the distal nephron where it is exchanged for potassium or excreted in the urine. The unusual combination of elevated plasma angiotensin II and aldosterone levels and a normal blood pressure suggested that the disorder might be accompanied by synthesis of abnormally large amounts of a vasodepressor substance. Subsequently, Gill and his co-workers have demonstrated that patients

with Bartter's syndrome excrete large amounts of $PGE_2$,[27] Halushka and his co-workers have found increased urinary kallikrein excretion.[26] As indomethacin prevents the synthesis of all the products of the cyclooxygenase reaction, including $PGE_2$, this agent was used to treat patients with Bartter's syndrome[78] and was found to be remarkably effective in reversing the characteristic pathophysiologic disorders of this syndrome. In these patients, the administration of indomethacin resulted in partial correction of the elevated plasma renin, angiotensin, and aldosterone levels; the renal loss of salt and water was reduced, and the pressor responsiveness to angiotensin and norepinephrine was restored.[26,27]

It is attractive to attribute all these effects to the inhibition of one or more products of the cyclooxygenase reaction. However, as noted previously, indomethacin and all other aspirin-like drugs have a variety of actions which might account for some of these effects. These compounds alter the activity of the kallikrein-kinin systems,[79] inhibit phosphodiesterase,[80] and inhibit reacylation of lysophospholipids.[81] Thus, indomethacin might correct the hyperreninemia characteristic of Bartter's syndrome either by preventing the production of cyclic endoperoxides, thus reducing the stimulus to renin release, or by preventing the reacylation of lysophospholipids, compounds formed when arachidonic acid is released from phospholipids. As lysophospholipids inhibit renin,[82] there is a possibility that their accumulation might result in diminished renin activity when indomethacin is given.

Just as it is important to keep in mind that indomethacin might have a variety of effects which lead to the correction of the abnormalities of Bartter's syndrome, the multiplicity of effects of indomethacin and other nonsteroidal anti-inflammatory agents on arachidonic acid metabolism in the kidney must also be recognized. The first step in prostaglandin synthesis is the release of arachidonic acid by the action of an acylhydrolase as phospholipase $A_2$ (Fig. 2). The second is the cyclooxygenase step which leads to production of the cyclic endoperoxides. It is this step that is inhibited by indomethacin and similar compounds.

Downstream from generation of endoperoxides is the formation of a number of vasoactive products in different cellular elements within the kidney. Within the vascular wall, stimulation of cyclooxygenase results primarily in the production of $PGI_2$, a compound which prevents aggregation of platelets and which causes vasodilatation.[70] Within the interstitial cells of the renal medulla, stimulation of the cyclooxygenase step results primarily in the production of $PGE_2$.[48] Within the collecting tubules, prostaglandin synthesis becomes intimately involved with the kallikrein-kinin system and with antidiuretic hormone. The major product of prostaglandin synthesis at this site is unknown. Further, there are products of the prostaglandin endoperoxides which require special conditions for their synthesis. Thus, thromboxane $A_2$, a potent vasoconstrictor, is synthesized in negligible quantities by the normal kidney. However, renal injury, as that induced by ureteral ligation, results in the synthesis of large amounts of thromboxane within the kidney,[83] which may contribute to the increase in renovascular resistance which occurs in response to ureteral obstructions.[84]

## Prostaglandins and Blood Vessels

The mechanisms by which prostaglandins influence peripheral vascular resistance can be subdivided into three general categories. The first is the direct vasodilatory or vasoconstricting effects of locally synthesized prostaglandins, e.g., $PGE_2$, $PGI_2$, and $PGF_{2\alpha}$ (Fig. 5). The first direct demonstration of the prostaglandin biosynthetic capacity of vascular tissues was made by Terragno et al.[15] The second mechanism is modulation by locally synthesized prostaglandins of the effect of circulating or locally synthesized vasoactive compounds. For example, locally synthesized $PGE_2$ interferes with adrenergic transmission primarily by impairing release of norepinephrine from nerve terminals.[8] The third mechanism involves the indirect effects of prostaglandin synthesized elsewhere; e.g., synthesis of $PGE_2$ is important in maintaining renal blood flow, particularly to the inner cortex and medulla, in the face of noxious stimuli.[19] Prostaglandins also play a role in salt and water excretion; the latter is partially accomplished by interfering with the action of ADH on the collecting tubules.[56] Prostaglandins synthesized in the kidney, therefore, can influence total body sodium and water, thus influencing plasma and intracellular fluid volume and sodium balance and, thereby, the reactivity of vascular smooth muscle to pressor agents.

An additional mechanism has been postulated but not confirmed. All prostaglandins known to be released into the circulation are destroyed on passage through the lung. Thus, evidence is lacking that the prostaglandins play a role other than as locally active hormones. An exception to this is $PGA_2$ which, when infused intravenously, is not destroyed on passage through the pulmonary circulation[85] and effects vasodilatation, natriuresis, and diuresis and has an antihypertensive effect.[86] Early studies suggested that $PGA_2$ was released from the kidney in response

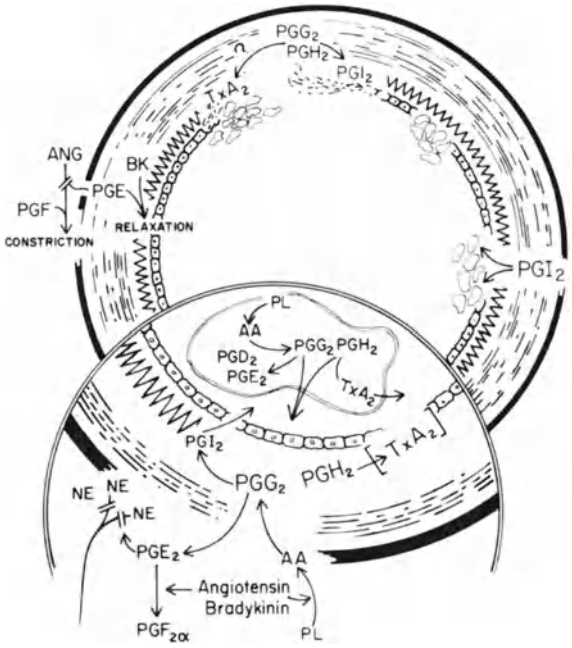


**Figure 5.** Cross section of the vascular wall showing possible interactions of prostaglandins and vasoactive hormones. Magnification of the vascular wall, interfaced with blood and a circulating platelet, is shown at the lower portion of the figure. At the endothelial surface and the subendothelial zone of vascular tissues, the major product of arachidonic acid (AA) metabolism arising from tissue stores of phospholipids (PL) is prostacyclin ($PGI_2$). A major product of arachidonic acid metabolism within the aggregating platelet is thromboxane $A_2$ ($TxA_2$). Formation of $TxA_2$ within the vasculature may occur only under pathologic conditions. Angiotensin and bradykinin, which activate acylhydrolases within the vascular wall, promote prostaglandin synthesis. In addition to $PGI_2$, $PGE_2$ is a major product of arachidonic acid metabolism in the vascular wall. Its main function may be to modulate release of the adrenergic neurotransmitter, norepinephrine (NE). Further, $PGE_2$ may be converted by $PGF_{2\alpha}$ on activation of the enzyme PGE-9-ketoreductase by either angiotension or bradykinin. Outside the area of magnification additional interactions of prostaglandins are shown. On the right, the formation of $PGI_2$ repels aggregating platelets. At the top, the failure of formation of $PGI_2$ in an area of damaged endothelium results in platelet aggregation which may be related to the evolution of atherosclerosis. On injury of vascular tissues, formation of $PGI_2$ may be compromised and thromboxane $A_2$ formation, both by platelets and vascular tissue, may predominate (top). On the left, possible interactions of angiotensin (ANG) and bradykinin (BK) with prostaglandins are indicated: $PGE_2$ may contribute to the vasodilator effects of bradykinin (relaxation). In contrast, $PGE_2$ usually antagonizes the vasoconstrictor effect of angiotensin, whereas $PGF_{2\alpha}$ may facilitate this action of angiotensin.

to sodium deprivation, thus functioning as a systemic hormone.[87] More recent studies which were based on highly sensitive and specific mass spectrometric methods for the measurement of $PGA_2$ failed to provide evidence for its presence in circulating blood.[88,89] $PGA_2$ is presumably an artifact resulting from spontaneous breakdown of $PGE_2$ during extraction and purification of plasma.

In 1969, Piper and Vane reported that one or more substances released from guinea pig lung during anaphylaxis contracted the rabbit aorta.[90] Later, it was found that indomethacin blocked the formation of this rabbit-aorta–contracting material (RCS), suggesting that it might be related to a precursor of prostaglandins. The eventual discovery of the endoperoxides and their isolation in pure form enabled them to be distinguished from RCS by their longer half-life in aqueous solution. In an exciting series of experiments involving the synthesis of prostaglandins in blood platelets, Hamberg and Samuelsson found that endoperoxides within platelets are converted into a hemiacetal derivative with an oxane structure, and malondialdehyde and a C17-hydroxy acid.[91] The first compound, now designated thromboxane $B_2$, is the breakdown product of thromboxane $A_2$, an unstable intermediate (Fig. 2). Thromboxane $A_2$ is formed when platelets aggregate, and in other tissues subjected to injury, contributes to platelet aggregation and produces vasoconstriction.[92] RCS was shown to be a mixture consisting primarily of thromboxane $A_2$; only a small amount of the activity of RCS was due to endoperoxides.

Recently, Bunting et al. have demonstrated another unstable product of the transformation of the endoperoxides.[66] The structure of this substance, initially called prostaglandin X, has now been elucidated, and the compound has been renamed prostacyclin and designated $PGI_2$. This compound, which is produced by blood vessels, has two important biologic effects: vasodilatation and inhibition of platelet aggregation (Fig. 5).

Moncada, Higgs, and Vane have demonstrated that vascular rings from human colic or gastric blood vessels will synthesize prostacyclin, the veins producing more than the arteries.[93] This effect occurs spontaneously but disappears with time or with washing of the specimens. Incubation of washed vascular tissue with arachidonate then restores production of prostacyclin. This production can be blocked in two ways: first, by the addition of indomethacin which, by inhibiting cyclooxygenase, prevents the conversion of arachidonic acid into endoperoxides, and second, by the addition of 15-hydroxyperoxyarachidonic acid, which blocks the conversion of en-

doperoxides to prostacyclin by inhibiting the prostacyclin synthetase step.

The addition of prostacyclin-synthesizing vascular rings to platelet-rich plasma inhibits platelet aggregation. It is possible that endothelial production of prostacyclin is the mechanism by which the body prevents thrombus formation throughout the healthy vascular tree. Vascular tissue, injured either by trauma or by atherosclerosis, might not be able to synthesize prostacyclin adequately, thus allowing the deposition of platelets, formation of thrombi, and perhaps initiation or acceleration of atherosclerosis (Fig. 5). It can also be postulated that failure to synthesize $PGI_2$ might result in elevated vascular resistance.

As noted previously, local synthesis of $PGE_2$ in the vessel wall can interfere with adrenergic transmission, primarily by inhibiting the release of norepinephrine from nerve terminals.[8] This would result in vasodilatation, or at least diminished vasoconstriction, thus playing a potentially important role in local or systemic regulation of blood flow and pressure. In addition, local synthesis of $PGE_2$ in vascular walls antagonizes the effect of angiotensin II and may play a role in angiotensin tachyphylaxis. Aiken used femoral and celiac arterial strips to study the effects of angiotensin II.[94] Repeated doses (every 30 min) continued to contract the femoral strips but had progressively less effect on the celiac artery strips. When inhibitors of cyclooxygenase were given, tachyphylaxis did not develop in the celiac strips. The addition of $PGE_2$ had no effect on the contraction of femoral arterial strips evoked by angiotensin II but reduced its effect on the celiac arterial strips. These experiments suggested that angiotensin II can stimulate and release prostaglandins in the vascular wall, thus blunting the vasoconstrictor effect of angiotensin II, at least in the mesenteric vascular bed. As $PGI_2$ was unknown at this time, its role in these events is not clear.

One of the most provocative experiments regarding the systemic hemodynamic effects of prostaglandin synthesis was published in 1974 by Wennmalm.[10] Six normal subjects underwent arterial cannulation and right-heart catheterization. Blood pressure and cardiac output were measured before and after intravenous administration of 25 mg of indomethacin. Diastolic blood pressure rose by 16% and systemic vascular resistance rose by 49%. None of the individuals had side effects. Similar findings have been made in the conscious rabbit.[9] In view of current knowledge, several explanations are possible. Intravenous indomethacin might have prevented the formation of vascular $PGE_2$ or $PGI_2$, thereby allowing vasoconstriction to take place unimpeded by the modulating influence of the prostaglandins, or the inhibiting effects of $PGE_2$ on norepinephrine release might have been removed, allowing adrenergically induced vasoconstriction to take place. This study suggests an important role for the prostaglandin system in the regulation of blood pressure in humans.

## The Blood Platelets and Prostaglandins

As knowledge of the pathways of prostaglandin metabolism has evolved, it has become apparent that compounds having different actions are synthesized from the same precursors in blood vessels and in blood platelets; these products of the endoperoxides, thromboxane $A_2$ of platelets and prostacyclin of vascular tissues, play counterbalancing roles. In the blood vessel wall, conversion of the cyclic endoperoxides into prostacyclin results in the formation of a product which prevents platelet aggregation and promotes vasodilatation.[93] On the other hand, in the aggregating platelet the endoperoxides $PGG_2$ and $PGH_2$ are converted largely to thromboxane $A_2$ (Fig. 2), a potent vasoconstrictor whose formation is associated with platelet aggregation. This compound, thromboxane $A_2$, has a half-life in aqueous solution of only 30 sec and is a vasoconstrictor. Ellis and colleagues have postulated that thromboxane $A_2$ causes coronary spasm when released locally.[95] Like the endoperoxides, thromboxane $A_2$ also stimulates platelet aggregation. However, work by Needleman and his associates, using imidazole, an inhibotor of the microsomal enzyme thromboxane synthetase, suggests that the endoperoxides themselves can cause platelet aggregation without being converted to thromboxane $A_2$.[96]

Both aspirin and indomethacin inhibit cyclooxygenase activity, thus preventing the conversion of arachidonic acid to endoperoxides and thereby their breakdown products, thromboxane $A_2$, $PGI_2$, and $PGE_2$. An experiment of nature has confirmed the importance of this pathway and has provided the first definite evidence for a biologic role of the prostaglandins. Malmsten and his co-workers have reported a patient with a bleeding disorder due to congenital deficiency of platelet cyclooxygenase.[97] The platelets from this subject contained normal stores of ADP but showed impaired aggregation in response to collagen, epinephrine, or arachidonic acid; yet the platelets aggregated in response to $PGG_2$. Studies with radiolabeled arachidonic acid proved that the patient's platelets failed to form endoperoxides.

## Prostaglandins, Kinins, and the Control of Blood Pressure

At this point, we are now able to review the physiology of the regulation of the circulation and identify control points at which disorders of prostaglandin or kinin metabolism might contribute to alterations in blood pressure. According to the hemodynamic expression of Ohm's law, mean arterial blood pressure equals the product of peripheral vascular resistance times cardiac output. Patients with uncomplicated, established essential hypertension ordinarily have a normal cardiac output and an elevated peripheral vascular resistance. Peripheral vascular resistance is controlled by factors intrinsic and extrinsic to the vascular wall. The interplay of these factors offers multiple sites for interactions with prostaglandins or kinins which might result in a disturbance of blood pressure regulation (Fig. 6).

Peripheral vascular resistance is profoundly influenced by blood-borne substances; for example, intense vasoconstriction can be effected by circulating angiotensin II or catecholamines. As prostaglandins function primarily as local hormones, they oppose the actions of circulating hormones by virtue of their synthesis on demand at the site of action of the circulating hormone in vascular smooth muscle (Fig. 5).

Another mechanism which affects peripheral vascular resistance is local release of norepinephrine from terminals. This results in vasoconstriction and is an important component of the overall integrative function of the central nervous system in circulatory control. Local production of $PGE_2$ may influence vascular tone by interfering with release of norepinephrine from nerve endings.[8] Genetic or environmental influences which impair local $PGE_2$ production or hasten destruction of this compound might well account for the enhanced vascular reactivity which is known to occur in the earliest phases of essential hypertension.

There are three intrinsic mechanisms important in the regulation of vascular resistance.[98] The first determines basal vascular tone. The cell membrane of vascular smooth-muscle cells is unstable and undergoes spontaneous depolarization followed by muscle contraction. This basal vascular tone is influenced by blood-borne humoral factors and by the activity of the sympathetic nervous system and is decreased by the local production of vasodilator substances.

The second factor has been called the Bayliss effect.[99] As arterial blood pressure rises, the tone of vascular smooth muscle increases. This mechanism serves as a counterbalance to the vasodilating effect of local tissue metabolites. The influence of prostagladins or kinins on the Bayliss effect has not been investigated.

Finally, and perhaps most important relative to the production of prostaglandins and kinins, is the influence of local tissue metabolites on vascular resistance. As tissue perfusion pressure falls, oxygen delivery becomes inadequate, local ATP breakdown exceeds synthesis, and a number of vasodepressor substances accumulate. Which compound, if any, bears the greatest influence on local autoregulation has not been established. It is here that the kinins and prostaglandins undoubtedly exert an important effect on overall circulatory regulation. Local production of $PGI_2$ and of $PGE_2$ would result in vasodilatation, while production of thromboxane and $PGF_{2\alpha}$ may contribute to vasoconstriction.

The second major component in the regulation of blood pressure, cardiac output, is the product of heart rate and stroke volume. Young patients, in the labile phase of hypertension, were found to have a hyperkinetic circulation characterized by a high cardiac output.[100] It has been observed that patients with essential hypertension ordinarily have higher heart rates than patients with a normal blood pressure.[100] Although this has been attributed to overactivity of the sympathetic nervous system, it is conceivable that deficient prostaglandin synthesis or increased destruction would remove their modulat-

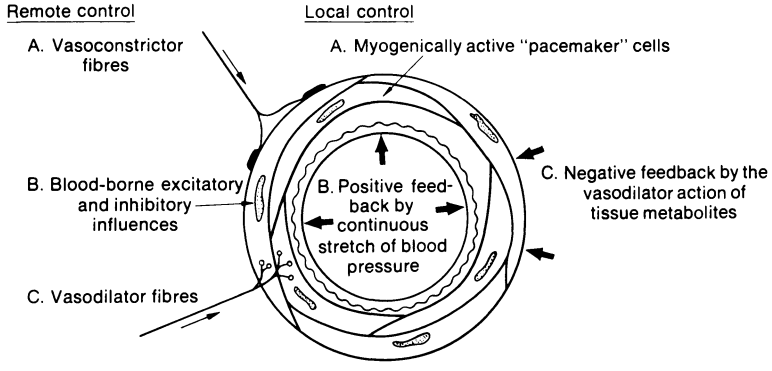


**Figure 6.** Regulation of peripheral vascular resistance. Control of peripheral vascular resistance by local and remote influences, illustrating sites at which prostaglandins and kinins could interact with other control mechanisms to alter vascular tone. Reproduced with permission from Folkow B, Neil E, ref 98

ing effect on norepinephrine release, thus resulting in a higher heart rate which could contribute to an increased cardiac output.

The other determinant of cardiac output is stroke volume which, in turn, is determined by the size of the left ventricle at the end of diastole and the extent of myocardial fiber shortening during systole. Fiber shortening is determined by preload, afterload, and contractility. Preload can be defined as the degree of stretch of the myocardial fibers at the end of diastole. This results from the compliance characteristics of the ventricle and the filling pressure. The latter reflects venous tone and intravascular volume. The prostaglandins are potentially important in regulating both factors. $PGF_{2\alpha}$ is a venoconstrictor,[101] increased production of which would result in increased venous return and a subsequent increase in cardiac output. Afterload is a term initially used in isolated muscle experiments. In the intact heart, afterload refers to systolic myocardial wall tension, which is determined by intraventricular pressure and ventricular size. When preload and contractility are held constant, decreased afterload increases myocardial fiber shortening. In the intact circulation, a decrease in venous return reduces preload and left ventricular size, while a fall in peripheral vascular resistance reduces left ventricular systolic pressure. Thus, afterload can be altered in either of two ways. The vasodilator effects of $PGI_2$ and $PGE_2$ would decrease afterload and might contribute to decreased preload by dilating veins. On the other hand, the vasoconstrictor effect of $PGF_{2\alpha}$ and of thromboxane $A_2$ may increase preload and afterload.

Contractility determines the level of myocardial performance at a given preload and afterload. In experimental animals, prostaglandins have variable effects on contractility, depending upon experimental conditions and species. Most studies have shown that prostaglandins of the E and A series increase cardiac output and have a positive inotropic effect.[102] In humans, infusions of $PGE_1$ increase stroke volume and heart rate, thus increasing cardiac output which gives rise to the possibility that abnormal synthesis of prostaglandins of the E series contributes to a hyperkinetic circulatory state, which may initiate a chain of events leading to hypertension.[103]

## Conclusion

The renin-angiotensin system is subject to regulation by neural, hormonal, and local influences. A similar regulatory network seems probable for the kallikrein-kinin-prostaglandin system, which may be considered the vasodilator-diuretic protagonist, as the renin-angiotensin-aldosterone-ADH system is the vasoconstrictor, salt- and water-conserving protagonist. To establish the antihypertensive function of kallikrein-kinin-prostaglandin system, it is important to consider the contribution of the extrarenal vascular tissues to the integrity of this system as well as that of the renal components of the system. The present evidence supports the proposal that some forms of chronic hypertension of unknown cause are dependent on a deficiency of the kallikrein-kinin-prostaglandin system. However, there are many avenues of investigation that remain to be explored, and conclusive evidence for the role of this antihypertensive system in the gensis of hypertension has yet to be presented.

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# Hypertension and Oral Contraceptives

# 14

Ch. Lauritzen

In 1967, initial reports appeared in the American and British literature on an association between the use of oral contraceptives and the occurrence of high blood pressure.[28] This observation was soon confirmed by other authors. Blood pressures in excess of 140/90 mm Hg are generally considered to be hypertensive.

## Incidence

One early publication reported an 18% incidence of arterial hypertension, i.e., 9 of 51 women in a prospective study.[25] According to Woods[28] and Harris,[15] the hypertension that occurs may involve a considerable systolic and diastolic blood pressure increase in some cases. By 1969 the association between oral contraceptives and high blood pressure was so well-established that it could no longer be attributed to chance. Smith then reported that in his study population only a slight rise of average blood pressure, usually systolic, developed in about 1% of all patients.[23] According to Smith, the findings of earlier studies apparently were the result of a selection effect. More statistically reliable information based on a large prospective study was published by the Royal College of General Practitioners.[20a] This study showed a ratio of 2.59 ($p < 0.01$) between women taking oral contraceptives and controls with regard to the incidence of essential hypertension. In past oral contraceptive users, the incidence ratio was 0.99, i.e., there was no increase. According to the study by Fisch et al. on 13,355 women ("Kaiser Permanent Contraceptive Drug Study," Walnut Creek, 1972), the risk of developing hypertension among oral contraceptive users was 1.76 relative to nonusers.[12] There was an average increase of 5–6 mm Hg systolic and 1–2 mm Hg diastolic. However, if we consider that the authors arrived at their ratio by monitoring blood pressure changes more closely in oral contraceptive users than in nonusers, we must revise their figure down to 1.29. In Europe it may be assumed that about 1% of women taking contraceptive steroids will develop hypertension[16] (Table 1).

**Table 1.** Importance of Age Factor in Development of Hypertension in Oral Hormonal Contraceptive Users and Nonusers

| | Blood Pressure Increase (%) | |
|---|---|---|
| Age (years) | Users | Nonusers |
| 20–30 | 18 | 6 |
| 31–35 | 30 | 22 |
| 36–40 | 42 | 18 |
| 41–45 | 57 | 30 |

## Symptoms

The development of hypertension in oral contraceptive users has no characteristic symptoms. Headache, head congestion, dizziness, and nervousness are sometimes reported.

**Table 2.** Changes in Renin-Angiotensin-Aldosterone System during Oral Hormonal Contraceptive Use

| Index | Change Relative to Initial Value |
|---|---|
| Plasma level of renin substrate | 2.5–4-fold increase |
| Plasma level of renin | 50% decrease |
| Plasma renin activity | 2–4-fold increase |
| Plasma level of angiotensin II | 3-fold increase |
| Plasma level of aldosterone | 2–3-fold increase |
| Aldosterone excretion in 24-h urine | 2-fold increase |

## Causes

An increase in renin-angiotensin, renin substrate, and aldosterone has been demonstrated (Table 2). These changes are mainly the result of a steroid-induced stimulation of the synthesis of angiotensinogen (renin substrate) in the kidney, which is increased by a factor of 2.5–4. This leads to a rise in the concentrations of angiotensin I and II, with a resultant increase of aldosterone secretion in the adrenal cortex and an elevated plasma aldosterone level. Aldosterone excretion increases less, probably owing to greater aldosterone binding to transport proteins in the plasma. Through a negative-feedback mechanism, renin release from the kidney is usually reduced by half in hypertensive women.[1,3] A striking feature is that practically all women with hypertension who take oral contraceptives have a family history of hypertension. The serum creatinine, urea, catecholamines, iv pyelogram, and radiorenogram are normal. Sodium and water retention is increased by estrogens and gestagens, as is the plasma volume and cardiac stroke volume. The patients occasionally exhibit left ventricular hypertrophy, but this can be corrected by treating the hypertension or discontinuing the oral contraceptive.[7] The role played by hormone-induced coagulation disturbances in the rare development of nephrosclerosis is still unclear.[13] Keifer and Scott report that combination products cause hypertension more frequently than sequential products, that decreasing the estrogen dose reduces the incidence of hypertension, and that hypertension incidence increases with duration of contraceptive use.[18] In the Royal College study, however, no relation could be found between high estrogen doses and an increased incidence of hypertension.[20a] On the contrary, the incidence tended to decline with higher estrogen doses. Nevertheless, the incidence of hypertension still increased with the duration of contraceptive use.

One possible source of error pointed out in the Royal College study were the facts that blood pressure readings are taken more frequently in contraceptive pill users than in control subjects and that physicians have become increasingly alerted to the problem of hypertension in women taking oral contraceptives. However, the Royal College study showed a definite correlation between the incidence of hypertension and gestagen dosage. The incidence ratio was 1.20 at gestagen doses below 3 mg, increasing to 1.97 at higher doses. When products with equal estrogen doses (50 mg) were used, a relation to the gestagen dose was also observed. The ratio was 1.0 below 3 mg gestagen per daily dose, but 1.41 at doses above 3 mg.

## Risk Factors

The principal risk factors for the development of hypertension in contraceptive pill users are: family history of hypertension and diabetes mellitus, manifest diabetes, and gestosis in prior pregnancies. It has been shown that a strong correlation exists between age and the development of hypertension in oral contraceptive users.[12,27] The correlation with parity is weak. Other authors have found no connection between hypertension and parity or the duration of contraceptive use.[5,12] They report that the blood pressure increase is independent of the duration of use and is always age-dependent after hormonal contraception is discontinued. Isolated cases of severe hypertension during oral contraceptive use are rare.[12] In cases of preexisting hypertension, the blood pressure must not increase further during contraceptive use. The hypertension caused by oral contraceptives persists for about 3 months after discontinuance of therapy.[23] No correlation has been established between weight gains and hypertension.[18] It is noteworthy that in the majority of hypertension cases increases in cholesterol, triglycerides, and phospholipids are observed during estrogen-gestagen therapy.

Since findings on the correlation between duration of oral contraceptive use and the development of hypertension are contradictory, it remains unclear whether the interruption of pill use at given intervals can reduce the incidence of hypertension. Further studies in this direction are needed. Even if we accept the highest figures on the incidence of hypertension in oral contraceptive users, however, we still find that 95% of all pill users will *not* develop hypertension after about 5-years' use. The 5% who develop hypertension cannot yet be reliably identified prior to treatment. In any event, the hypertension is reversible. Thus, intervals of nonuse will be

of unproved value in about 5% of all pill users and of no value in the remaining 95%. At the same time, such intervals increase the risk of unwanted pregnancy with its associated morbidity and mortality.

## Practices

When estrogens are prescribed, the blood pressure should always be measured before and during therapy. This is done in any case as part of the initial examination. Both the patient history and family history must be obtained. Risk factors for the development of hypertension should be noted (Table 3). If one or more of these risk factors are present, a relative contraindication exists for the use of the pill. If the blood pressure at rest is within the range 140–160/90–95 mm Hg, estrogen-gestagen may be prescribed on a trial basis. Since it has been shown that the use of low-estrogen doses and the reduction of sodium intake below 3 g/day can prevent the development of hypertension during estrogen use,[10] low-dose preparations are preferred.

## Treatment

If hypertension develops, it can frequently be relieved simply by reducing the dosage or changing to a different product. If the blood pressure exceeds 160/95, the estrogen product should in most cases be discontinued and alternative methods considered. However, if continued estrogen therapy is indicated or is desired by the patient, concurrent antihypertensive drugs may be given for a time. The blood pressure will usually normalize under this treatment and will remain normal when antihypertensive medication is withdrawn, provided the hypertension is not secondary to some other disease. Since evidence indicates that progesterone sometimes plays a role in the development of hypertension, one should consider stopping or changing the gestagen if an estrogen-gestagen preparation is being given.

**Table 3.** Risk Factors for Development of Hypertension in Oral Hormonal Contraceptive Users (Relative Contraindication for Use)

| |
|---|
| Family history of hypertension |
| Patient history of renal disease |
| Hypertension or gestosis in prior pregnancy |
| Vascular disease |
| Diabetes, obesity |
| Hyperlipidemia |
| Endocrine disorders of adrenal cortex |

Some authors have reported that the hypertension associated with oral contraceptive use returns to normal after a certain period despite continued use of estrogen-gestagen preparations. If normalization of the blood pressure has not occurred 3 months after the discontinuance of contraceptive use, the patient should receive antihypertensive treatment. All hypertension cases associated with pill use respond promptly and safely to the use of antihypertensive medications.[18,23] Spironolactone is suitable. Symptomatic treatment with sulfonamide saluretics (thiazides, furosemide) should be instituted only after exclusion of hyperkalemia. The beta-blocking drugs are also suitable for lowering the blood pressure in patients on contraceptive steroids; like beta-propranolol, the beta-blocking drugs simultaneously inhibit renin release. If the hypertension is severe or persists after discontinuance of the hormones, an underlying cause (e.g., renal disease) must be sought.

In pregnancy or otherwise, the goal of antihypertensive therapy is to lower the systolic and especially the diastolic blood pressure elevation in order to prevent a vascular placental insufficiency, with its heightened fetal morbidity and mortality, and to avoid premature placental detachment and maternal eclampsia. Physical rest is of prime importance. The patient should be placed on bed rest if at all possible, as this tends to improve the placental perfusion. The patient should lie on her side, rather than on her back, as the latter position may cause compression of the large ascending vessels from the pelvis. It has been shown that bed rest, by improving the placental blood flow, can produce an increase in plasma renin activity and concentration.[24a] The diet should be high in protein (eggs, milk, cottage cheese), particularly with low total albumin values and proteinuria, and low in fats and carbohydrates. Fruits and rice should be included periodically. Salt intake should be kept below 2–3 mg. Diuretics are not currently recommended for lowering the blood pressure, even in combination with antihypertensive agents. Most diuretics, in any case, do not lower the blood pressure significantly in toxemia of pregnancy and often even aggravate the tendency toward electrolyte imbalance and potassium loss. If potassium deficiency is present, it is corrected by potassium replacement. For low albumin values, albumin infusions are given in a dose of three to four bottles of 50-ml 20% human albumin per day. The infusion of amino acids in a dose of 500 ml/day may also be indicated. In severe hypertension of pregnancy, antihypertensive drug therapy may become necessary. This is done mainly to improve the maternal prognosis, less so that of the fetus. Suitable drugs include dihydralazine, clonidine, and $\alpha$-methyldopa. Where

sedation is warranted, reserpine or diazepam may also be given. The iv administration of Nepresol is done by drip infusion with a drop counter. Two ampules of 25 mg each are dissolved in 500 ml of electrolyte solution. The infusion rate is 20 drops/min initially and can be increased or decreased according to the blood pressure level. Accurate blood pressure monitoring at frequent intervals is necessary during the infusion, as is the continuous monitoring of fetal heart sounds, since an excessive or overly rapid fall of blood pressure can endanger the fetus through underperfusion of the uteroplacental blood vessels. If severe hypertension is accompanied by hyperreflexia and agitation as signs of preeclampsia, magnesium is administered. The initial dose is 3–4 g of magnesium sulfate iv for 5 min, corresponding to 15–20 ml of a 20% solution. This is followed by continuous drip infusion of 50 ml of 20% solution dissolved in 500 ml of 5% glucose, introduced at a rate of 20 drops/min. The blood pressure and reflexes must be monitored frequently during the therapy. The magnesium values in the serum and urine are checked. Calcium should be kept ready as an antidote.

## Hypertension during Postmenopausal Use of Estrogens

As a rule, natural estrogens are administered during the postmenopausal period. Apparently the incidence of hypertension is significantly lower in such cases, particularly since lower dose equivalents are prescribed during postmenopause than in oral contraceptive therapy.

There are numerous studies which indicate that the long-term use of natural estrogens by postmenopausal women causes no increase in the average or individual blood pressure reading. Such studies have been published on micronized estradiol, estradiol valerate, conjugated estrogens,[12,20] and estriol.[4,9,11] In cases where blood pressure elevations were determined, relatively high doses of conjugated estrogens were generally involved.[26] The role of the estrogens in the blood pressure increases was not always clearly defined. Nevertheless, natural estrogens apparently are responsible for the development of hypertension in a few cases. Again, the patients usually are women with a family history of hypertension or a personal history of serious renal disease. The mechanism of the hypertension is a disturbance in the regulation of the renin-angiotensin-aldosterone system based on an impaired feedback inhibition of the renin substrate. The aldosterone level is usually elevated.[8,19]

Treatment is given by change or even withdrawal of estrogens. If the medication is to be maintained, reduction of sodium intake and the prescription of suitable antihypertensives is indicated.

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# Renal Hypertension

# 15

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Many types of hypertension exhibit a renal component. To characterize the role of the kidney in the development of hypertension in more emphatic terms: There are few types of hypertension in which a primary or secondary renal involvement can be excluded with certainty, even in the early stage. Every type of hypertension can lead to renal damage in the form of benign or malignant nephrosclerosis, which in turn can aggravate the hypertension. In the case of essential hypertension, for which many authors reject a primary renal component (see Ref. 40,) though both epidemiologic[10,47] and animal studies[2,10,47] point to insufficient renal sodium excretion due to genetic and nutritional influences as the cause of the hypertension. In this chapter, however, we shall deal mainly with types of hypertension that are caused exclusively by renal parenchymal changes and are not surgically correctable.

Kincaid-Smith states that practically all diseases that lead to renal failure can cause hypertension and that therefore a complete listing of these diseases is of no advantage.[25] We agree with this view and therefore will place special emphasis only on renal diseases which either are very common and thus of major clinical relevance or are associated with a more significant blood pressure increase than other diseases with corresponding degrees of renal failure. We shall also consider the renal changes caused by hypertension and discuss several systemic diseases with renal involvement and hypertension.

## Hypertension in Primary Renal Disease

### Glomerulonephritis

The prevalence of hypertension varies among the different forms of glomerulonephritis (Table 1). Surprisingly, the blood pressure often is elevated even in patients who have apparently recovered completely from glomerulonephritis. In other cases,

**Table 1.** Prevalence of Hypertension in Different Histologic Forms of Glomerulonephritis

| Form of Glomerulonephritis | No. of Patients Studied | No. of Hypertension Cases | % |
|---|---|---|---|
| Endocapillary (acute) of poststreptococcal type | 43 | 22 | 51.2 |
| Mesangioproliferative | 531 | 181 | 34.1 |
| Minimally proliferative intercapillary | 1004 | 245 | 24.4 |
| Focal sclerotic | 65 | 22 | 33.8 |
| Perimembranous | 191 | 58 | 30.4 |
| Membranoproliferative | 70 | 40 | 57.1 |
| Rapidly progressive | 56 | 29 | 51.8 |

From Bohle A et al., ref 4.

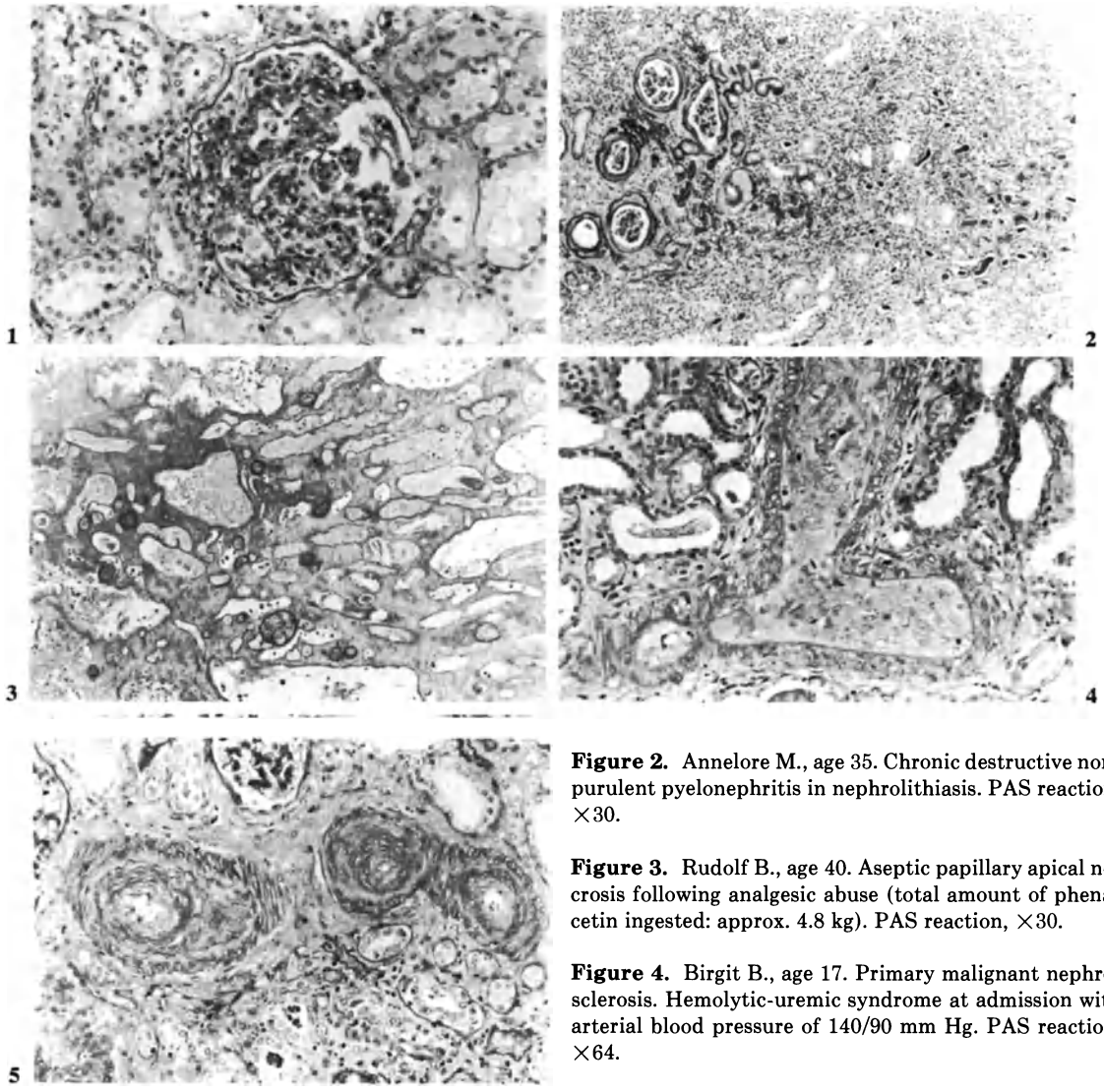

**Figure 1.** Philipp S., age 50. Endocapillary glomerulonephritis of poststreptococcal type. PAS reaction, ×64.

**Figure 2.** Annelore M., age 35. Chronic destructive nonpurulent pyelonephritis in nephrolithiasis. PAS reaction, ×30.

**Figure 3.** Rudolf B., age 40. Aseptic papillary apical necrosis following analgesic abuse (total amount of phenacetin ingested: approx. 4.8 kg). PAS reaction, ×30.

**Figure 4.** Birgit B., age 17. Primary malignant nephrosclerosis. Hemolytic-uremic syndrome at admission with arterial blood pressure of 140/90 mm Hg. PAS reaction, ×64.

**Figure 5.** Ernst R., age 47. Secondary malignant nephrosclerosis. Three-year history of hypertension, accelerated arterial hypertension for previous 4 months. PAS reaction, ×64.

hypertension may return after a prolonged normotensive interval. Thus, it is practically impossible to answer the extremely important question, both in terms of prognosis and disability evaluation, of whether the hypertension is glomerulonephritic or essential in origin without performing a renal biopsy. Even then, it may be difficult or impossible to ascertain the cause of the hypertension (Fig. 1). The mechanism of hypertension in acute glomerulonephritis may involve sodium and water retention resulting from the glomerular lesion. It remains unclear whether a relative activation of the renin-angiotensin-aldosterone system (i.e., inadequate suppression relative to the degree of sodium and water retention) also plays a role. In chronic glomerulonephritis with minimal glomerular changes, vascular changes also could precede the development of hypertension.[24]

One difficulty for the clinician should be mentioned in this regard: The severity of the hypertension, renal function impairment, and sedimentation findings (proteinuria, erythrocyturia, leukocyturia, cylindruria) in renalized essential hypertension and, more rarely, in other forms of malignant hypertension may resemble the findings in glomerulonephritis. If renal biopsy is omitted in these patients, the

course of the disease can be useful in determining whether hypertension with secondary renal damage or glomerulonephritis with hypertension is involved. If proteinuria (>0.2 g per 24 h) and erythrocyturia (>2000/min) persist despite blood pressure normalization, a primary renal lesion is probably present.

Like Sarre et al.,[39] we found in our study population that hypertension is generally more pronounced in glomerulonephritis with serum creatinine values of up to 8 mg per 100 ml than in pyelonephritis and cystic kidney. At creatinine values above 8 mg per 100 ml, the patients with glomerulonephritis showed a slight fall of blood pressure, so that differences with respect to the other two renal diseases mentioned were not so pronounced. It would appear that this degree of renal function loss leads to numerous complex disturbances of blood pressure regulation which outstrip the influence of the underlying disease. We also found that in patients with histologically proven glomerulonephritis, those who had normal renal function at the time of examination but later developed renal insufficiency had higher blood pressure readings than patients whose renal function remained normal during the next 5 years' observation. Whether impaired renal function in these patients was due at least partly to the hypertension or whether the hypertension represented a predictor of an unfavorable course of the glomerulonephritis cannot be determined, particularly since no serial biopsy data are available. It appears doubtful that the histologic type of glomerulonephritis is entirely responsible for the development of the hypertension, because the described trend was also observed when patients with mesangioproliferative glomerulonephritis were investigated. Of course it must be pointed out that an assessment of the renal interstitium, which apparently is important for renal excretory function even in primary glomerular disease,[5] was not included in this investigation.

### Pyelonephritis

On the basis of our experience, hypertension is extremely rare in acute pyelonephritis with no significant impairment of renal function. In chronic pyelonephritis established radiologically or pathoanatomically, the incidence of hypertension reportedly ranges from 30% to 75%. In cases of recurrent urinary tract infection with no radiologic signs of renal scarring, the incidence of hypertension is less than 10%; if parenchymal scars are demonstrated, this percentage rises sharply. On the basis of earlier observations of vascular changes in the region of pyelonephritic scars[23] and results of our groups showing elevated renin values in the venous blood of the scarred kidney, high renin levels, and hyperplasia of the juxtaglomerular apparatus in the vicinity of scarred renal areas[19] (Fig. 2), we suggest that an ischemia-induced increase in renin secretion is at least partly responsible for hypertension in pyelonephritis (see also Ref. 20).

### Polycystic Renal Disease

Cystic ectasis of the renal tubules is a feature common to all polycystic renal diseases. In the adult form of the disease hypertension is often the leading symptom, while it is rare in the juvenile form and practically absent in medullary carcinoma of the kidney.

Very severe hypertensive states can result from cystic renal disease, regardless of the degree of renal failure. For example, in a 32-year-old man with cystic kidneys and a creatinine of 1.5 mg per 100 ml, we observed malignant hypertension with blood pressure readings up to 270/170 mm Hg.

Besides the sodium and water retention that can occur in all forms of renal disease, we must also consider ischemic processes due to cystic renal changes as a potential cause of hypertension. We found in our study population that in cases of terminal renal failure requiring dialysis, blood pressure control generally presented no particular difficulty in patients with cystic kidneys.

## Special Forms of Renal Hypertension

### Analgesic Nephropathy

Analgesic nephropathy has been associated mainly with phenacetin and phenacetin derivatives in Europe,[16] whereas aspirin is cited in the Australian literature as the main nephrotoxic ingredient of analgesics.[25] Animal studies have shown that both types of drug are nephrotoxic with different sites of action.[16,25] The earliest sign of damage is a decreased perfusion of the renal medulla; further damage also is restricted mainly to this region (Fig. 3). The cause of the diminished medullary blood flow in the case of phenacetin may be a toxic microangiopathy.[1]

Close inspection reveals certain differences between the clinical pictures of the European and Australian forms of analgesic nephropathy. Besides renal damage, phenacetin abuse leads to hematologic changes (excessive anemia for degree of renal insufficiency, hemolysis with high reticulocyte count, sometimes splenic enlargement and methemoglobinemia) as well as nervous system distur-

bances (nervousness, tremor, headache, mood swings). Proteinuria is usually slight, and few leukocytes, erythrocytes, and casts are found in the urine. Urinary tract infections are observed in 20%–50% of cases; bacterial inflammations are particularly common if renal function is already impaired. Papillary necrosis is frequently observed. The blood pressure is rarely elevated at the onset of the nephropathy. In the Australian form of the disease, early papillary necrosis with calcification is described, and hypertension is reported in more than 80% of cases. Half the hypertensive patients have diastolic readings above 120 mm Hg. The severe hypertension may result from destruction of the interstitial cells of the renal medulla, with a diminished secretion of prostaglandins.[25] It should be noted, however, that the concept of "aspirin nephropathy" is not unchallenged.[16] The results of a cooperative study in New Zealand[37] and further studies[32] dispute the nephrotoxicity of aspirin while demonstrating that phenacetin and its degradation products are important in the development of analgesic nephropathy.

### Acute Renal Failure

In acute renal failure, moderate elevations of blood pressure can occur at the onset of the oliguric phase, regardless of the etiology of the disease. As the duration of the oliguria increases, elevated blood pressure values are observed in up to 85% of cases.[46] It is surely incorrect to hold hypervolemia solely responsible for all these cases. Various authors have pointed out increased renin levels in acute renal failure.[8,27] We also found elevations of plasma renin in patients with acute renal failure, normal central venous pressure, and hypertension, but there was not necessarily a correlation between hypertension and an elevated plasma renin.

### Terminal Renal Failure

Practically any renal disease can progress to terminal renal failure with hypertension. The development of hypertension is ascribed to interactions between hypertension-promoting factors and the failure of hypertension-preventing mechanisms.[41]

After chronic intermittent hemodialysis therapy enabled the treatment of terminal renal failure, it was soon learned that hypertension represented one of the most important problems in this form of treatment. It was found that the blood pressure of most dialysis patients could be normalized by salt and water restriction (salt- and volume-dependent hypertension[48]). Various authors point out that fluid restriction is of greater importance in the control of hypertension than a low sodium content of the dialysate.[30] On the basis of our experience with more than 20 patients with terminal renal failure and hypertension, sodium concentrations of 140–150 mEq/liter in the dialysate allow better ultrafiltration and blood pressure control than concentrations of 125 mEq/liter. At the low sodium concentration, the patients continually complain of calf muscle spasticity and faintness during dialysis, with inadequate blood pressure control during the dialysis interval. Perhaps the low sodium content of the dialysate stimulates the renin-angiotensin system, and the high angiotensin II level counteracts the blood pressure reduction (see below). With the technique of hemofiltration, it is sometimes possible to effectively lower the blood pressure of patients difficult to control with conventional hemodialysis therapy.[42]

Brown et al. were able to show a positive correlation between blood pressure level and plasma renin values in dialysis patients, although this correlation was not valid for the individual patient in every case.[7] In some patients with severe hypertension who responded to extreme ultrafiltration and conventional antihypertensive drug therapy with a rise, rather than fall, of blood pressure, markedly elevated plasma renin values could be shown. In these cases the blood pressure could be effectively lowered, and bilateral nephrectomy avoided, by the use of minoxidil, a peripheral vasodilator which is not yet readily available commercially.[29,38] Following bilateral nephrectomy, the blood pressure generally is once again salt- and volume-dependent and amenable to control, although normotension is not attainable in all patients.[43] As a rule, dialysis patients with high renin levels appear to demonstrate a greater fall of blood pressure following nephrectomy than patients with low renin levels.

It should be pointed out that the percentage of dialysis patients with high blood pressure, and particularly those with intractable hypertension requiring bilateral nephrectomy, varies substantially from one dialysis center to the next. It is unclear whether this relates to differences in the underlying renal disease, the dialysis technique, or the antihypertensive drug therapy.

### Malignant Nephrosclerosis

Malignant nephrosclerosis actually encompasses two entirely different syndromes which show the same clinical and morphologic features only in their late stages.[3]

The first syndrome (primary malignant nephro-

sclerosis) begins normotensively, usually following gastrointestinal or pulmonary infections or the use of ovulation inhibitors, and is marked by severe hemolytic anemia, hypercoagulability, and rapidly progressive renal failure. The morphologic correlate consists of a stenosing intimal edema of the interlobular arteries and vas afferens with fibrinoid vascular necrosis and usually slight glomerular cell proliferation. This is accompanied by changes in the glomerular basement membrane as well as the tubular changes of acute renal failure (Fig. 4). Extrarenal vascular lesions are extremely rare. (For morphologic details, see Ref. 6.)

The disease may progress in stages. The morphologically abortive forms with lesions restricted to the glomeruli and with mild hypertension are distinguished from the severe forms in which the disease picture is complete and the hypertension is difficult to control despite dialysis therapy. In rarer cases the patient may improve or even recover completely. The picture was first described by Fahr in 1924[13] and Schürmann and MacMahon in 1933.[44] It then entered the medical literature under various names (see survey in Ref. 6), until 1973 when Bohle et al. pointed to a prior coagulation disturbance as the characteristic feature of the disease and suggested the term *primary malignant nephrosclerosis*.[3] This term probably should also include the hemolytic-uremic syndrome of Gasser et al.[14] Thrombocytopenic purpura,[36] by contrast, causes mainly extrarenal and particularly central nervous changes and so is not associated with significant renal insufficiency.

Malignant nephrosclerosis following prolonged hypertension (secondary malignant nephrosclerosis[3]) is characterized by fibroid necrosis and by focal fibrotic and sclerotic vascular lesions which are difficult to distinguish from the late changes in primary malignant nephrosclerosis. Clinically, there is a gradual progression of renal insufficiency with few hematologic and hemostasiologic changes. Secondary malignant nephrosclerosis can develop during the course of practically any hypertensive disease but is particularly common when the underlying disease is of renal origin. Sometimes glomerulonephritis can no longer be distinguished from malignant nephrosclerosis in the late stage ("end-stage kidney") (Fig. 5).

### Radiation Nephritis

Exposure of the kidneys to radiation (usually in doses over 2000 rad) can lead to the development of hypertension weeks or even years after the exposure (39% incidence of hypertension, of which 28% was malignant[31]). Differentiation into acute and chronic forms of the disease[31] is unnecessary since the transitions are fluid. If only one kidney was irradiated and radiation nephritis is established, unilateral nephrectomy is recommended if hypertension persists. If both kidneys are involved, antihypertensive therapy is indicated. The histologic changes in radiation nephritis resemble those in malignant nephrosclerosis, the individual histologic picture depending on the time elapsed since irradiation. Kincaid-Smith points out, however, that in cases of unilateral radiation nephritis and malignant hypertension, the malignant nephrosclerosis in the unirradiated kidney will "heal" in a few days with appropriate antihypertensive therapy; i.e., the fibrinoid changes in the unexposed kidney will undergo hyaline degeneration, while those in the exposed kidney may persist for years.[25]

## Renal Hypertension in Systemic Diseases

As mentioned, it is well known that any disease accompanied by the destruction of renal tissue and subsequent impairment of kidney function can lead to renal hypertension. Examples are the nephropathies that occur in malignant diseases,[15,28] in amyloidosis, in infectious diseases,[12] and in diabetes mellitus.

In the classic (generalized) form of Wegener's granulomatosis, renal involvement is present by definition, in this case in the form of focal necrotizing glomerulitis. Inflammatory processes in the small arteries and arterioles are present in the interstitium. Nevertheless, the reported incidence of hypertension is only 10%–20%.[21] Goodpasture's syndrome is characterized by glomerulonephritis and pulmonary hemorrhage with linear immunofluorescence (IgG, C3) of the glomerular capillaries and alveolar septa. However, many cases are probably assigned to this syndrome without histologic confirmation. Data on the prevalence of hypertension are not meaningful owing to a frequent lack of histologic confirmation of the diagnosis and small case numbers. In three cases of Goodpasture's syndrome we found no hypertension at the onset of the disease. Two of these patients have been treated and observed for 3 years and for 10 months, respectively, and so far have developed neither hypertension nor renal insufficiency.

In gout patients, hypertension is more frequent and more pronounced than the degree of renal insufficiency would suggest. Overweight and early sclerotic renal changes[35] sufficient to cause ischemia must be considered partly responsible for the development of hypertension in these patients.

We shall now discuss several systemic diseases in which the kidney is often involved and in which a severe, sometimes malignant hypertension develops as a result of renal vascular lesions.

### Scleroderma

In scleroderma, proteinuria is usually the first sign of renal involvement. Hypertension is present in about 25% of cases. About 15%–20% of patients develop a sudden malignant hypertension which responds poorly to therapy, is often accompanied by left-heart failure, and leads to terminal renal failure within a few weeks.[45] The plasma renin levels were determined in a few patients, and a marked to extreme increase was generally found.

The severe hypertension with elevated renin levels sometimes observed in scleroderma is caused by renal changes similar to those in primary malignant nephrosclerosis (Fig. 4). It is interesting to note that pregnancy in scleroderma can also bring on this fulminant course of hypertension,[22] again illustrating the clinical relation to primary malignant nephrosclerosis. Morphologically, the disease affects mainly the interlobular arteries whose narrowing is responsible for the elevation of blood pressure and plasma renin levels.

### Periarteritis Nodosa

As in malignant nephrosclerosis and scleroderma, the hypertension in periarteritis nodosa is produced by narrowing of the larger renal artery branches with subsequent ischemia. Recognition of the disease is often quite difficult owing to the varied clinical picture; it should be suspected whenever hypertension (in about 60% of cases) and eosinophilia occur simultaneously. Hypertension may be the predominant symptom in both children[34] and adults and can develop at any point during the course of the disease.

### Systemic Lupus Erythematosus

Dubois and Tuffanelli[11] report a 25.2% incidence of hypertension in systemic lupus erythematosus based on their analysis of 520 cases; other authors have found hypertension in 45% of cases.[9] Based on our own observations, we have the impression that the prevalence of hypertension depends on the acuteness of the disease. In five acute cases characterized by fever and later by rapidly progressive renal insufficiency, we found an early development of hypertension which responded poorly to treatment. In one case the disease was complicated by acute renal failure. The blood pressure in this woman could be effectively controlled during 8 weeks of dialysis therapy; after renal function returned without characteristic polyuria (creatinine values ~ 2.5 mg per 100 ml), it became increasingly difficult to control the blood pressure.

## Therapy

The therapy of renal disease and high blood pressure includes both causal and symptomatic treatments. The causal therapy of glomerulonephritis is today one of the most controversial chapters of nephrology. The reader is referred to literature surveys for information on this point.[26] The therapy of other renal diseases also requires no further discussion here, with the exception of malignant nephrosclerosis. Some authors suggest heparinization for primary malignant nephrosclerosis. We believe that fibrinolysis is too risky in view of the questionable prospects of success. As for the therapeutic value of thrombocyte-aggregation inhibitors, it is our opinion that experience with them is still insufficient to make a judgment. The prophylaxis and treatment of secondary malignant nephrosclerosis consists of effective blood pressure control. The treatment of systemic diseases with renal hypertension is also beyond the scope of this paper.

The symptomatic treatment of renal hypertension is similar to that of other forms[17] (see Chap. 33). In the case of renal hypertension, however, it is important to note that a transitory worsening of renal function may occur initially when the elevated blood pressure is lowered with antihypertensive drugs. This by no means implies that the hypertension is "necessary" and should consequently remain untreated; this would surely lead to an irreversible decline of renal function. On the contrary, a continued reduction of blood pressure eventually leads to an amelioration of renal function, as the renal vascular lesions caused by the hypertension regress. There may also be a marked improvement of cerebrovascular lesions, which are often associated with the renal changes.

In very severe hypertension with impaired renal function, early dialysis therapy may prove necessary after all conservative attempts at treatment have failed. As a rule, the blood pressure can be effectively controlled in this way. In other cases, terminal renal failure may develop in the setting of malignant hypertension; in some of these patients, dialysis therapy could be discontinued after a period of

weeks, months, or years.[18,33] Most of these cases were diagnosed as a form of malignant nephrosclerosis.[18,33]

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# Renovascular Hypertension

# 16

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A special chapter is devoted to renovascular hypertension because it is the most frequent form of secondary hypertension for which specific surgical treatment is available. This corresponds to the definition formulated by Maxwell and Prozan: "Renovascular hypertension is caused by an occlusive disease of the renal arterial vasculature, which is potentially curable by either reconstructive vascular surgery or by nephrectomy."[59] In the present survey we shall examine the incidence and causes of renovascular hypertension, cite clinical and diagnostic aspects of the disease, describe the various pathophysiologic relationships, and discuss surgical procedures and results. Finally we shall present critical recommendations concerning the cost/benefit ratio of diagnosis and treatment.

## Incidence

According to recent large-scale studies, the overall incidence of hypertension among the population is between 10% and 15%; i.e., 2 of 20 people suffer from elevated blood pressure exceeding 140/90 mm Hg. If we exclude persons with blood pressures of 140–160 mm Hg systolic and 90–95 mm Hg diastolic ("borderline" according to WHO classification), we still find an overall incidence of 7%–10% for hypertensive disease among the general population.

On the basis of results of renal arteriography, the only objective clinical method of demonstrating renovascular hypertension in hypertensive patient groups, as well as on pathoanatomic findings in autopsy material, it may be assumed that the incidence of hypertension due to renovascular causes is approximately 3%–6%.[12,24,43,47,59]

Not every constriction of a renal artery leads to hypertension; this is shown by postmortem pathoanatomic and angiographic studies. Thus, even in normotensive individuals, moderate to severe renal artery stenosis could be demonstrated in up to 49% of cases.[34] These cases all involved vascular changes of arteriosclerotic origin. Among 750 hypertensive patients, Kennedy et al. found renal artery stenosis in 5.7%, with ischemia of the stenosed kidney in 3.6%.[43] With a prevalence of about 5%, renovascular disease represents the most frequent cause of secondary hypertension.

## Causes

The causes of renovascular hypertension, which lead to the constriction or displacement of a main renal artery branch or segmental renal artery, can be quite varied. Besides congenital malformations and posttraumatic or tumorous changes, causes include inflammatory, immunologic, occlusive, and degenerative vascular disease (see Table in Ref. 11):

1. Congenital
   a. Fibromuscular hyperplasia
   b. Abdominal aortic stenosis
   c. Renal artery aneurysm
   d. Renal arteriovenous fistula
2. Acquired
   a. Arteriosclerosis
      (1) Of the renal artery

| Type of lesion | Prevalence |
|---|---|
|  Intimal fibroplasia | 1% |
|  Medial fibromuscular dysplasia | |
| Medial fibroplasia | 64% |
| Perimedial fibroplasia | 20% |
| Medial hyperplasia | 10% |
| Medial dissection | 5% |
|  Adventitial fibroplasia | < 1% |
| Periarterial fibroplasia | |

**Figure 1.** Morphologic classification of renal artery stenoses. Modified from Harrison EG, McCormack LJ, ref 30

(2) Of the aorta (with increasing thrombotic occlusion)

b. Thrombosis or embolism of the renal artery (with or without infarction)
c. Renal arteritis
d. Trauma of the renal artery (with thrombosis, perirenal hematoma, arteriovenous fistulas, occlusion by foreign bodies)
e. Tumor or fibromatosis of the renal artery

The most frequent cause of renal artery stenosis is arteriosclerosis, which is responsible for about 75% of cases. The second most frequent cause is the vascular changes of fibromuscular hyperplasia, accounting for 15%–20% of cases.[37] This dysplasia of the renal artery may have genetic causes and appears to progress in severity. Since 1971 a new classification has been generally accepted for fibromuscular hyperplasia,[30] which subdivides lesions into those involving the intima, the media, and the adventitia (Fig. 1).

1. Intimal fibroplasia: The infrequent involvement of the innermost layer of the vessel wall (about 1%) is characterized by a circumferential or eccentric thickening of the intima by loose, mucinous fibrous tissue.
2. Medial (fibromuscular) dysplasia: A distinction is made between medial hyperplasia with simple thickening of the smooth muscle (about 10%), medial fibroplasia with mural aneurysm (about 64%), perimedial fibroplasia with collagenous deposits in the outer half of the media (about 20%), and medial dissection within the external elastic membrane (about 5%).
3. Adventitial changes: Periarterial fibroplasia is the rarest form of arterial dysplasia (less than 1%), in which the adventitia is surrounded by a collagenous fibrous coating.

The demographic analysis of a large cooperative study in 2442 patients showed a general peak incidence of renovascular hypertension between ages 40 and 50.[54] The average of men with renal artery stenosis due to arteriosclerosis was about 52, while the peak age of women with fibromuscular renal artery stenosis was in the 30–40 range. Thus, of 554 patients with arteriosclerotic renal artery stenosis, 60% were men and 40% were women. Of 284 patients with fibromuscular renal artery stenosis, on the other hand, 82% were women and only 18% were men. In 60% of patients with unilateral stenosis, arteriosclerotic changes were demonstrable on the left side; 30.6% of the arteriosclerotic stenosis and 25% of the fibromuscular stenoses were bilateral. On the basis of these findings, it can be stated that renal artery stenosis of arteriosclerotic origin is more frequent in men and is usually left-sided, whereas fibromuscular stenosis is usually right-sided (74%) and is much more frequent in women.

## Pathophysiology of Renovascular Hypertension

A principal factor in the pathogenesis of renovascular hypertension is the *renin-angiotensin-aldosterone system.* The control of renin release can take place by numerous mechanisms:

1. There is evidence that two intrarenal receptor mechanisms are involved in the control of renin release. The renal vascular receptor appears to be located in the afferent arteriole in the area of the juxtaglomerular cells and is apparently sensitive to changes in vascular wall tension. This *baroreceptor mechanism* triggers the release of renin from the juxtaglomerular cells if there is a fall in the perfusion of the afferent arterioles.[7,15,26,98]

The *macula densa* appears to be a sodium-sensitive receptor capable of stimulating renin secretion in response to changes in the tubular sodium environment. The precise mechanism by which the macula densa effects renin release is unclear.[27,70,88,91] Nevertheless, previous experimental data indicate that the renal vascular receptors play a primary role

in the liberation of renin from the juxtaglomerular apparatus.

2. Renal nerves also exert an influence on renin secretion.[49,64,65] An increase of renin secretion has been demonstrated in response to neural electrostimulation as well as to blockade of the baroreceptors with papaverine. Beta-adrenergic receptors are probably responsible for the nervous transmission. Renal nerves and catecholamines can influence renin release by various mechanisms, as noted below.
   a. Renal nerves and catecholamines produce a change in the constriction of the renal arterioles. Since vascular receptors are localized in the afferent arteriole, renal nerves and adrenal hormones can exert an effect on these receptors and regulate renin release.
   b. Changes in the arterial lumen influence the glomerular capillary pressure, an important factor in the control of the glomerular filtration rate. Afferent vasoconstriction leads to a fall of the glomerular filtration pressure and thus to a decrease in the filtration rate. This in turn causes a decrease in filtered sodium, leading to a change in the amount of tubular sodium reaching the macula densa.
   c. The renal nerves terminate directly in the glomerular cells, thus permitting the nerves or catecholamines to act directly on renin production.
   d. A redistribution of the renal blood flow from the cortical renin-rich regions into the medullary renin-poor regions can be induced.
   e. Adrenergic receptors appear to transmit the responses of the renal nerves and catecholamines.
3. Since an increased release of *prostaglandins* into the renal venous blood or urine has been reported in renovascular hypertension,[19,61,95] it can be assumed that the unilateral decrease of sodium resorption and PAH excretion is the result of an increase of intrarenal prostaglandin synthesis and release in the stenosed kidney. Animal experiments have shown an increase of renal prostaglandin $E_2$ synthesis in the medulla;[18] these substances appear to exert a protective effect on renal function.[76] In particular, a marked increase in renal blood flow can be demonstrated primarily in the renal medullary area.[48] Moreover, prostaglandin $E_2$ appears to exert a regulatory influence on the renin system, since $PGE_2$ causes an increase in renin secretion when administered intravenously.[99] In renovascular hypertension, a fall of blood pressure can also be measured after intravenous prostaglandin infusion.[69]

## The Role of Angiotensin in the Pathogenesis of Experimentally Induced Renal Hypertension

Since the pioneering work of Goldblatt et al.,[25] it has been known that the constriction of one renal artery causes the development of sustained arterial hypertension. The renal production of renin, the vasoconstrictive action of angiotensin II, and the observation that constriction of a renal artery causes renin release[81] led investigators to conclude that the renin-angiotensin system was the cause of hypertension. But while it could be shown that unilateral or bilateral experimental lesions of the kidneys led to a rise in blood pressure, numerous observations indicated that the pathogenic mechanisms varied with the nature of the lesion and that the renin-angiotensin system probably did not play an exclusive, uniform role.

### Goldblatt Hypertension (Unilateral Renal Artery Constriction and Contralateral Nephrectomy)

In experiments with Goldblatt hypertension, doubt was cast on the exclusive pathogenic role of the renin-angiotensin system by the observation that normal renin values are sometimes measured when the blood pressure has reached a constant level.[28,87] The renin-angiotensin system could not be responsible for maintaining this type of hypertension, because neither passive renin immunization[94] nor passive immunization against angiotensin II[13] had an effect on the blood pressure; neither was it influenced by administration of a converting enzyme inhibitor.[46] On the other hand, the development of hypertension could be prevented by active immunization against angiotensin II before experimental constriction of the renal artery.[50] The most probable explanation for the absence of renin secretion and maintenance of the hypertension is the observation that unilateral renal artery constriction with contralateral nephrectomy is accompanied by a positive sodium balance, and that this sodium excess is responsible for maintaining the hypertension. The positive sodium balance is the result of a decrease in the glomerular filtration volume caused by renal artery stenosis, combined with an increase of sodium reabsorption in the proximal tubule. The blood pressure can be lowered by sodium and water withdrawal, and increased again by sodium infusion.[87] Numerous experiments have demonstrated that renin release can be inhibited by a positive sodium

balance[90] or by expansion of the extracellular volume.[63]

### Hypertension with Unilateral Renal Artery Constriction and Intact Contralateral Kidney

In this type of hypertension, the renin-angiotensin system apparently plays a more important role than the sodium balance. In all stages of this experimental hypertension the increase of plasma renin activity correlates with the increase of renin in the poststenotic kidney, while the renin content of the contralateral intact kidney is decreased.[28] Aldosterone secretion is increased in this form of hypertension, whereas normal aldosterone levels are measured in the Goldblatt form.[80] It is known that the renin-angiotensin system is involved in maintaining the hypertension under conditions of unilateral renal artery stenosis with an intact contralateral kidney, because the blood pressure can be lowered by giving renin antibodies,[94] a renin preinhibitor,[78] or pepstatin. Converting enzyme inhibitors,[67] competitive angiotensin II antagonists,[72] and angiotensin II antibodies[13] also exert an antihypertensive effect. At the same time, it has been shown that the total urinary sodium excretion in the presence of unilateral renal artery stenosis does not differ from that in normal subjects.[45] The normal sodium balance in this type of hypertension results from the combination of a unilateral stenosed kidney and a contralateral intact kidney. The initial increase in sodium absorption caused by renal artery stenosis is offset by the possibility of increased sodium excretion via the contralateral kidney. The demonstrably reduced renin content of the contralateral, unstenosed kidney is attributed to the elevated blood pressure and possibly to the decrease in sodium excretion.[90] Regulation of the sodium balance by the contralateral kidney accounts for the stimulating effect of renal artery stenosis on renin release.

### Hypertension from Bilateral Renal Artery Constriction

Activation of the renin-angiotensin system in bilateral renal arterial stenosis has been shown to be unreliable and inconsistent in experimental studies.[28] An increase of renin was found if the renal artery constriction had led to shrinkage of the kidney, while normal values were measured if no renal atrophy was apparent. If the degree of stenosis is equal on both sides, biological conditions appear to be similar to those in Goldblatt hypertension; i.e., an initial increase of renin secretion is suppressed by increasing sodium retention. If one kidney is more severely stenosed than the other, however, the less stenosed kidney can respond more sensitively to the elevated blood pressure and excrete increased amounts of water and sodium, thereby normalizing the sodium balance. In this case an increase of renin release can be measured on the more severely stenosed side.

## Clinical Aspects of Renovascular Hypertension

There are numerous clinical differences between essential hypertensive patients and patients with fibromuscular hyperplasia.[79] Patients with essential hypertension are typically older than patients with fibromuscular hyperplasia, but younger than patients with renal artery stenosis of arteriosclerotic origin. The duration of essential hypertension tends to be longer than that of renovascular hypertension. The onset of hypertension occurs beyond age 50 in over one-third of hypertensives with arteriosclerotic disease, in contrast to patients with essential hypertension (7%) or fibromuscular hyperplasia (3%). A relatively early onset of hypertension before age 20 is rarely seen in patients with arteriosclerosis (2%) but occurs in 12% of essential hypertensives and in 16% of patients with fibromuscular hyperplasia. Patients with essential hypertension and arteriosclerotic renovascular hypertension are predominantly male, while patients with fibromuscular hyperplasia are mostly female (80%). Benign hypertension progresses to the severe malignant form more frequently in patients with arteriosclerosis than in patients with essential hypertension or fibromuscular hyperplasia. A family history of hypertension and stroke is much less common in patients with fibromuscular hyperplasia than in patients with essential hypertension or renovascular hypertension of the arteriosclerotic form; the latter patients often have a history of occlusive arterial disease. Patients with essential hypertension have twice the incidence of overweight that patients with renovascular hypertension have, while one-third of patients with renovascular hypertension due to fibromuscular lesions have a slender physique. Serious stage III or stage IV retinopathy is considerably more frequent in patients with arteriosclerotic renovascular hypertension. Abdominal stenotic or flank bruits are audible in about 48% of patients with renovascular hypertension as compared to only 9% of patients with essential hypertension.

## Renovascular Hypertension Versus Essential Hypertension

In comparison with patients with essential hypertension, patients with renovascular hypertension have:

1. Shorter duration of hypertension
2. More frequent onset of hypertension after age 50 (arteriosclerosis-related)
3. 50% lower incidence of family history of hypertension
4. Higher incidence of serious retinopathy
5. Higher incidence of abdominal bruit
6. Higher incidence of proteinuria

The presence of renovascular hypertension should be suspected in:

1. Juvenile and adolescent patients (fibromuscular lesions)
2. Older patients who show a recent progression of hypertension
3. Patients who have developed hypertension secondary to abdominal trauma

## Diagnostic Measures

Noninvasive diagnostic methods, i.e., methods that do not involve arterial or venous catheterization of the renal vessels, are useful mainly in cases of unilateral renal artery stenosis. In bilateral cases, however, functional or morphologic changes are difficult to assess owing to the lack of a healthy kidney for comparison. Often a diagnosis in such cases is possible only if the degree of stenosis is different on each side, i.e., there is some lateralization of function. Moreover, the intrarenal hemodynamics and renal endocrine system in bilateral renovascular hypertension differ from those in patients with one stenosed kidney and one healthy kidney.

### Intravenous Urography

Owing to its convenience, intravenous urography is becoming increasingly important in the diagnosis of renovascular hypertension. Findings suggestive of renovascular hypertension include:[57]

1. Disparity in renal sizes. It has long been known that renal ischemia caused by renal artery stenosis leads to a decrease in the size of the affected kidney. The kidney retains its typical shape if the stenosis involves the main renal artery branch. A clear indication of this is a decrease in renal length by more than 1.5 cm. (Note that the somewhat greater physiologic size of the left kidney must be taken into account when assessing renal dimensions.)[16]
2. Disparity in visualization of the renal parenchyma. The iodinated contrast medium is excreted almost entirely by glomerular filtration. If the glomerular filtration rate is reduced as a result of stenosis, the excretion of the medium will be delayed. To document this process fully and thus enhance the diagnostic value of the test, roentgenograms should be made at 1-min intervals during the first 5 min.[55]
3. Lateral disparities in the concentration of the medium in the renal collecting system. The physiologic result of renal artery obstruction is increased water reabsorption in the affected kidney, which leads to an increased concentration of the unabsorbed medium. Although the glomerular filtration rate is diminished, an increased concentration of contrast medium in the collecting system is found during the excretory phase.[12]
4. Ureteral stenosis or notching. The constriction of a ureter by collateral vessels is considered a sign of renal artery stenosis; the upper segment is usually affected.[29]

#### Technique of intravenous urography

Fluids should be withheld for about 8–12 h before the examination, since some changes are visible only in a state of adequate dehydration. About 30 ml of contrast medium is rapidly injected as a bolus, and roentgenograms are made at 1, 2, 3, 4, 5, 10, 15, and 30 min (rapid-sequence urography).

The appearance of urographic abnormalities in renovascular hypertension is dependent on the severity of the stenosis. If stenosis is less than 50%, only a slight difference will appear in the form of delayed visualization of the parenchyma and hyperconcentration of the contrast medium, though both signs are subtle and difficult to distinguish from normal findings. In more severe degrees of stenosis, the frequency of abnormal signs increases. With renal artery stenosis greater than 80%, an abnormal urogram is seen in over 80% of cases,[8] with delayed parenchymal visualization being the most common pathologic sign. A size decrease of the poststenotic kidney is usually seen only in high-grade stenosis with consequent ischemia. However, all pathologic signs in the urogram may be masked by good collateralization of the poststenotic kidney.

### Transverse indirect arteriography

During intravenous urography it is possible to visualize the abdominal aorta and renal arteries up to the intrarenal branches by the intravenous injection of contrast material by the bolus technique (10–15 ml/s). After empirical determination of the circulatory time of the contrast medium as a function of the patient's age,[101] or the addition of a radioactive substance to the contrast medium and measurement of its arrival via the aorta,[106] the abdominal aorta and renal arteries are visualized by means of zonography[101] or simultaneous tomography with a polycassette of several x-ray films.[106] Especially with the latter technique, full visualization of the renal arteries is obtained in at least 70% of patients, with a clear demonstration of stenoses up to the branches of the main renal arteries.

A recently developed method of renal artery imaging is digital subtraction angiography.[108] This digital video arteriography following intravenous single injection of 30–50 ml of contrast medium into a peripheral vein allows for visualization of the abdominal aorta and both renal arteries. A comparison of this procedure with conventional angiography of the aorta and renal arteries demonstrated an overall accuracy of 71%. Sensitivity of the new technique was 93%, specifity 91.5% after exclusion of cases of inadequate visualization of the renal arteries.[100]

## Computed Tomography (CT)

Developments of dynamic investigations by computed tomography abnormalities of renal perfusion can be recognized more readily by sequential CT than by plain CT scan. Hemodynamically significant stenoses of the renal arteries can be diagnosed in this way demontrating a delayed accumulation of contrast medium in the renal cortex.[105,111]

## Radionuclide Studies

Adam et al. have shown in experimental animals that a fall in the poststenotic renal perfusion pressure resulting from luminal narrowing of the renal artery is accompanied by typical changes in the isotope renogram owing to the reduction of blood flow.[1] The changes in renal blood flow associated with renal artery stenosis can be assessed by simple, qualitative radionuclide methods, as well as by more involved, quantitative techniques, some of which require catheterization of the renal artery. Noninvasive methods that cause little stress to the patient include isotope renography with $^{131}$I-iodohippurate, renal function scintigraphy, sequential renal blood flow scintigraphy (radionuclide aortoangiography) for qualitative assessment of lateral disparities of renal blood flow, and the determination of tubular or glomerular isotope clearance in the separate kidneys for a quantitative assessment of renal blood flow. Newer techniques such as computed tomography offer additional possibilities for the noninvasive diagnosis of renovascular hypertension (see also Chap. 27). Invasive methods that necessitate renal artery catheterization include selective renal blood flow scintigraphy with $^{99m}$Tc and radioactive gas washout. These methods make it possible to determine the mean transit time and provide quantitative information on general or compartmental renal blood flow.

In the *isotope renogram* with $^{131}$I-iodohippurate, renal artery stenosis is characterized by a time-shift of the activity maximum in the secretory phase and an associated prolongation of the excretory phase. The changes are seen only in hemodynamically significant stenoses but provide little information on renal blood flow. Thus, despite some very optimistic results,[56] the isotope renogram is less valuable than other methods as a screening test for renovascular hypertension. Its limited reliability has considerably reduced the use of the renogram in the diagnosis of renal perfusion disorders.

*Renal function scintigraphy* with the Anger camera after the injection of $^{131}$I-*o*-iodohippurate of $^{99m}$Tc-DTPA makes it possible to classify a disturbance of radionuclide kinetics as prerenal, intrarenal, or postrenal. Thus, this method provides more detailed information than the renogram and enables a diagnosis of renal function impairment. It is considerably superior to renography as a screening method.[6a]

A recently developed noninvasive method for the general diagnosis of impaired renal blood flow is *sequential renal blood flow scintigraphy* (radionuclide aortoangiography) with $^{99m}$Tc complexes. With this method it is possible within 30 s to assess aortic perfusion and to localize renal artery stenoses or occlusions. Lateral disparities in renal blood flow are assessed qualitatively.[21,44] In the "region of interest" technique, the time-dependent activity curves recorded over the healthy kidney show a high perfusion-specific peak with an abrupt decline, while the diseased kidney shows only a weak perfusion. According to a collaborative study by Peters et al.,[72a] the sensitivity of this method is 80%, and its specificity is 93% in the presence of angiographically proven renal artery stenosis.[71a]

A standard method for assessing the renal plasma flow is the determination of *isotope renal clearance* by the slope or single-shot technique. For the si-

multaneous determination of glomerular and tubular clearance, the double-radionuclide technique with $^{131}$I-*o*-iodohippurate and $^{99m}$Tc-DTPA on the Oberhausen apparatus or camera has proved useful. The principal application of this method is in urologic diagnosis, however.

A quantitative study of renal blood flow is possible only by invasive means. By the injection of specific radionuclides (radioactive gases, $^{99m}$Tc) into the renal artery during selective renal angiography, it is possible to assess renal perfusion and intrarenal hemodynamics. The perfusion curves obtained by external measurements are either plotted graphically or evaluated by computer program. The transit times of the radionuclides correlate closely with angiographic findings; they are significantly prolonged in poststenotic kidneys. The *washout curve* for the renal clearance of radioactive gases further provides quantitative values for blood flow through the renal cortex and deeper compartments by computer analysis of the time-activity curves. In the presence of renal artery stenosis, one finds a decrease in total renal blood flow,[33] with a redistribution of intrarenal flow from the cortex to the medulla. Kidneys with arterio-arteriolosclerotic vascular changes show a decrease in the percentage of total blood flow distributed to the cortex.[4,33]

## Angiography

The most important diagnostic procedure for the detection of renovascular hypertension is renal angiography, the only method available for establishing a final diagnosis. This applies in particular to bilateral renovascular diseases, which often escape diagnosis by noninvasive means. The radiographic visualization of the renal vessels provides information on the nature and localization of stenoses and changes in parenchymal vessels, thus affording a basis for selecting an appropriate surgical treatment (Fig. 2). Angiographic findings are also useful in judging postoperative results. Renal artery stenoses caused indirectly by aneurysms, tumor compression, or periarterial hematomas can also be verified. It is assumed that a hemodynamically significant renal artery stenosis is present if a high-grade stenosis has narrowed the arterial lumen to less than 1.5 mm, the transverse diameter of the affected kidney is visibly reduced, and there is a demonstrable collateral supply via capsular, adrenal, or ureteral vessels.[9] The most widely accepted method of demonstrating the renal arteries angiographically is the transfemoral percutaneous catheter technique of Seldinger. Translumbar aortography under general anesthesia is reserved for patients with high-grade kinking and severe arteriosclerotic luminal reduction of the abdominal aorta or pelvic arteries. Proximal renal artery stenoses or constrictions of the main renal artery branches can be demonstrated by survey angiography via a pigtail catheter placed with its tip above the origin of the renal artery. Extrarenal or intraparenchymal lesions, usually associated with fibromuscular hyperplasia, can best be demonstrated by selective renal arterial angiography (Fig. 3). In many cases a straight posteroanterior projection cannot clearly demonstrate stenoses of the renal arteries; additional oblique views are recommended in such cases.

## Split Renal Function Studies

Function studies in the poorly perfused kidney are based on the observation that the ischemically damaged kidney reabsorbs an excessive amount of water and sodium per unit volume glomerular filtrate. As a result of this, higher concentrations of nonreabsorbed substances, such as PAH or inulin, can be detected in the urine. The following tests are based on this phenomenon: the Howard test,[36] the Rapoport test,[74] the Stamey test,[82] the combined Howard-Stamey test,[37] and the Kaplan test.[42] However, it appears that the results of these tests are not very reliable in terms of assessing the functional significance of a renal artery stenosis. Hence, these tests are largely of historical interest only.

## The Renin-Angiotensin-Aldosterone System

The functional diagnosis of renal artery stenosis has been greatly enhanced by observations of an interrelationship between the kidneys, adrenal glands, hypothalamus, and adrenergic system. Methods for determining the plasma renin activity have been described since 1964. It was originally thought that only hypertensive patients with high renin levels could be made normotensive by vascular reconstructive surgery or nephrectomy and thus that renin levels provided a criterion for predicting surgical curability. However, false-positive results were obtained in patients with high preoperative renin levels who failed to benefit from surgery, while false-negative results were obtained in patients with normal preoperative renin who responded favorably to surgery. The value of the determination of peripheral plasma renin activity was compromised by the fact that multiple factors such as position, medications, and diet can influence peripheral renin values. Only by the additional assay of renin activity in the venous blood of the separate kidneys did it become possible

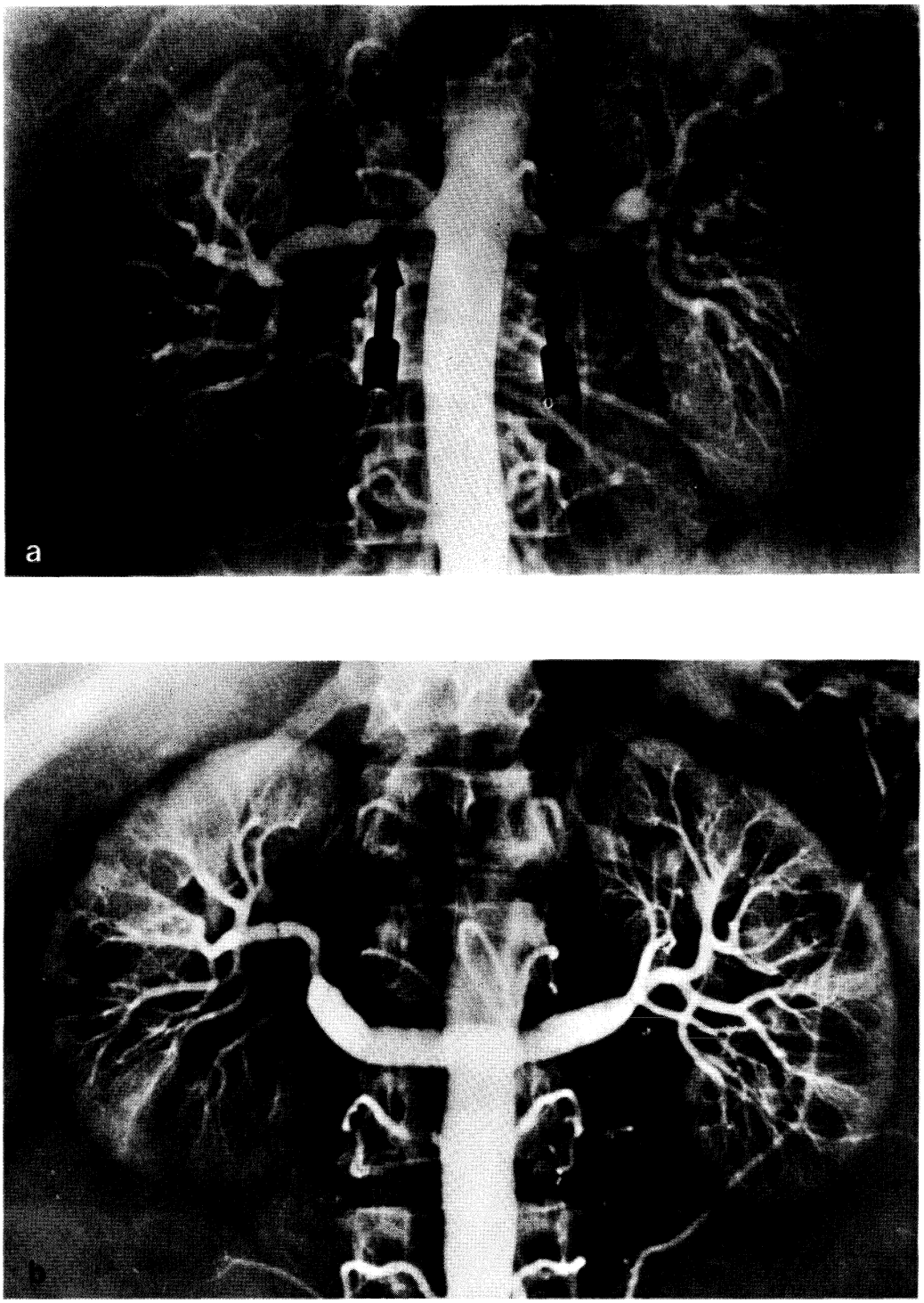


**Figure 2.** **a** Preoperative angiographic findings in bilateral arteriosclerotic renal artery stenosis. **b** Postoperative angiographic findings in the same case (bridge graft).

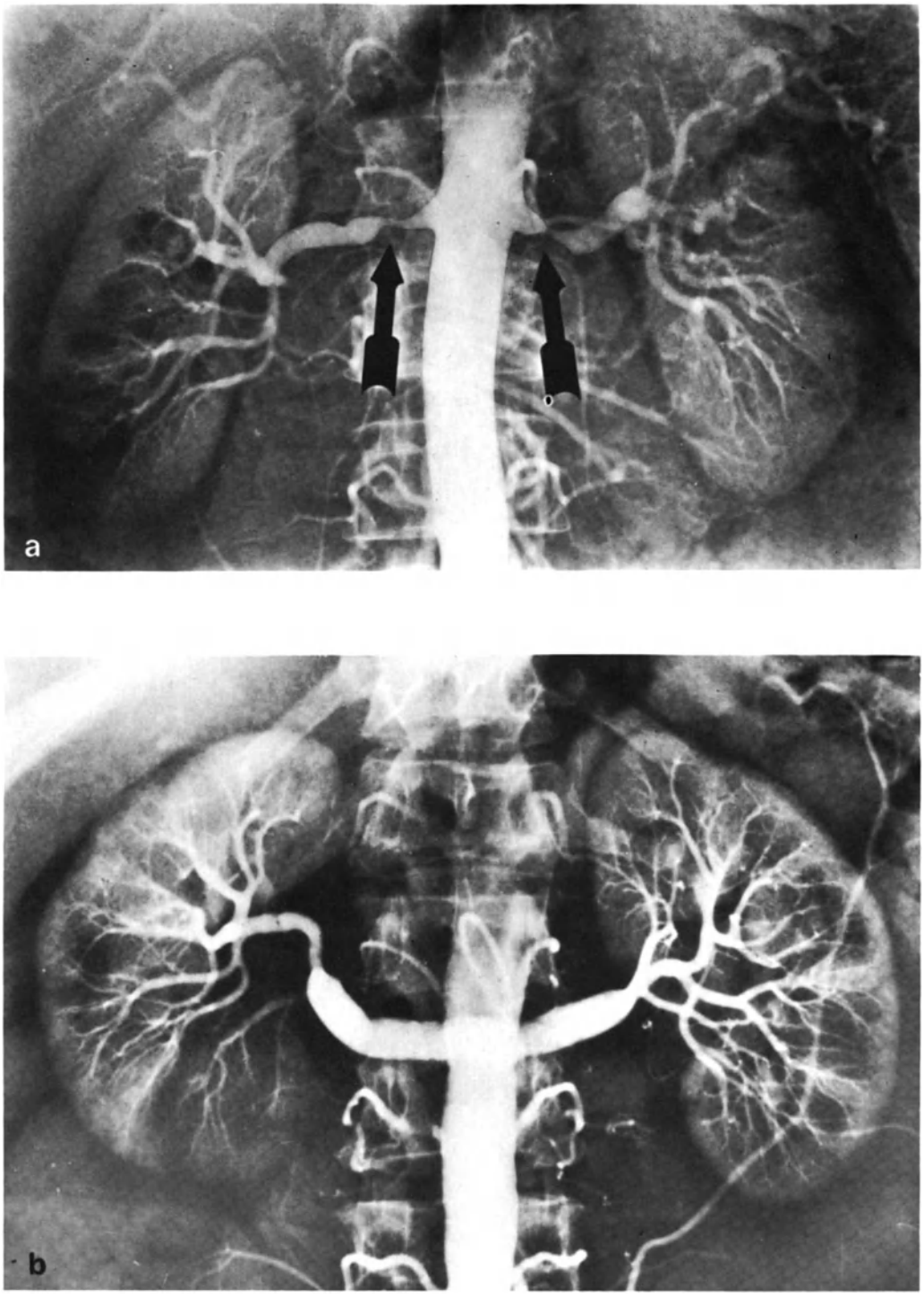


**Figure 3.** **a** Preoperative angiographic findings in unilateral (right-sided) fibromuscular medial dysplasia. **b** Angiographic findings in the same case after bypass surgery.

to assess accurately the endocrine activity of a poststenotic kidney with impaired blood flow. Comparison of the renin activity of the separate kidneys offered a promising means of obtaining diagnostic and prognostic information in patients with renovascular hypertension. Helmer and Judson were the first to report successful surgical results with the aid of this method.[32] Further successful results have been published by other authors,[2,10,20,38-40,58,65,83,84,92,97] thus confirming the functional importance of renal venous renin in hypertensive patients with renal artery stenosis. In 1973, Vaughan et al. recommended a scoring system with three criteria for determining the surgical curability of hypertension.[92] These criteria are as follows:

1. An abnormally high peripheral plasma renin activity in relation to sodium excretion as an indication of increased renin secretion.
2. A complete suppression of renin secretion in the contralateral, nonstenosed kidney (renal venous renin minus arterial renin $\simeq 0$).
3. An abnormally high renin content in the stenosed kidney as compared to the arterial renin level (renal venous renin minus arterial renin divided by arterial renin $> 0.48$), reflecting the degree of renal ischemia. Some authors consider that the criterion for operability is a ratio of 2.0 or more of the renin on the stenosed side to the peripheral renin; others state that a ratio of 1.5[84] or 1.6 or more[10] is sufficient.

### Influence of drugs on the renin-angiotensin system

Several tests have proved useful for determining the cause of a surgically curable renovascular hypertension. Besides the very simple *orthostatic test*, which provokes an increase of renin secretion,[66] drug stimulation of the renin system appears to be a particularly valuable source of information on the endocrine relevance of a renal artery stenosis.

The increase in plasma renin activity that follows the injection of tubule-active *diuretics* was primarily regarded as a response to a fall in blood volume,[71] although possible direct actions on the kidney were also considered.[63,77] On the one hand, these drugs (of which *furosemide* is the most widely used) can serve to distinguish patients with true low-renin essential hypertension from essential hypertensive patients with normal or elevated renin levels.[41] On the other hand, it has been found that furosemide, when given to renovascular hypertensive patients, can markedly stimulate renin secretion in the poststenotic kidney in comparison to the nonstenosed kidney. This has made it possible to demonstrate unilateral, hemodynamically significant renal artery stenosis even in hypertensives with angiographically proven stenosis but without significant lateralization of renal vein renin under basal conditions.[86]

In the examination, 40 mg of furosemide is administered intravenously followed 20 min later by renal vein blood sampling, or 80 mg of furosemide is given orally on the day before the test. As an alternative, *dihydralazine* may be administered iv in a dose of 20 mg or hydralazine in appropriate dosage to provoke an increase of renin secretion in the stenosed kidney.[5,51] It has been postulated that hydralazine acts by lowering the arterial pressure, by stimulating sympathetic nervous influence on the kidney, by a direct action on the juxtaglomerular cells, or by altering intrarenal hemodynamics. The criterion for a positive test is a renal vein renin ratio of 1.8–2.0 or more.[5]

A major obstacle to the detection of renovascular hypertension without invasive means is the lack of a simple, reliable screening method for differentiating patients with renovascular hypertension from those with essential hypertension. Such a test would considerably simplify diagnostic measures and lessen their cost. It would also provide a means of demonstrating the activity of segmental or bilateral stenoses which escape detection by conventional function studies. Since it has become possible to competitively block the action of angiotensin on its receptor (peripheral vascular muscle) by means of competitive antagonists, this sought-for test appears to be within reach. Numerous authors in recent years have stated that, on the basis of their results, the infusion of *saralasin* (1 sar/8 ala/angiotensin 2) a competitive angiotensin II inhibitor, represents a valuable screening test for the detection of renovascular hypertension.[3,53,85,96] The usual method consists in the continuous intravenous infusion of 10 $\mu$g of saralasin/kg/min for 30 min after the prior oral administration of 80 mg of furosemide (or stepwise increase of saralasin dose). The main sign of angiotensin-dependent hypertension is a fall of systolic and diastolic blood pressure, and fall amounting to at least 10% of the initial value in the case of diastolic pressure. There is also a measurable increase in plasma renin activity, which is significantly higher in the renal venous blood of the stenosed side than on the nonstenosed side. The main disadvantage of the method is that the effect of saralasin on the blood pressure is directly dependent on the renin levels and sodium balance in the body. Thus, it has been shown that even patients with normoreninemic essential hypertension show a fall of blood pressure in response to saralasin following adequate salt depletion, while sodium loading can even cause a pressor response to occur.[23] These varying effects at the

receptor, which are partly antagonistic and partly agonistic, make it difficult to draw unequivocal conclusions as to whether the hypertension is angiotensin-dependent. Also, the administration of saralasin carries a certain risk owing to the possibility of a hypertensive reaction.

A more reliable method of unmasking the renin-angiotensin system as the causative factor in hypertension may consist in the inhibition of the *converting enzyme* necessary for producing angiotensin II from angiotensin I. When this *inhibitor* is administered intravenously or (more recently) orally to patients with unilateral renovascular disease, it produces not only a fall of blood pressure but also a significant increase in renal vein renin activity only on the affected side, with a corresponding marked rise in the renal vein renin ratio.[75] The advantage of this method is that possible variations in the sensitivity of the angiotensin II receptors are no longer a problem, as in the case of saralasin. Thus, this converting enzyme inhibitor shows promise not only in the diagnosis of angiotensin-dependent hypertension but also, and most importantly, as a therapeutic agent.

According to recent studies with a synthetic inhibitor of the growth hormone somatotropin, the intravenous administration of this substance *(somatostatin)* in patients with hypertension of renovascular origin produces a slight fall of blood pressure together with a significant decrease in the stimulated plasma renin activity in the stenosed kidney, while effecting no significant change in the nonstimulated renin on the contralateral side.[6] It remains to be seen whether this substance will find diagnostic or therapeutic applications in angiotensin-dependent hypertension.

## Treatment of Renovascular Hypertension

### Drug Therapy

As a general rule, every attempt should be made to treat renovascular hypertension conservatively, since corrective surgery on the aorta or renal arteries represents a major operation with possible immediate and delayed complications. Besides acute restenosis and arterial thrombosis (8.5% according to Morris et al.,[68] 78% according to Van Dongen,[17] 7.5% according to Maxwell and Varady[60]), suture insufficiency, aneurysms, and bypass dilatations can occur. The postoperative mortality, usually from myocardial infarction, cerebrovascular accident, or uremia, is between 0.7 and 5.9%, depending on the author.

Since this form of hypertension is generally angiotensin-dependent and the increased renin secretion in patients with renal artery stenosis is often accompanied by a heightened sympathetic tone,[22] beta-adrenergic blocking drugs[73]—alone or combined with saluretics, $\alpha$-methyldopa or dihydralazine—have proved effective.[14] Drug therapy is indicated in any case for patients with advanced arteriosclerosis, especially coronary and cerebral sclerosis, the lower age limit being 50 to 55 years. It is advisable to perform split renal function tests in these patients at yearly intervals since progression of the stenosis is likely. The best test for this is probably a separate isotope renal clearance study with $^{131}$I-*o*-iodohippurate since it involves minimal patient stress while providing important quantitative comparative data for follow-up. Surgical treatment should be done (assuming the patient is operable) only if the stenosis of one renal artery is so severe that destruction of the kidney is inevitable.

If the hypertension does not respond adequately to conservative therapy despite optimum drug selection and dosage, or if the patient experiences serious side effects from the medication, surgical correction of the renovascular disease should be attempted.

### Percutaneous Transluminal Angioplasty

The percutaneous transluminal dilatation of stenosed renal arteries for the treatment of renovascular hypertension or maintenance of renal function has been practiced for only a short time, yet is a highly promising and elegant procedure.[66a,104,107] It basically involves the dilatation of a hemodynamically significant stenotic lesion or the rechannelization of a short arterial occlusion by pressing the atheromatous material against the vessel wall. Initially, coaxial catheters were used for this purpose,[102] but now double-lumen balloon catheters[103] are employed.

Most recent reports on percutaneous transluminal angioplasty (PTA) in patients with renal artery stenosis were able to demonstrate its usefulness in improving or curing hypertension.[106,109] A follow-up study by Tegtmeyer et al.[110] in 50 cases of renal artery stenosis treated with percutaneous transluminal angioplasty resulted in a successful dilatation of 90% of stenoses and redilatation was necessary in 22% with a success rate of 84%. Forty-two percent of the patients had normotensive blood pressure following PTA, 47% demonstrated an improvement of hypertension, only 11% retained unchanged high blood pressure values. Thus PTA appears to be a technically feasible and clinically effective method of treating renovascular hypertension. A further ad-

vantage of the catheter dilatation is its application in patients who cannot be operated on, in cases of evident restenosis or in order to improve renal function and to preserve the kidneys.

## Surgical Treatment

Since PTA increasingly yielded successful results in renal artery stenosis, invasive renovascular corrective surgery seems to be superseded by this method in many cases. Only in selected patients with a very peripheral renal artery stenosis, stenosis of a segmental artery, severe extensive stenosis, or following failure of PTA are surgical procedures of value.

In selecting candidates under age 50 for vascular surgery, preference should be given to patients with fibromuscular renal artery disease, because the operative results are substantially better in this group than in patients with stenosis due to arteriosclerotic lesions. Since the arteriosclerotic stenosis of a renal artery usually represents only one angiographic finding within a setting of generalized sclerotic changes in all the arteries, one must assume sclerotic damage to the peripheral vessels of both the stenosed and nonstenosed kidney, as well as additional stress on the arterial vascular system, especially of the nonstenosed kidney, due to the presence of hypertension. These factors considerably reduce the prospect of a surgical cure, particularly if the hypertension is of long standing.[62] The best operative results have been achieved in patients with renal artery stenosis due to fibromuscular hyperplasia and whose hypertension is of short duration. The perfusion and functional state of the contralateral kidney in cases of unilateral renal artery stenosis can be assessed qualitatively by noninvasive radiologic and radionuclide studies. The renal vein renin levels of the contralateral kidney also are often useful in providing evidence of possible preexisting damage. In the renovasogram, the peripheral arteries can be evaluated for course and luminal size, and the width of the functional renal cortex can be estimated. Most informative is the quantitative measurement of renal perfusion by radioactive gas washout, done during selective angiography. It is a costly and involved procedure but provides very accurate information on blood flow conditions in the contralateral kidney.[3,6a] Depending on the level of the determined cortical and medullary blood flow variables, it is possible to predict whether unilateral nephrectomy or vascular reconstruction is likely to normalize the blood pressure, assuming the operated kidney has normal blood flow.

### Operative procedures

***Nephrectomy.*** Nephrectomy is indicated if the kidney is nonfunctioning owing to a prerenal lesion or occlusion, is severely infarcted, has undergone ischemic shrinkage as a result of stenosis, has multiple intrarenal branch stenoses, or displays inadequate revascularization after surgery.[35]

***Vascular Reconstruction.*** In most cases, the goal of the corrective surgical treatment of renal artery stenosis is to improve renovascular hypertension; in a few cases, it is done to forestall renal failure from vascular causes. The operative outcome not only represents a problem of indication but depends in large measure on the quality of the vascular reconstruction. The primary objective in any case is to restore renal hemodynamics to normal. Various corrective operations may be considered, depending on the localization of the stenosis in the course of the extra- or intrarenal arteries.

*Proximal Stenoses (Ostium and Proximal Third).* Thromboendarterectomy (TEA) is done only if the arteriosclerotic stenosis is strictly localized. Transluminal endarterectomy of the ostium carries the risk of recurrent occlusion or rest stenosis from a residual intimal stump. The open technique with transverse arteriotomy of the aorta extending to the poststenotic portion of the renal artery permits a far better poststenotic luminal control and is particularly suited for unilateral or bilateral proximal renal artery stenosis. A patch graft is usually required in this procedure. If access to the aortic segment is difficult, an aorticorenal bypass graft is the procedure of choice in bilateral stenosis. In proximal renal artery stenosis with poststenotic elongation, surgeons are making increased use of the reinsertion method, in which case a venous patch is used to close the newly created aorticorenal anastomosis.[30]

*Peripheral Stenoses (Middle and Distal Third, Segment Arteries).* The majority of cases involve fibromuscular hyperplasia, which generally requires reconstructive grafting, especially when a long vascular segment is affected. The preferred method is autologous unilateral or bilateral aorticorenal venous bypass (usually a saphenous graft) or Dacron bypass. Dilatation is not usually attempted.[50a] In the majority of cases, partial *ex situ* reconstruction, in which the artery is divided while the vein and ureter are left intact, represents a time-saving procedure. The much-publicized complete *ex situ* reconstruction, with division of all renal vessels, cold perfusion of the organ, and reimplantation in the pelvic area, is indicated only in exceptional cases. The simulta-

neous correction of peripheral, poorly accessible stenoses is of particular importance. The segmental arteries, which are frequently involved in fibromuscular hyperplasia, are dilated before the completion of distal graft attachment by the introduction of olive-tipped dilators or by angioplasty using microsurgical techniques.[66a]

*Combined Vascular Stenoses and Occlusions.* The most frequent operations are for occlusive lesions of the terminal aorta, aneurysms of the aorta, or occlusive lesions of the superior mesenteric artery or celiac trunk. Because such combined procedures carry a correspondingly greater risk, their indications must be strictly defined. Accompanying complete or partial occlusions of the aortic bifurcation are best corrected with bypass grafting, while simultaneously correcting the unilateral or bilateral renal artery stenosis with an aorticorenal Dacron bypass or (for proximal arteriosclerotic stenosis) by transluminal endarterectomy or open TEA with aorticorenal arteriotomy. For accompanying stenoses of the superior mesenteric artery, the preferred procedure is reinsertion of the vessel into the anterior wall of the aorta or vascular prosthesis.[93] Prostheses are acceptable if no suitable venous graft is available and if the time factor is important in high-risk cases (e.g., in combined procedures on the aorta and renal arteries).

### Results of surgical treatment

The principal immediate complications of arterial reconstructive surgery are hemorrhage, arterial thrombosis, renal vein thrombosis, restenosis, and acute renal failure.

In the large cooperative study of Maxwell and Varady, the overall mortality in a total of 502 operations was 5.9%, the main causes of death being postoperative uremia, hemorrhage, and myocardial infarction.[60] Patients with arteriosclerotic disease had a significantly higher mortality (9.3%) than patients with fibromuscular hyperplasia (3.4%). The mortality rate was particularly high among patients with coronary heart disease whose operations for bilateral renal artery stenosis were prolonged and complicated. A surprisingly large number of patients whose blood pressure did not improve after surgery showed thrombosis of the reconstructed artery in the postoperative renovasogram. Of the patients for whom lateralization was established by preoperative tests and who suffered no postoperative thrombosis of the reconstructed vascular segment, 78.7% responded favorably to the vascular reconstruction, i.e., displayed an improvement or normalization of blood pressure. The results in patients with fibromuscular hyperplasia were markedly better on the whole than in patients with renal artery stenosis due to arteriosclerotic causes. If complications associated with errors of technique are disregarded, arterial reconstruction yielded better postoperative results than nephrectomy; however, postoperative vascular complications tended to negate this difference. Our own studies indicate that of 56 patients with angiographically proven unilateral renal artery stenosis who received operative treatment (42 bypass, 14 nephrectomy), 32 (55%) became normotensive after surgery, while 19 (32%) were improved, and 7 (13%) were unimproved. Of the 51 patients who benefited, 47 showed lateralization in preliminary radionuclide studies ($n$ = 43) or renal vein renin assays ($n$ = 40). Four patients benefited from surgery despite normal nonlateralized renin levels and unremarkable radionuclide findings; vascular surgery in such cases was prompted by high-grade stenosis established angiographically.[5,6a]

In a study recently published by Maxwell et al. dealing with the prognostic value of renin assays in renal artery stenosis,[58] mention is made of 23 patients who benefited from surgery despite the absence of lateralization. In two patients, renin-angiotensin activity could be excluded on the basis of normal renin and aldosterone levels as well as the absence of a depressor response to the angiotensin II antagonist, saralasin.[51] This prompted the authors to postulate an angiotensin-independent form of renovascular hypertension.

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# Urologic Aspects of Renal Hypertension

# 17

M. Ziegler, G. J. Mast

Renal hypertension is the most frequent form of secondary hypertension and accounts for 25% to 30% of hypertensive disease. Since renal hypertension is in principle amenable to causal surgical therapy, its diagnostic differentiation from other forms of hypertension is of therapeutic importance. For this, a knowledge of the pathophysiology of renal hypertension is required, derived on the basis of experimental and clinical findings.

## History of Renal Hypertension Research

Bright first postulated a connection between renal disease and high blood pressure in 1836.[18] In 1898, Tigerstedt and Bergman were able to show that the kidney performs endocrine functions in addition to its excretory role.[171] In aqueous extracts from the renal cortex of normal rabbits, they discovered a thermolabile, nondialyzable substance with a hypertensive action; they called this substance *renin*. Since then, researchers have attempted to induce high blood pressure in many species of laboratory animals by subjecting the kidney to various surgical manipulations. The results of such research have frequently been unsatisfactory or contradictory.[103]

For example, while hypertension was not induced by bilateral nephrectomy, the blood pressure could be raised by resecting up to five-sixths of the renal parenchyma. Physical trauma to the renal parenchyma by cauterization or deep X-irradiation was accompanied by a moderate hypertension. Chemical lesion of the renal parenchyma by mercury and lead or by intrarenal injection of trypsin was not convincing in terms of hypertensive effects. Masugi employed a specific antigen-antibody reaction in rabbits to produce a disease syndrome that resembled human glomerulonephritis and that was accompanied by an elevation of blood pressure. Hypertension could also be induced by urinary stasis produced by ureteral clamping or ligature, as well as by clamping of the renal vein.[75] External compression of the renal parenchyma with an oncometer caused only slight blood pressure increases in acute experiments. By contrast, Page conducted chronic experiments with dogs in which the kidney was wrapped in cellophane film; this produced a scarring "cellophane perinephritis" which compressed the kidney and led to hypertension.[67]

Attempts to induce hypertension by restricting the arterial blood flow to one kidney were first described by Katzenstein in 1905.[83] Influenced by Volhard, who employed the clinical classifications of "red" and "pale" hypertension and assumed a humoral agent of renal origin (renin?) for the latter, Hartwich was able in 1930 to induce hypertension in dogs by ligature of individual renal artery branches as well as by clamping the main artery.[75] In 1934, Goldblatt et al. first produced persistent renal hypertension in dogs, with blood pressure values above 200 mm Hg.[62]

Since then it has been shown that hypertension can be induced in a wide variety of experimental animals by restricting the blood flow to one kidney, with or without contralateral nephrectomy, or by clamping the aorta above or between both renal arteries. The best experimental animal in terms of reproducibility of hypertension has been the rat.[67]

After Tigerstedt and Bergman pointed out that their discovery, renin, might be of importance in the development of renal hypertension,[171] this substance

became the focal point of hypertensive research for more than 50 years.

In 1940 it was shown that renin does not itself exert a hypertensive action but acts as an enzyme to liberate the vasopressor angiotensin from its substrate angiotensinogen.[17,125] Angiotensin was first isolated in 1956[50,148] and was first synthesized in 1957.[19,158] Since then the site of origin of renin has been more accurately determined, the extrarenal occurrence of renin has been demonstrated, and the biochemical reaction scheme leading to angiotensin has been largely elucidated.[68]

Further investigations have shown that besides the renin, erythropoietin, and vitamin D systems, the kidney also possesses a renal prostaglandin system as well as a renal kallikrein-kinin system.[180]

## The Renin-Angiotensin System

The reaction scheme characteristic of the renin-angiotensin system is illustrated in Figure 1.[68] Renin is a proteinase which liberates the decapeptide angiotensin I from the substrate angiotensinogen, a protein of the $\alpha_2$-globulin fraction. In the presence of chlorine ions, the converting enzyme splits off two *C*-terminal amino acids from angiotensin I, changing it to the octapeptide angiotensin II, a powerful vasopressor. The latter is immediately broken down into inactive polypeptides by ubiquitous endo- and ectopeptidases (angiotensinases).

More recent investigations have shown that this reaction involves additional inhibitors and activators from the renal prostaglandin and kallikrein-kinin systems, which interact with the renin-angiotensin system. According to these studies, the converting enzyme is identical to kininase II, which catalyzes the breakdown of the kinins.[159]

By substituting sarcosine and alanine for the *N*-terminal and *C*-terminal amino acids of angiotensin II, respectively, the angiotensin II analog 1-sarcosine-8-alanine-angiotensin II is obtained. This octapeptide is a competitive inhibitor of angiotensin II and is undergoing experimental and clinical testing under the name *saralasin*.[124,166]

### Site of Formation and Storage of Renin

The site of renin formation and storage is the juxtaglomerular apparatus (JGA) of the glomerulus[34,64] (Fig. 2). It forms a spatial and functional unit which is permeated by a dense network of adrenergic terminal nerve fibers. Reportedly, cholinergic nerve fibers are also present.[127] The juxtaglomerular apparatus is formed by the following structures:

1. *Granular epithelioid cells,* which are located in the wall of the afferent arteriole just before its juncture with the glomerulus. The microstructure of these cells shows the typical characteristics of endocrine-active cells. The granules in the cells, which are demonstrable by histochemical, fluorescent-microscopic, and electron-optical means, are closely associated with the Golgi complex and are considered the morphologic substrate of renin. Under experimental conditions

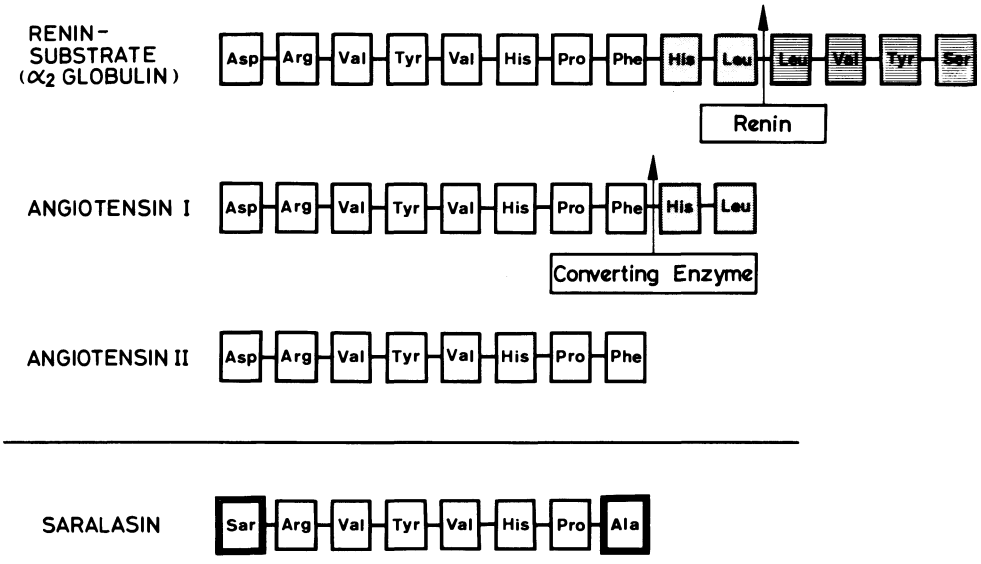


**Figure 1.** Reaction scheme of the renin-angiotensin system.

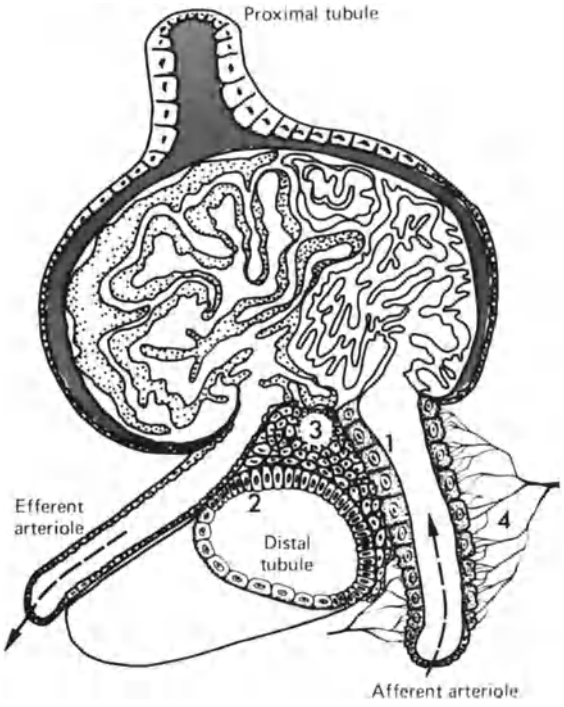


**Figure 2.** Juxtaglomerular apparatus: (1) granular juxtaglomerular cells; (2) macula densa; (3) agranular juxtaglomerular cells (Goormaghtigh cells, polkissen); and (4) adrenergic nerve endings.

the number of granules correlates with the renin content of the kidney.

2. The *macula densa*, a zone located in the distal renal tubule where it makes contact with the vascular pole of the glomerulus. This part of the tubule differs from the rest by the denser arrangement and more cylindrical shape of its cells. The macula densa is separated from the epithelioid granular cells by only a simple continuous basement membrane.
3. The *granular juxtaglomerular cells* (called also *Goormaghtigh cells* and *polkissen*), located in the angle formed by the afferent and efferent arterioles. They are modified smooth-muscle cells which interconnect the afferent and efferent arterioles, macula densa, and mesangium of the glomerulus by means of long, highly ramified cytoplasmic extensions. Their functional significance is still obscure.[34]

## The Regulation of Renin Formation and Release

The regulation of renin formation and release in the juxtaglomerular apparatus is extremely complex. Renin release in the kidney is influenced by changes in hemodynamic factors such as blood volume or renal perfusion pressure as well as by changes in sodium intake; i.e., an indirect correlation exists both between the circulating blood volume[190] and renin release, and between sodium intake and renin release. Four mechanisms are known whereby renin release is controlled.[39,68]

1. By *vascular baroreceptors* in the wall of the afferent arteriole, which respond to changes in wall tension. A decrease in wall tension due to a fall of renal perfusion pressure (blood volume) stimulates renin release, while a rise of perfusion pressure suppresses it.
2. By *adrenergic nerve endings*, renin release in the JGA can be controlled through direct and indirect stimulation independently of the vascular receptors. Intrathoracic pressure and blood-volume changes appear to influence renin secretion via a reflex mechanism.[112,190]
3. By *humoral substances* such as catecholamines, angiotensin II, and sodium, which have varying mechanisms of action.
4. By the *macula densa mechanism* (Fig. 3). A fall of renal perfusion pressure (sodium restriction?) (1) causes a decrease in the glomerular filtration rate (2) which in turn leads to a decrease in the sodium (chloride?) concentration in the distal tubule fluid at the macula densa (3). Via a negative-feedback mechanism the macula densa stimulates renin release (4), which leads to a local increase in the production of angiotensin II (5)

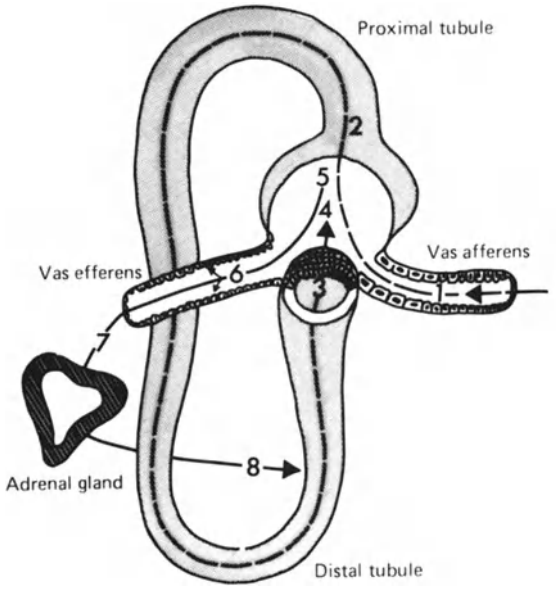


**Figure 3.** Macula densa mechanism.

Angiotensin II can again increase the glomerular filtration rate by constricting the vas efferens (6), while simultaneously stimulating the secretion of aldosterone in the glomerular zone of the adrenal cortex (7). Aldosterone itself leads to an increase in tubular sodium reabsorption (8).

## Physiological Functions of the Renin-Angiotensin System

Before Gross demonstrated physiologic functions for renin in 1958,[69] it was thought that the renin-angiotensin system played an exclusively pathogenic role in renal hypertension, owing to the vasoconstricting action of angiotensin. On the basis of studies in rats, Gross postulated that renin controls the secretion of aldosterone in the adrenal cortex via angiotensin and thus plays a role in the regulation of the sodium balance. Subsequent studies have demonstrated several physiologic functions for renin-angiotensin geared toward the maintenance of a constant blood pressure. This is accomplished by the direct action of angiotensin II on the resistance vessels as well as indirectly by maintaining homeostasis of the electrolyte and water balance, and thus of the blood volume. In summary, angiotensin II regulates the electrolyte and water balance both by renal mechanisms, such as glomerular filtration rate and tubular sodium reabsorption, and by its influence on aldosterone secretion in the adrenal cortex, the thirst center in the hypothalamus, and the secretion of antidiuretic hormone in the hypothalamus and neurohypophysis.[39,68]

## The Renin-Angiotensin System and Experimental Renal Hypertension

The significance of the renin-angiotensin system in the pathogenesis of renal hypertension has been investigated most frequently using renovascular hypertension as a model. The most suitable animal for such experiments has proved to be the rat, in which—analogous to human disease syndromes—renovascular hypertension can be produced by various surgical procedures (Fig. 4).

*Clamping a renal artery* (0.2 mm) *while leaving the contralateral kidney intact* in rats weighing 80–120 g leads to an increase in the renin content of the ischemic kidney within 3 days, while the renin content of the contralateral kidney falls within 21 days. The increase in the renin content of the ischemic kidney is paralleled by an increase in plasma renin activity; the blood pressure starts to rise 1–2 days thereafter and reaches hypertensive levels after 3–4 weeks.[190] Thus, while the blood pressure is not a direct temporal correlate of the rise in plasma renin activity, this rise is accompanied by a parallel increase in the plasma aldosterone level.[149] On the one hand, the increased formation of angiotensin II that accompanies the elevated plasma renin activity

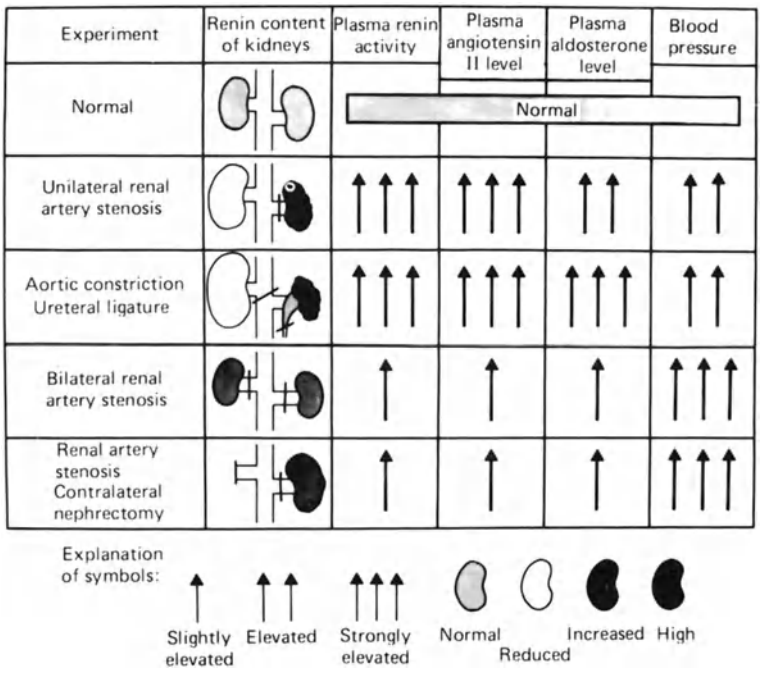


**Figure 4.** Renin content of the kidneys, plasma renin activity, plasma level of angiotensin II, plasma level of aldosterone, and blood pressure behavior in various hypertension models in the rat.

causes a natriuresis with water loss in the contralateral kidney; on the other, angiotensin exerts a sodium-conserving effect by the stimulation of aldosterone secretion.

The significance of secondary hyperaldosteronism in the pathogenesis of renal vascular hypertension is demonstrated by studies in adrenalectomized rats which received small replacement doses of cortisone. The clamping of a renal artery did not cause hypertension in these animals, although the renin content of the ischemic kidney increased markedly.[80] In other experiments it could be shown that in rats with hypertension induced by the narrowing of a renal artery, adrenalectomy leads to a normalization of blood pressure. This fall of blood pressure cannot be prevented by aldosterone replacement alone but can be averted if sodium or common salt is administered concurrently.[185] The importance of salt or sodium in renovascular hypertension is demonstrated by the fact that the blood pressure of rats with renovascular hypertension can be lowered by salt restriction, while the renin concentration in the blood continues to rise.[113] This suggests that the renin-angiotensin system is only indirectly involved in the origin and maintenance of renovascular hypertension, probably through the stimulation of aldosterone secretion. The accompanying increase in the sodium content of the arterial walls is associated with a heightened reactivity of the vascular system to vasopressor substances such as norepinephrine and angiotensin.[185]

Evidence for the importance of the renin-angiotensin system in the origin of renovascular hypertension is provided by studies in animals with renovascular hypertension, in which the effect of the inhibition of renin or angiotensin on blood pressure was investigated. While the results obtained with antirenin and antiangiotensin[185] were contradictory, the blood pressure could be lowered by administering specific competitive inhibitors of angiotensin II (angiotensin II analogs) or by inhibition of the converting enzyme.[20,124,134]

In rats weighing 150 g, clamping a renal artery (0.2 mm) while leaving the contralateral kidney intact produces a blood pressure elevation which is accompanied in some animals by a sodium- and water-losing syndrome, and thus by a further stimulation of the renin-angiotensin system and a further rise of blood pressure. This creates a vicious cycle (malignant hypertension) which often leads to the death of the animal. The sodium and water loss results both from an increase in angiotensin II production and from the pressure load on the contralateral kidney, which may exhibit malignant vascular changes during this phase.[43]

*Constriction of the aorta between the right and deeper-branching left renal artery* in rats also produces a malignant hypertension accompanied by sodium and water loss. In this situation the left kidney retains sufficient blood flow to maintain vitality but loses its excretory function, so that simultaneous ureteral ligature produces no stasis symptoms. Morphologically, the left kidney resembles an endocrine organ (Selye: "endocrine kidney") whose renin content is markedly increased, while the renin content of the contralateral pressure-loaded kidney is reduced.[28] The high-renin content of the left kidney is accompanied in turn by a rise in the plasma concentration of renin, angiotensin II, and aldosterone, as in rats with a clamped renal artery and intact contralateral kidney.

If, on the other hand, *one kidney* of the rat *is extirpated and the artery of the remaining kidney is clamped,* hypertension indeed develops within a few days, but the renin content of the ischemic kidney and the plasma renin and aldosterone levels occupy the range of concentrations found in rats with intact kidneys.[149,191] However, it is known that the plasma renin activity is strongly reduced after unilateral nephrectomy alone;[112,185] as a result, restricting the blood supply to a solitary kidney is accompanied by a slight rise of plasma renin activity. The failure of the plasma renin activity to increase further is explained by the absence of a contralateral sodium- and water-losing kidney. The slight increase in the plasma levels of renin or angiotensin II and aldosterone is accompanied by sodium retention. This leads on the one hand to hypernatremia with an elevated cardiac output and on the other to a heightened reactivity of the resistance vessels to tonicizing substances such as catecholamines and angiotensin II, owing to the increased deposition of sodium in the walls of these vessels.[185]

A similar mechanism must be assumed for the pathogenesis of hypertension in rats in which the *clamping of both renal arteries* is accompanied by high blood pressure but no significant change in plasma renin levels. Again, this is apparently due to the absence of an "intact" sodium- and water-losing kidney.[67,70]

Increased sodium and water retention must also be considered the pathogenic mechanism in "cellophane perinephritis." After one kidney is wrapped in cellophane in the dog, cat, and rabbit, a perinephritis develops which produces renal scarring and compression.[67] In this situation the blood pressure rises only slightly in the presence of a contralateral kidney, whereas simultaneous extirpation of the contralateral kidney leads to hypertension accompanied by a normal or subnormal plasma renin activity—similar to the case in which the blood supply to a solitary kidney is restricted. Thus, the mecha-

nism of hypertension in this model is apparently similar to that involved in restricting the blood flow to a solitary kidney.[27]

Whereas in renovascular hypertension renin secretion in the kidney appears to be stimulated by baroreceptors located in the vas afferens, other studies indicate that the increased renal renin secretion that accompanies hypertension due to *urinary stasis*[174] is controlled by the macula densa receptor. This was proved in experiments on isolated canine kidneys in which increased renin secretion was observed following ureteral clamping at a constant renal perfusion.[82] Other experimental findings indicate that, at least at the onset of hypertension in urinary stasis, renin secretion is increased in the affected kidney,[175] and clinical evidence shows that the hypertension in chronic urinary stasis is accompanied by hyperreninemia of the involved kidney.[2,6,29,38,57,87,119,155,157,168,181]

## The Renal Prostaglandin and Kallikrein-Kinin Systems

Until recently, interest was focused primarily on the renin-angiotensin system in explaining the pathogenesis of experimental hypertension in the models discussed. However, more recent studies have shown that an interrelationship exists between this system and the renal prostaglandin and kallikrein-kinin systems. These renal tissue hormones exert an effect which is more or less antagonistic to the renin-angiotensin system through their influence on vascular resistance and renal salt and water excretion. There is not only a close biochemical interaction among the three systems (as mentioned earlier), but also an interrelationship of physiologic regulatory mechanisms. As a result, several factors must be taken into account when assessing the role played by individual systems in certain physiologic or pathophysiologic states.

The physiologic functions of the renal kallikrein-kinin system are still largely unknown. This system is probably involved in the regulation of renal blood flow and salt and water excretion, whereby the natriuretic and diuretic action of the kinins is mediated by the renal prostaglandins. The prostaglandins, moreover, have varying effects on vascular tone.

Prostaglandin $E_2$ administered intra-arterially leads to vasodilatation in the arterial system and antagonizes the vasopressor effects of angiotensin II and norepinephrine. It also reduces neurotransmission, stimulates sodium transport at biological membranes, and inhibits the action of ADH in the distal tubule. Prostaglandin $F_{2\alpha}$, on the other hand, directly or indirectly enhances the vasoconstricting effect of such vasopressors as angiotensin II and norepinephrine.[180]

Although the exact physiologic interaction of these systems is still obscure, it may be assumed that both systems participate with the renin-angiotensin system in the regulation of salt and water homeostasis and blood pressure through their synergistic and antagonistic effects on the sodium chloride and water balance and the adjustment of vascular tone.[81,96]

Uncertainty still exists as to the pathogenic importance of the renal prostaglandin and kallikrein-kinin systems in renal hypertension. It is known that prostaglandins are capable of lowering the blood pressure both in normotensive animals and in hypertensive animals with various forms of experimental hypertension. It is probable, therefore, that the renal prostaglandins act on renal blood flow and natriuresis to antagonize the renin-angiotensin system and sympathetic nervous system and so carry out the antihypertensive function of the kidney.[95]

A correlation was shown to exist between the degree of hypertension and the decline in renal prostaglandin production in rats with a clamped renal artery and intact contralateral kidney.[151] By contrast, patients with renovascular hypertension have demonstrated an increased prostaglandin content in the papilla of the ischemic kidney[167] as well as an increased serum prostaglandin level in the affected kidney.[48] Further research is needed before a final assessment can be made of the significance of the renal prostaglandin and kallikrein-kinin systems in renal hypertension.

## Clinical Forms of Renal Hypertension

All forms of experimental renal hypertension have their clinical correlates. Prerenal, renoparenchymal, and postrenal diseases, whether unilateral or bilateral, may be associated with hypertension. On the other hand, renal disease and hypertension may coexist independently of each other. Then, when hypertension is discovered, it is necessary to determine whether a renal disease is present and, if so, whether it triggered the hypertension or exists independently of it.

The demonstration of a renal cause for hypertension is particularly important when a urologic (i.e., surgically correctable) disease is involved, and thus causal treatment is possible in principle. Only the forms of renal hypertension listed in Table 1 under facultative unilateral renal diseases will concern us here.

**Table 1.** Renal Diseases Which May Be Associated with Hypertension

1. *Bilateral renal diseases*
   Acute and chronic glomerulonephritis
   Acute and chronic interstitial nephritis
   Pyelonephritis
   Glomerulosclerosis (Kimmelstiel-Wilson syndrome)
   Amyloid kidney
   Nephropathy of pregnancy
   Bilateral cystic renal degeneration
   Inflammatory vascular diseases of the kidney (Periarteritis nodosa, lupus erythematosus, scleroderma, endangiitis obliterans)
2. *Facultative unilateral renal diseases*
   a. *Prerenal factors*
      Renal artery stenosis
      Arteriovenous fistula
      Renal artery aneurysms
      Multiple renal arteries
      (Ligature of a segmental artery)
      Renal infarction
      Renal vein thrombosis
      Trauma with intimal lesion
   b. *Renoparenchymal factors*
      Pyelonephritis
      Segmental hypoplasia (Ask-Upmark)
      Renal tuberculosis
      Renal trauma (perirenal hematoma)
      Solitary acquired renal cysts
      Tumors of the juxtaglomerular apparatus
      Hypernephroma
      Nephroblastoma (Wilms' tumor)
   c. *Postrenal factors*
      Urinary stasis of varying etiology
3. *Hypertension due to chronic renal failure*
   Indication for bilateral nephrectomy
4. *Hypertension following renal transplantation*

## Diagnosis

The diagnostic procedures available for detecting renal hypertension are numerous and varied; they cannot and should not all be employed in every case. Only if the underlying disease warrants, or if the outcome of the basic diagnosis is positive (Table 2), should further, more sophisticated diagnostic investigations be performed.

The *anamnesis* is seldom informative, especially in the case of renovascular hypertension. Only in hypertension due to inflammatory renal disease are anamnestic data in the form of recurrent urinary tract infections important. The level of the blood pressure itself and the course of the hypertension cannot be taken as differential diagnostic criteria, although the diastolic blood pressure values of patients with renal hypertension are slightly higher than in patients with essential hypertension. Nor does the age of the patient represent a useful criterion, since essential hypertension commonly occurs at a young age. Audible abdominal bruits are rare and, if present, are difficult to distinguish from aortic sounds. Nevertheless, the first step in the differential diagnosis is to obtain a detailed anamnesis and conduct a clinical examination in order to locate possible nonrenal causes of the hypertension. This is followed by a qualitative and quantitative urinalysis as well as a determination of serum creatinine, urea, sodium, and potassium (hyperaldosteronism?).

Excretory urography, perhaps in the form of an early urogram, plays a central role in further diagnosis. If lateral disparities in the excretion or pole-to-pole diameter of the kidneys or changes in the contour or collecting system of a kidney point to impaired blood flow or parenchymal destruction, a renal cause for the hypertension must be considered. A hypermobile kidney, which may cause hypertension as a result of impaired blood flow or intermittent urinary outflow obstruction, is demonstrated by excretory urography in a standing position. In cases of chronic urinary tract infection and demonstrable parenchymal damage, vesicorenal reflux should be excluded as a cause (see Chap. 27).

Of even greater importance in the diagnosis of renovascular as well as renoparenchymal hypertension are the separated renal clearances of Hippuran 131 and phase scintigraphy, which are useful in detecting functionally significant renal artery stenoses and unilateral parenchymal diseases in the separate kidneys (see Chap. 28).

The saralasin infusion test may prove to be another valuable aid in the diagnosis of renal hypertension.[21,107,124,166] In this test saralasin is in-

**Table 2.** Diagnosis of Renal Hypertension

1. *Basic diagnostic investigations*
   a. Anamnesis
   b. Urogram (early urogram) (see Chap. 27)
   c. Radioisotope studies (see Chap. 28)
      (1) Hippuran 131 clearance
      (2) Phase scintigraphy
   d. Saralasin test
2. *Further diagnostic investigations*
   a. Renovasography (see Chap. 27)
   b. Determination of plasma renin activity in the peripheral venous blood and in the renal venous blood of the separate kidneys

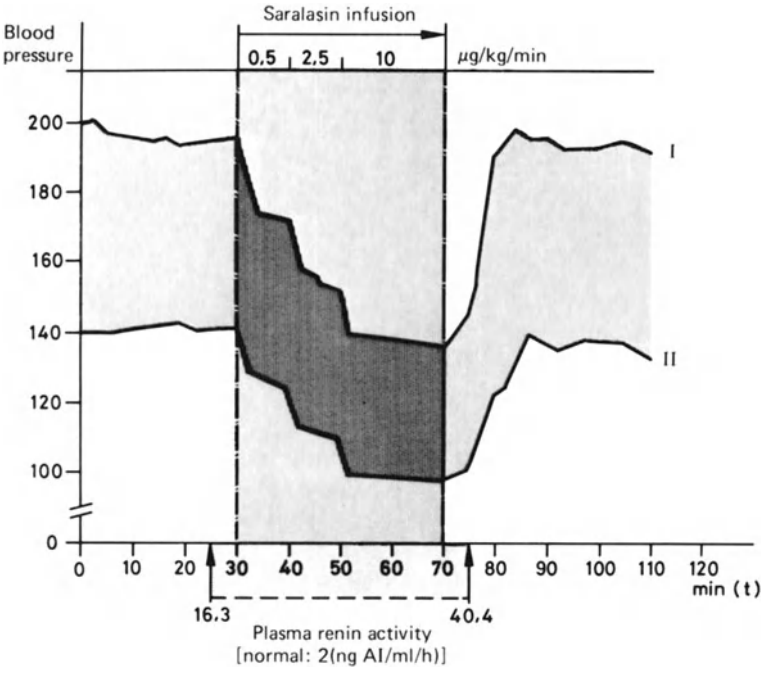


**Figure 5.** Saralasin infusion test in 22-year-old woman with left renal artery stenosis due to fibromuscular disease; dose-dependent fall of blood pressure during saralasin infusion; marked rise of peripheral venous renin activity during saralasin infusion; immediate rise of blood pressure to initial values after completion of infusion; blood pressure normalized following correction of stenosis by venous interposition. (I, systolic; II, diastolic.)

fused under standard conditions, causing a competitive inhibition of angiotensin II present in the blood. If this provokes a fall of blood pressure, it may be assumed that the hypertension is due to stimulation of the renin-angiotensin system. However, this test is still in the clinical trial stage, and so a final assessment cannot yet be made regarding its suitability as a screening method (Fig. 5).

If the excretory urogram and radioisotope studies show signs of a unilateral renal disease, it is necessary to proceed with further diagnostic investigations. The only method of demonstrating renal artery disease, for example, is renal arteriography (see Chap. 27). Because not every angiographically demonstrated renal artery stenosis nor every morphologically or functionally recognized unilateral renal lesion produces hypertension, a connection between proven unilateral renal disease and elevated blood pressure can be established only by assaying the plasma renin activity in the peripheral venous blood as well as in the renal venous blood of the separate kidneys.

The importance of determining the peripheral venous renin activity lies primarily in the detection of functionally significant renal artery stenoses. The determination should be made both at rest (following 8-h bed rest before rising) and during stimulation (1 h of activity or 40 mg of furosemide orally). Stimulation, particularly in the case of hypertension from renal artery stenosis, leads to a much greater renin release than in other forms of hypertension. If no increase in peripheral venous renin activity is seen under conditions of stimulation, the cause of this and the hypertension may be primary hyperaldosteronism due to a solitary adrenocortical adenoma (Conn's syndrome). Supplementary diagnostic tests in the form of aldosterone analyses are necessary in such cases.[45]

Based on clinical results, the peripheral venous renin assay is reliable in terms of associating a unilateral renovascular or renoparenchymal disease with hypertension only if its outcome is positive during rest and stimulation. Further diagnostic evidence can be obtained with the aid of the separated renal vein renin assay. This test is based on the principle discovered in the animal experiments described above, namely, that the renin content of the ischemic kidney is increased while that of the contralateral intact kidney is reduced. Corresponding disparities in the renal vein renin activity of the separate kidneys can be measured in patients with functionally significant renal artery stenosis. Demonstration of the suppression of renin secretion in the normal kidney and an elevated renin secretion in the affected kidney relative to the contralateral side is the determining factor for a diagnostic or preoperative prognostic assessment of the functional significance of a renal artery stenosis. The final re-

quirement is met if the ratio of the plasma renin activity of the affected kidney to that of the normal kidney is greater than 1.5. The suppression of renin secretion in the contralateral kidney is expressed in a ratio of less than 1.3 between the contralateral renal vein renin activity and the inferior vena cava renin activity below the renal veins. Under these conditions, the blood pressure can be normalized by correcting the stenosis.[13,52,164,176,184] The same conditions in terms of peripheral and renal vein renin activity must be satisfied in hypertension due to unilateral renoparenchymal disease or urinary stasis if the hypertension is to be amenable to surgical cure.

In certain situations, such as pyelonephritic parenchymal scars, segmental renal infarction, and tumors of the JGA, hypertension is the result of a segmental renal hyperreninemia. This is not manifested during separate determinations of serum renin activity in the main renal veins but can be demonstrated only by selective determination of the renin activity in the segmental veins of one or both kidneys.[91,101,145,163]

Radioisotope techniques and the separated renal vein renin assay have substantially improved the preoperative prognosis of blood pressure behavior after surgery and have replaced other techniques which today are of only historical interest. These include the split renal function studies with bilateral ureteral catheterization by the technique of Howard, Rapoport, and Stamey.[74] The key to recent advances was the development of methods for determining the plasma renin activity, which today is done by radioimmunoassay.[31] The strict maintenance of standardized conditions is essential for every determination. Aside from the determination under conditions of rest and stimulation, it is important that the patient remain on a normal sodium diet and that no medications be given which would alter the plasma renin activity. When obtaining the anamnesis, moreover, the physician must be particularly alert for the use of ovulation inhibitors, as these may raise the plasma renin activity as well as angiotensinogen levels and thus elevate the blood pressure.[183]

## Facultative Unilateral Renal Diseases

### Prerenal Factors—Renovascular Hypertension

In accordance with experimental findings, *renal artery stenosis* may be associated with hypertension in humans as well. What is required is a specific narrowing of the lumen of the renal artery; in other words, not every angiographically proved renal artery stenosis is functionally significant. This can be assumed only if the ratio of the renal vein renin activities of the separate kidneys is greater than 1.5, or renin suppression in the contralateral kidney is demonstrated. In these cases, relief of hypertension by surgical correction of the vascular stenosis has a success rate of approximately 90% (Fig. 6). Most failures result from the fact that the hypertension has already caused vascular lesions in the contralateral kidney which are manifested preoperatively in an undetected suppression of renin secretion.[13,52,164,176,184,185]

Although the correction of renal artery stenoses has been largely the domain of the vascular surgeon in the past, new urosurgical techniques now enable the urologist to treat these diseases in many cases. Most important are the techniques of organ conservation and transplantation developed for homologous renal transplant surgery. These have led to improved techniques in the surgical treatment of renal artery stenoses, such as the practice of retroperitoneal, rather than transperitoneal, arterial reconstruction to reduce the surgical stress on the patient.

According to Gil-Vernet et al,[60] a left-sided renal artery stenosis is corrected retroperitoneally by bringing the splenic artery into the retroperitoneal space, where it is anastomosed end-to-end to the renal artery. The operation is performed after hypothermal renal perfusion so that the anastomosis can be formed without time pressure. For correcting a right-sided renal artery stenosis by autogenous arterial bypass, the right internal iliac artery can be used. The right kidney is exposed by an inguinal renal transplantation incision lengthened proximally, the vascular pedicle is sectioned, and the kidney is revascularized heterotopically by anastomosis with the iliac vessels.

Renal transplantation techniques are applied even more extensively in the treatment of intrahilar renal artery stenoses or renal artery aneurysms. Here the kidney is extirpated along with the proximal ureter and, following hypothermal perfusion of the organ, the necessary arterial repairs are done with microsurgical techniques. Afterwards the kidney is reimplanted heterotopically in the iliac fossa.[85,143] As for experimentally tested techniques of achieving revascularization by interposition of the omentum or splenic artery into the parenchyma of the ischemic kidney, it is doubtful whether these will find clinical application.[79,169]

In older patients with an increased operative risk, nephrectomy should be considered as a lower-risk alternative for functionally significant renal artery stenosis if such a procedure can relieve the hypertension or improve prospects for drug therapy (Fig. 7). Nephrectomy should always be considered if the

**Table 3.**

| | Hipp. 131 Cl (ml/min/1.73m²)* | | Plasma Renin Activity (ng AI/ml/h)† | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Kidney | | | | Kidney | | | | | | Blood Pressure (mm Hg) | |
| No. | Right | Left | Rest | Stress | Right | Left | Vena Cava | Affected Kidney/ Contralateral Kidney | Contralateral Kidney/Vena Cava | Aldosterone (ng/100ml)‡ | Preoperative | Postoperative |
| 1 | 165 | 180 | 1.8 | 5.6 | 10.1 | 4.6 | 4.3 | 2.2 | 1.1 | 7.4 | 230/120 | 145/90 |
| 2 | 202 | 61 | 7.0 | | 5.9 | 19.4 | 5.7 | 3.3 | 1.03 | | 300/140 | 140/90 |
| 3 | 412 | 0 | 18.7 | 30.9 | 20.5 | 84.5 | 19.8 | 4.12 | 1.03 | 155 | 240/140 | 140/85 |
| 4 | 173 | 84 | 4.9 | 12.5 | 10.5 | 31.5 | 12.1 | 3.0 | 0.86 | 69 | 230/140 | 140/85 |
| 5 | 378 | 13 | 2.8 | 5.4 | 3.8 | 15.5 | 3.4 | 4.1 | 1.11 | 64 | 200/120 | 130/85 |
| 6 | 370 | 15 | 4.8 | 7.1 | 7.0 | 11.0 | 4.9 | 1.6 | 1.43 | 80 | 220/120 | 140/80 |
| 7 | | | 1.4 | 4.0 | 3.8 | 6.7 | 3.8 | 1.8 | 1.0 | 5.1 | 175/95 | 130/80 |
| 8 | 76 | 255 | 2.1 | 4.5 | 4.2 | 2.2 | 2.3 | 1.9 | 0.95 | 42.2 | 175/105 | |

*Normal value: >400 ml/min/1.73 m².

†Normal values: Rest—0.3–2 ng AI/ml/h; stress—0.5–4 ng AI/ml/h.

‡Normal value: 2–10 ng/100 ml.

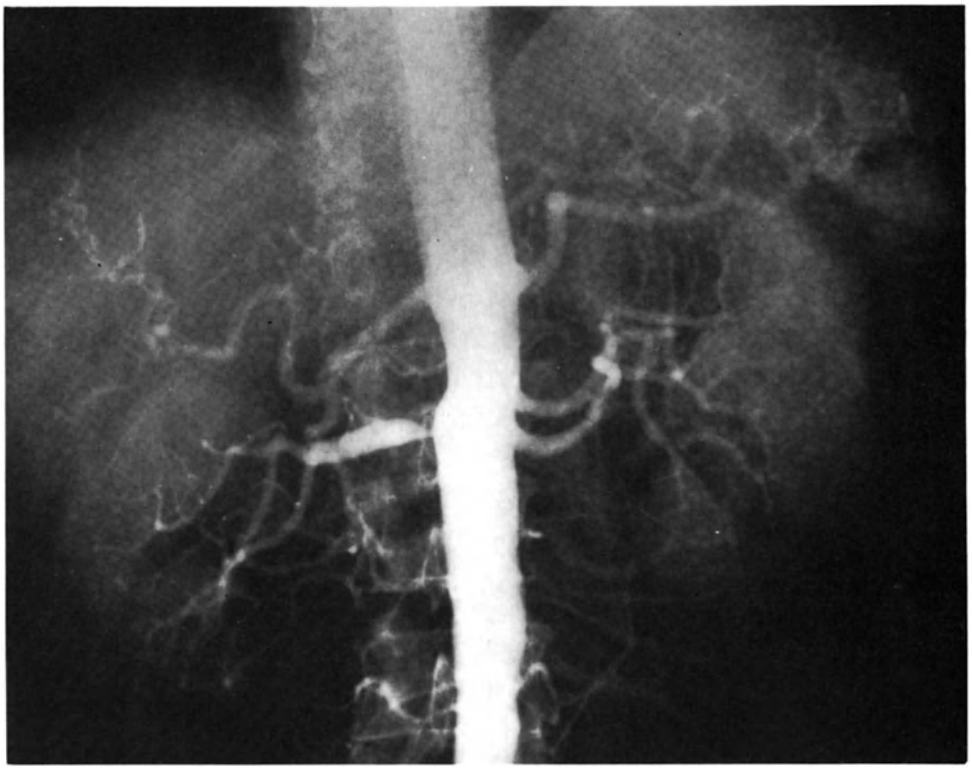

**Figure 6.** Survey aortogram of 56-year-old man showing atherosclerotic stenosis of the right renal artery, and centrally located hypernephroid renal carcinoma on left side. Peripheral venous renin activity increased during stimulation; significant lateralization of renin activity in renal venous blood; suppression of renin release in left kidney; blood pressure normalized following enlargement of the right artery lumen by patch graft with simultaneous left nephrectomy (see Table 3, no. 1).

renal artery is already obliterated to the extent that the renal tissue is still supplied via collaterals but has lost all excretory function. According to the experimental situation of the "endocrine kidney" described by Selye, the hypertension in such cases is caused by the "endocrine organ" (Fig. 8).

It is difficult to establish a connection between hypertension and *renal artery stenosis in solitary kidneys.* Even a normal-range plasma renin activity is considered to be elevated in such situations, since a markedly decreased renin activity is found in otherwise intact individuals with a unilateral nephrectomy,[40] similar to the situation in experimental dogs.[112,190] The indication for correction of the stenosis is facilitated by the fact that such treatment leads to an amelioration of kidney function. Similarly, in *bilateral renal artery stenoses* a marked lateral disparity in renal vein renin activity is found only if the stenoses are of different degrees of severity (Fig. 9), as in the experiments.

Hypertension resulting from impaired blood flow to a kidney may be due to stenotic changes in the artery wall but can also result from intrahilar *compression of the renal artery.* The latter has been variously attributed to aneurysms of the aorta[78] and to tumors localized in the renal hilus (neuroblastoma, neurofibroma, pheochromocytoma).[137]

The rare *aneurysms of the renal artery* are localized mainly at the bifurcation and major branches of the renal artery. The clinical symptoms are usually nonspecific. The aneurysm can cause renovascular hypertension through compression, thrombosis, or stenosis of associated or adjacent arteries. Figures on the coincidence of renal artery aneurysms and hypertension range from 13% to 80%; thus, a possible connection between hypertension and an angiographically proven aneurysm can be established only by separated renal vein renin assays. However, the patient with a proven aneurysm is in greater danger from a potentially fatal ruptural hemorrhage (12%) than from hypertension, and so surgical correction is indicated in every case. Because this procedure is extremely difficult[49,56] or impossible *in situ,* the recommended procedure

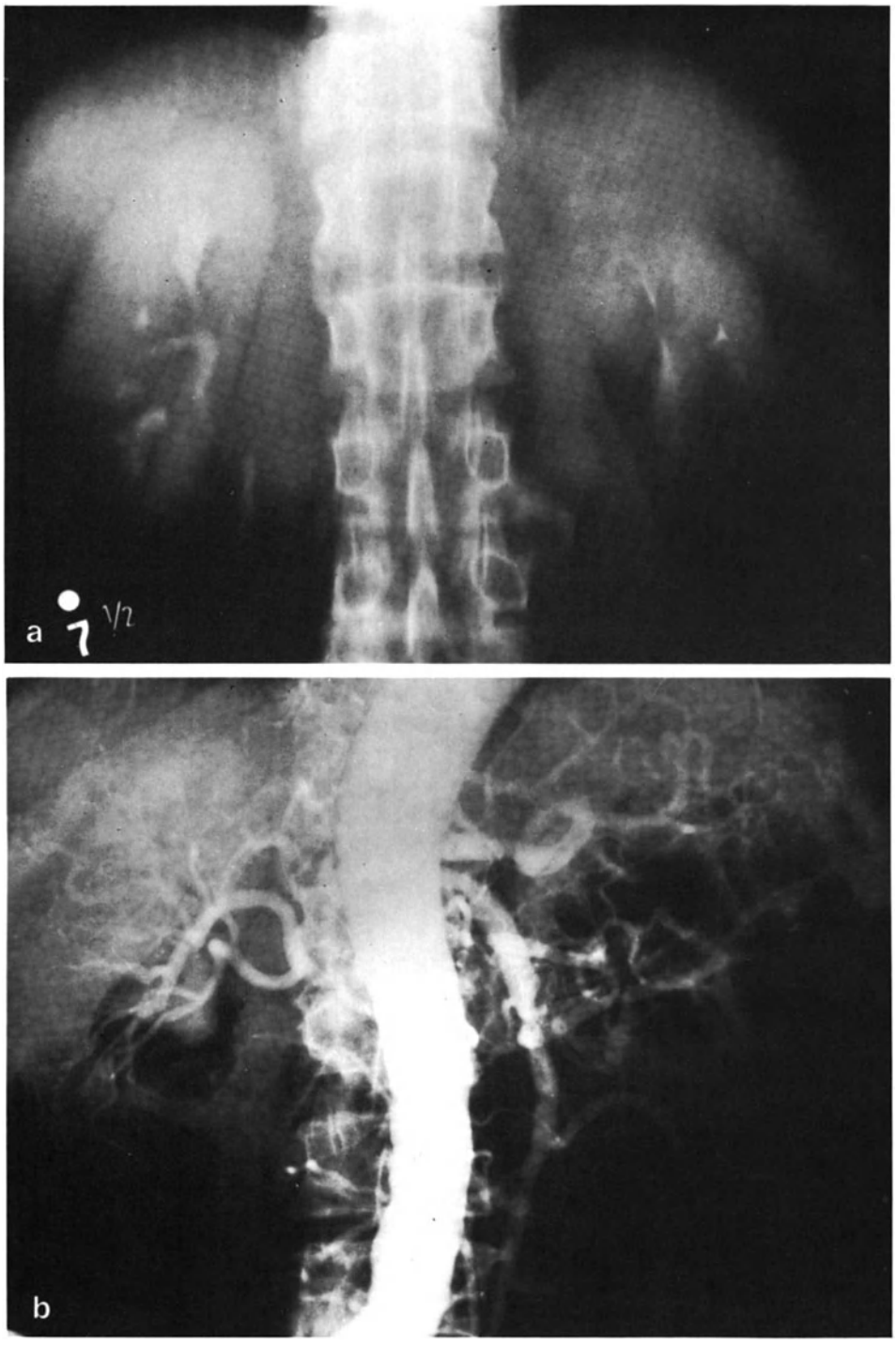


**Figure 7.** A 69-year-old man with hypertension unresponsive to drug therapy. **a** Excretory urogram (tomogram): Pole-to-pole diameter of right kidney 14 cm, of left kidney 11.5 cm. **b** Survey aortogram showing filiform stenosis of left renal artery. Marked impairment of excretory function and significant hyperreninemia on left side with renin suppression on right side; blood pressure normalized following left nephrectomy (see Table 3, no. 2).

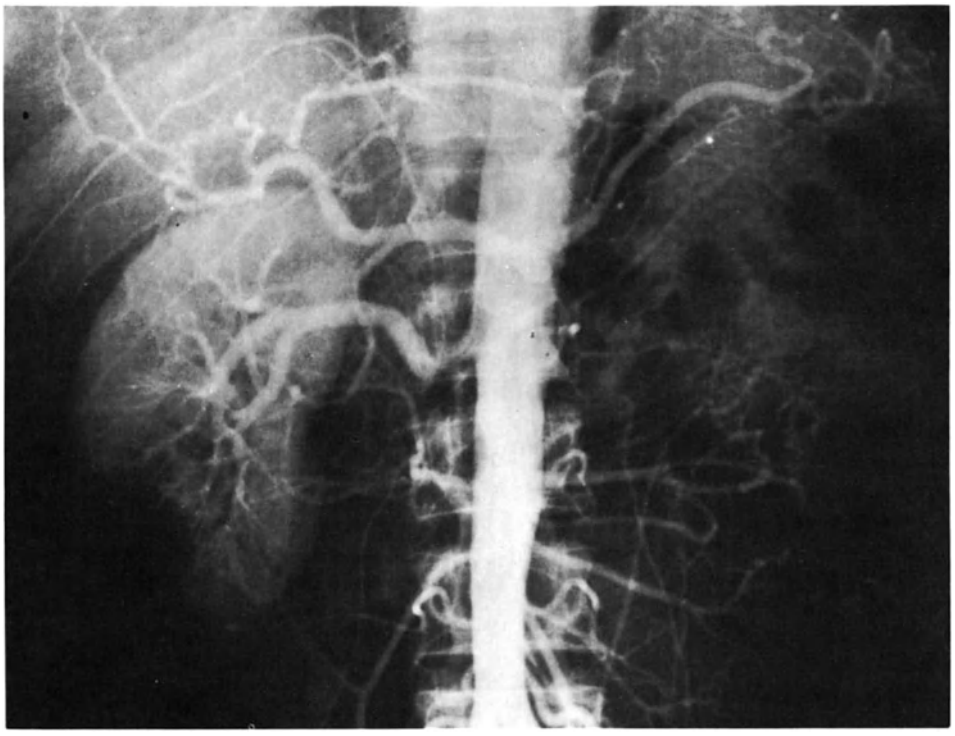

**Figure 8.** Survey aortogram of 36-year-old man showing occlusion of left renal artery and stenosis of right renal artery. Complete loss of excretory function in left kidney with compensatory hypertrophy of right kidney; marked elevation of peripheral venous renin activity; strong lateralization of renal vein renin activity; secondary hyperaldosteronism (endocrine kidney); blood pressure normalized following left nephrectomy and simultaneous correction of right artery stenosis by interposition of left renal vein (see Table 3, no. 3).

is extracorporeal repair with subsequent reimplantation[132] or, if the findings and patient's general condition warrant, a nephrectomy.

*Arteriovenous fistula* is rare as a cause of hypertension.[109,131] Etiologically, arteriovenous fistulas are classified as congenital or acquired. While congenital fistulas are located extrarenally, acquired arteriovenous fistulas occur both extrarenally and intrarenally. Extrarenal arteriovenous fistulas include those that occur after nephrectomy (see Chap. 27) as a result of a common ligature of artery and vein, which is the reason these must always be ligated separately. Intrarenal fistulas are observed after trauma, after surgery on the renal parenchyma, and particularly after blind needle biopsy.[111] A rare form of arteriovenous fistula between the renal artery and inferior vena cava that causes hypertension has been observed following renal trauma.[142]

Arteriovenous fistulas are accompanied by hypertension in about 45% of cases, the latter resulting from a hemodynamically significant increase in the circulating blood volume or from parenchymal ischemia with an increase in renin release. Abdominal or flank pain, hematuria, and, in 57% of cases, a systolic bruit in the renal bed are symptomatic of an arteriovenous fistula. The urogram rarely shows evidence of the fistula, such as extension of the calyces, compression of the calyceal necks, or calcification. The definite diagnosis is established by the arteriogram, which also determines the operative tactics; i.e., the fistula is repaired after renal exposure or the kidney is extirpated, depending on the localization. Parenchymal arteriovenous fistulas with macrohematuria following renal biopsy can sometimes be closed elegantly by the arterial injection of a tissue adhesive by the Seldinger technique.[72]

The presence of *multiple renal arteries* is a developmental aberration in which the main renal artery divides prematurely into segmental arteries, which may even arise directly from the aorta.[65] The kidney is supplied via five segmental arteries, which is the reason the greatest number of arteries that theoretically can supply a kidney is five. Peter, on the basis of postmortem findings, postulated a con-

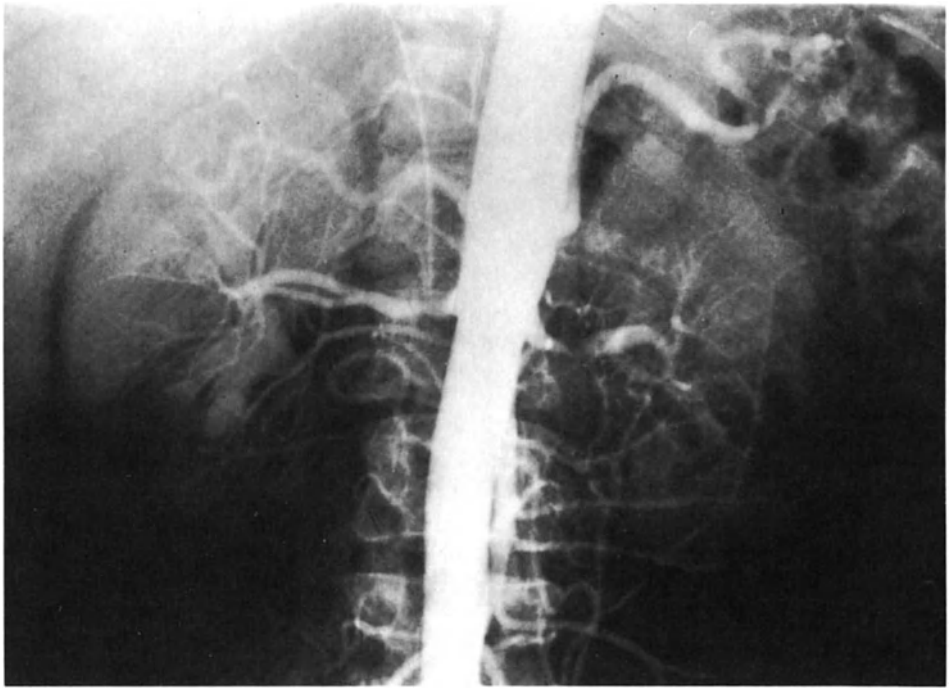

**Figure 9.** Survey aortogram of 39-year-old woman showing filiform stenosis of left renal artery, lower-grade stenosis of right renal artery, and bilateral poststenotic dilatation with fibromuscular dysplasia. Marked impairment of left kidney function, moderate impairment of right kidney function; elevated peripheral venous renin activity; left renal vein renin activity three times higher than right renal vein, expressing stronger hemodynamic activity of the left stenosis; secondary hyperaldosteronism; blood pressure normalized by bilateral aorticorenal Dacron bypass (see Table 3, no. 4).

nection between multiple renal arteries and essential hypertension.[129] According to this theory, the narrower-lumened multiple renal arteries are relatively more severely stenosed by atherosclerotic changes at the arterial branches than are solitary renal arteries. Since the effect of the stenosis is multiplied by the increased number of arteries, secondary renovascular hypertension should develop more frequently in the presence of multiple renal arteries than when the main artery branches normally.

The same postmortem statistics showed a frequency of 28% for unilateral or bilateral multiple renal arteries in the controls.[129] This figure is consistent with arteriographic findings demonstrating uni- or bilateral multiple renal arteries in 32% of normotensive controls.[37] However, arteriography showed no significantly higher incidence of multiple renal arteries in hypertensive patients; this would indicate that the association between multiple renal arteries and hypertension is merely coincidental.[41,42]

In hypertension resulting from *segmental artery stenosis,* the blood pressure can be normalized by vascular reconstruction in suitable cases. By contrast, ligature of the segmental end-artery is seldom curative, because afterwards the hypertension will be maintained by the infarcted renal segment; in 20% of cases, ligature of a lower segmental artery (e.g., as a cause of hydronephrosis) leads to hypertension accompanied by hyperreninemia.[9,59,156] This has been attributed to the presence of a capillary anastomosis from an adjacent segment which "revascularizes" the ischemic boundary zone.[41] However, a more likely explanation is that the ischemic segment is supplied by capsule arteries. Such collaterals have already been observed as a cause of hypertension with hyperreninemia after the total occlusion of a segmental artery[58,115] and after occlusion of the main artery in the "endocrine kidney." If the collaterals are demonstrated arteriographically and an elevated plasma renin is found in the associated segmental vein, relief of the hypertension can be achieved by segmental resection.[35,115] The typical signs of ischemia can be demonstrated histologically; they differ markedly from those of total infarction.[59]

*Occlusion of the main renal artery* may be associated with hypertension, depending on its etiology. An *arterial* thrombosis can develop on the basis of

local arterial wall changes, such as atherosclerosis, periarteritis nodosa, lupus erythematosus, endangiitis obliterans, renal artery aneurysms, or scleroderma. These conditions lead to protracted arterial occlusion, which results in the "endocrine kidney" situation with a collateral blood supply and hypertension. By contrast, acute arterial occlusion by *embolism* (thrombi in the case of aortic and mitral defects, myocardial thrombosis in cardiac infarction) affects an intact kidney before a collateral circulation has had the opportunity to form.[179] Thus, the resulting acute total infarction lacks the prerequisites for an endocrine activity accompanied by hypertension. Unilateral or bilateral *renal vein thrombosis,* which usually arises from pelvic vein thrombosis via the inferior vena cava or ovarian vein, may also be associated with hypertension.

*Renal anomalies,* such as malrotation, dystopia, and horseshoe kidney, are often combined with arterial anomalies. These may involve variations in both the number of arteries and their origins. Anomalous arteries can aggravate urinary stasis caused by an abnormal ureteral course. They can also restrict the mobility of the kidney and hamper renal blood flow. Thus, several factors must be considered when determining the etiology of hypertension associated with renal anomalies.[123]

Impaired blood flow resulting from increased renal mobility can be observed in the *hypermobile kidney* and is demonstrable by radioisotope studies or by an increase of renal LDH secretion in an upright position. A higher incidence of hypertension in such cases has not been established, although it has been suggested that the constant tension on the renal artery may cause intimal or medial fibroplasia accompanied by stenosis and hypertension (see Chap. 27, Fig. 15).

*Hypertension following surgery of the renal parenchyma* is based on both renovascular and renoparenchymal factors. The causes include faulty suture technique, such as the inadvertent inclusion of large or intermediate arteries, especially when suturing near the hilus; perirenal scars as a result of hematoma formation; kinking of the main artery after mobilization of the kidney without fixation; and intimal lesions of the main artery after faulty clamping to produce ischemia.[121,133] Most errors can be avoided by adopting certain precautionary measures during parenchymal operations, particularly the use of shallow, plane sutures to preserve the parenchyma, and limiting incisions and resections to a particular renal segment without crossing intersegmental lines.[14,66]

The preservation of parenchymal tissue requires that a special suturing technique and suture material be employed. For example, chromic and nonchromic catgut as well as silk are basically nonirritating, whereas Perlon and twisted suture cause a marked foreign-body reaction accompanied by inflammation and parenchymal destruction.[150] First the larger bleeding vessels are tied off with a purse-string ligature, and the collecting system is sealed. The parenchyma may be sparingly sutured close to the cortex with a cross-stitch suture that includes the renal capsule and incorporates it into the wound area. The interposition of muscle and fatty tissue or foreign material should be avoided. A U suture, on the other hand, may be secured by a piece of fat or fibrin sponge pushed beneath the suture on the tissue surface. Drainage of the collecting system in a simple polar resection is not only unnecessary but can interfere with the course of healing.

## Renal Factors—Renoparenchymal Hypertension

Following initial doubt about the connection between *pyelonephritis* and hypertension, Butler reported in 1937 on the surgical relief of hypertension by the removal of a unilateral pyelonephritic kidney.[26] The cause of hypertension in chronic pyelonephritis lies in obstructive vascular lesions which produce ischemic parenchymal damage. This creates a situation comparable to that seen in renovascular hypertension; i.e., impaired renal blood flow leads to activation of the renin-angiotensin system,[89] as in patients with renal involvement in periarteritis nodosa who have hypertension with hyperplasia of the JGA.[25,36]

Plasma renin assay, particularly in the separate renal veins, is meaningful only if a unilateral process is present, and thus the blood pressure can be lowered by unilateral nephrectomy. This pertains only to unilateral pyelonephritic "small kidneys" resulting from hypoplasia or other malformations, as well as from unilateral urinary flow obstructions or vesicorenal reflux[27] (Fig. 10).

In the case of *renal tuberculosis,* it is reported that 4.5% of unilateral nephropathies cause hypertension that can be cured by nephrectomy.[153] These include not only organs without excretory function,[84] but also segmental changes accompanied by diminished blood flow and lateralized or segmental hyperreninemia.[110]

Nephrectomy for hypertension resulting from unilateral renoparenchymal disease is indicated only after all findings obtained by urography, radioisotope studies, arteriography, and separated renal vein renin assays have been evaluated. Of particular importance is the demonstration of intact morphology and function in the contralateral kidney in order to exclude a bilateral process.

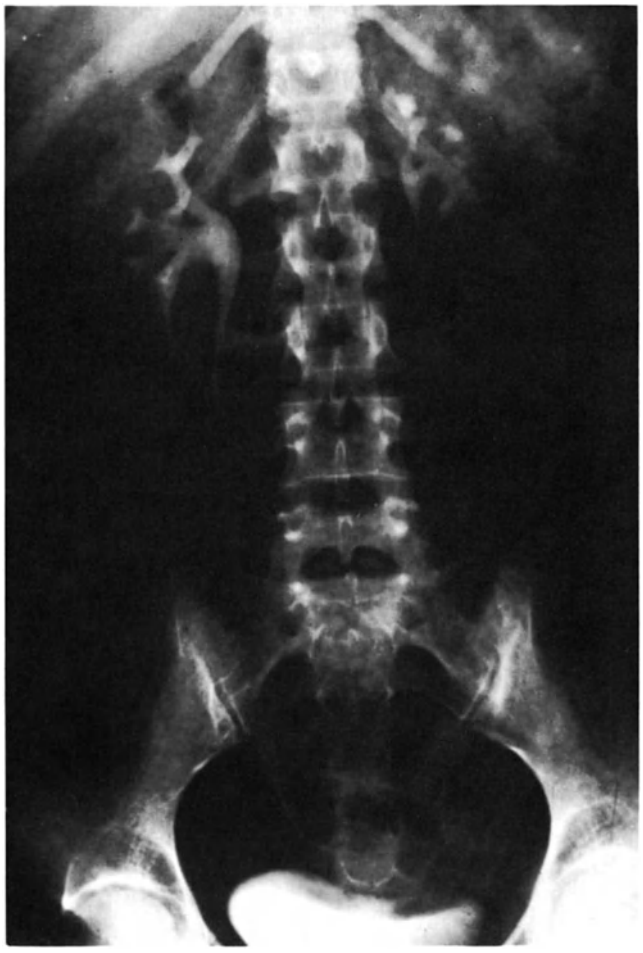

**Figure 10.** Excretory urogram of 17-year-old girl showing pyelonephritic small left kidney. Loss of most excretory function in left kidney with compensatory hypertrophy of right kidney; elevated peripheral venous renin activity; strong lateralization of renal vein renin activity; suppression of renin release in right kidney; secondary hyperaldosteronism; blood pressure normalized following left nephrectomy (see Table 3, no. 5).

Special diagnostic tests are necessary to establish a possible connection between hypertension and segmental parenchymal lesions of inflammatory or traumatic origin. For example, a *segmental hyperreninemia* may be overlooked owing to mixing effects in the main vein and can be demonstrated only by selective determination of the plasma renin activity in the associated segmental vein. If the result is positive, the hypertension can be cured by excision of the affected renal segment.[91,104,145,163]

Determination of the segmental venous plasma renin activity is also necessary in hypertension associated with *segmental hypoplasia of the kidney.* In contrast to simple renal hypoplasia, in which the kidney has a normal internal structure,[186] the internal renal structure in segmental hypoplasia shows pathologic segmental changes which may be unilateral or bilateral, symmetrical or asymmetrical.[138] The condition is variously called *hypoplasia of the kidney,*[3] *hypogenetic nephritis,*[53] or *segmental glomerular hypoplasia.*[5] Histologically, the normal tissue is sharply delineated from the dysplastic tissue. The latter is characterized by an absence of glomeruli and Henle's loops, a narrow medulla, and thickened walls of the arteries, which are stenosed or totally obliterated. Unlike chronic pyelonephritis, there is no inflammatory interstitial infiltration.

The disease appears predominantly in girls after the tenth year but may occur earlier in some cases.[118] The principal features are growth disturbances and severe hypertension. Owing to the absence of the JGA, however, the origin of the observed segmental hyperreninemia remains unclear;[61] the only remarkable finding is the presence of hypertrophic glomeruli in the boundary region of the adjacent normal renal tissue with increased granulation of the juxtaglomerular cells. Proteinuria and renal failure correlate with the size of the dysplastic areas.

The urogram shows diverticular calyces with a narrow parenchymal seam; the angiogram shows a normal renal artery. If involvement is unilateral, segmental resection or nephrectomy is prognostically favorable; in bilateral involvement the localization and extent of morphologic changes determine

whether operative or conservative treatment is preferred (Fig. 11).

*Renal trauma* can cause hypertension in various ways. Aside from ruptures of the renal parenchyma, any accident which causes tension to be exerted on the renal pedicle can lead to intimal ruptures and consequent arterial thrombosis or to the division of segmental or main arteries and veins. In one study, vascular involvement could be demonstrated angiographically in 16% of cases.[51] Vascular lesions of this type should be surgically repaired at once, lest segmental infarction with hypertension[94] or total infarction[1,116] result. Fifty percent of renal artery injuries lead to hypertension;[162] arteriovenous fistulas following trauma are not uncommon.[142]

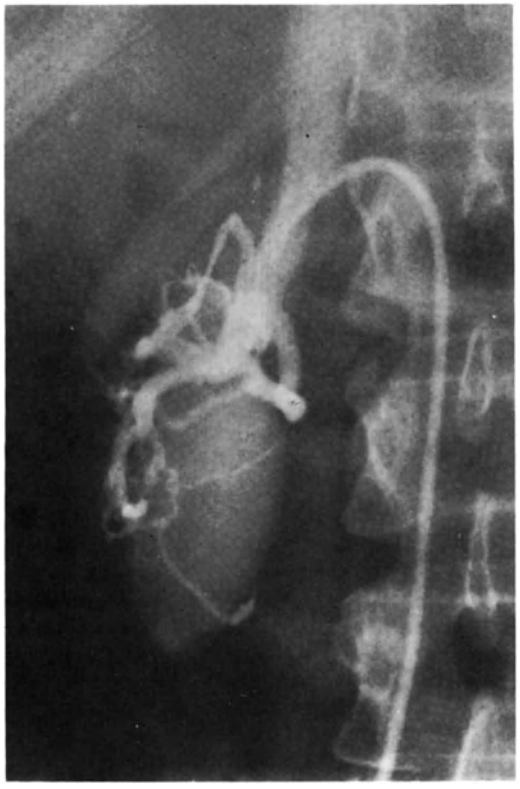

**Figure 11.** Phlebogram of right kidney of 34-year-old woman showing segmental hypoplasia (Ask-Upmark, histologically confirmed). Arteriography further showed segmental artery stenosis in the left kidney. Almost complete loss of right renal excretory function with compensatory left renal hypertrophy; elevated peripheral venous renin activity; significantly higher renal vein renin activity in left kidney with segmental artery stenosis than in right kidney, but also a significantly higher renin activity in the right renal vein than in the vena cava distal to the renal vein juncture; secondary hyperaldosteronism; blood pressure normalized following removal of hypoplastic right kidney despite continued segmental artery stenosis in contralateral kidney (see Table 3, no. 6).

Also important are perirenal hematomas, which are usually the result of very minor parenchymal injuries and often can be treated only by parenchymal suture or drainage. The most frequent late complication of untreated perirenal hematomas is compression of the parenchyma caused by organization of the hematomas, resulting in hypertension. The pathogenic mechanism corresponds to that in experimental cellophane perinephritis.[147]

In caring for parenchymal wounds or resecting ischemic tissue parts, the criteria for parenchymal resection described above must be observed. Proper hemostasis in plane tissue defects cannot always be achieved by the suture technique. Besides the danger of severance of the threads, there is a risk of impaired blood flow if an artery is inadvertently included in the suture. The possible results are impaired function of remaining parenchyma and the development of hypertension. These difficulties are overcome by the use of tissue adhesive, which is well-tolerated and ensures the preservation of parenchymal tissue. In multiple bursting ruptures, the application of plastic bands to the kidney should be avoided. As in perinephritis, these will arrest the normal pulsation of the organ and lead to hypertension.[160,170]

*Solitary renal cysts* are relatively common in urologic patients. The peak frequency during middle age as well as in experimental studies in animals indicates that the cysts are acquired, occur chiefly at the poles, and are localized in the middle part of the parenchyma only in about 20% of cases.[186]

The symptoms of solitary renal cysts are dependent on the size and growth rate of the cyst. Hypertension is a not uncommon symptom of a solitary renal cyst.[4,44,54,77,92,136] The pathogenic mechanism in such cases is assumed to be a compression of the renal parenchyma with stenosis of intrarenal arteries, particularly in the case of centrally located cysts. Thus, this hypertension is considered to be of the renovascular type. This has been confirmed by our own investigations[108] as well as those of other authors,[4,77,136] which demonstrated an elevated plasma renin activity in the venous blood of the affected kidney. In these cases, decompression of the renal parenchyma by removal of the cyst produces a normalization of blood pressure (Fig. 12).

*Malignant renal tumors* such as Wilms' tumor and hypernephroid renal carcinoma are associated with hypertension in about 30% of cases,[10,15,102,141] and blood pressure is normalized after tumor nephrectomy, provided no metastases are present.

In the pathogenesis of tumor-related renal hypertension, three mechanisms have been discussed as possible stimulants of the renin-angiotensin system. First, a tumor of appropriate localization and size could compress one or more intrarenal arteries,

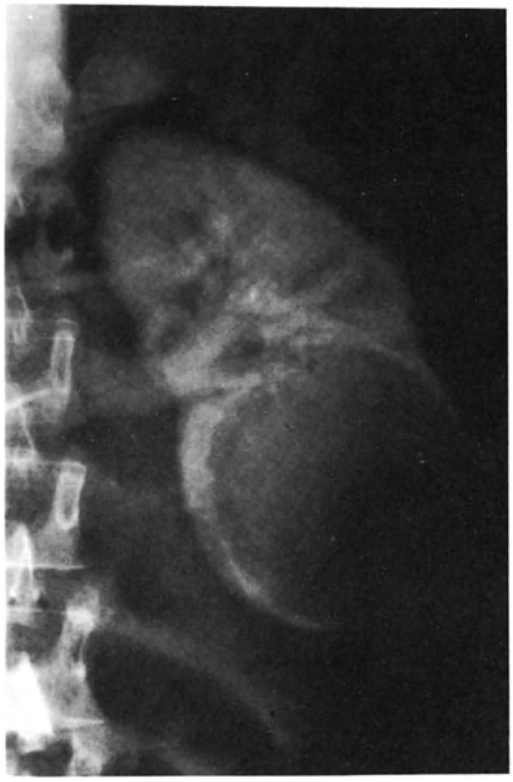

**Figure 12.** Selective arteriogram of left kidney (parenchymal phase) of 19-year-old male showing solitary cyst on inferior renal pole. Strong lateralization of renal vein renin activity; suppression of renin release in right kidney; blood pressure normalized following removal of cyst (see Table 3, no. 7).

thereby reducing the blood flow to the associated areas. However, this could also be the result of arteriovenous shunts, which are typical of malignant renal tumors. Both mechanisms represent a special case of renovascular hypertension.

A third causal mechanism of tumor-related renal hypertension was first proposed by Linder in 1947.[101] On the basis of his studies, he suggested that tumor cells are capable of elaborating and releasing their own vasopressors (renin?), which could cause hypertension. This hypothesis has since been confirmed both for Wilms' tumors and for hypernephroid renal carcinomas.

In the case of *Wilms' tumor* with hypertension, both hyperreninemia[114,161,178] and a renin activity in the tumor tissue[114] have been demonstrated. The tumors which produce renin appear mainly to be those which have glomerulus-like structures.[114] The connection between renal tumors and hypertension is further demonstrated by the fact that irradiation of a Wilms' tumor is followed by regression of hypertension, which later recurs when metastases develop. After irradiation of the metastases, a normalization of blood pressure is again recorded.[16] The behavior of the blood pressure in this case is indicative of an ectopic production of vasopressors by the metastatic tumors, as in another case of left-sided Wilms' tumor with metastases, in which neither the elevated plasma renin nor the blood pressure was normalized after removal of the primary tumor.[106] In this case, the renal vein renin activity of the tumorous kidney was about three times higher than that of the healthy kidney.

The extirpation of a *hypernephroid renal carcinoma* can also produce relief of preexisting hypertension. Here it has been shown that renin is present in the tumor tissue[192] and that the tumor cells are capable of renin production.[187] This appears to prove Linder's theory that malignant tumors of the kidney are capable of autonomous renin production and can thus be the cause of hypertension.[108] Renal carcinomas have also been associated with the secretion of erythropoietin and parathormone, as well as prostaglandins, which exert a hypotensive effect.[193]

A benign renal tumor as the cause of hypertension was first described by Robertson et al. in 1967.[135] The tumor, which was 3 cm in diameter, arose from the juxtaglomerular cells of the vas afferens and corresponded morphologically to a hemangiopericytoma, as first described by Stout and Murray in 1942.[165] The clinical signs were a refractory hypertension and elevated potassium excretion. Bioassay showed a renin-like substance in the tumor extract. Since then, further such benign renal tumors have been described which were associated with hypertension and hyperreninemia[12,22,33,47,76,88,146] or secondary hyperaldosteronism.[22,33,47] Owing to their small size, these benign renal tumors are usually not demonstrated by urography and can be localized angiographically in only about 50% of cases. Thus, with arteriographically normal kidneys, the cardinal symptom is an elevated plasma renin activity and secondary hyperaldosteronism with hypokalemia. An essential diagnostic criterion is the separated renal vein renin assay, preferably as stage renin for exact localization of the tumor, which can be removed by segmental resection.

## Postrenal Factors—Hypertension due to Urinary Stasis

Congenital and acquired *urinary flow obstructions* of varying etiology may also be associated with hypertension. In recent years several reports have been published on hypertension accompanied by hyperreninemia as a result of unilateral urinary stasis.

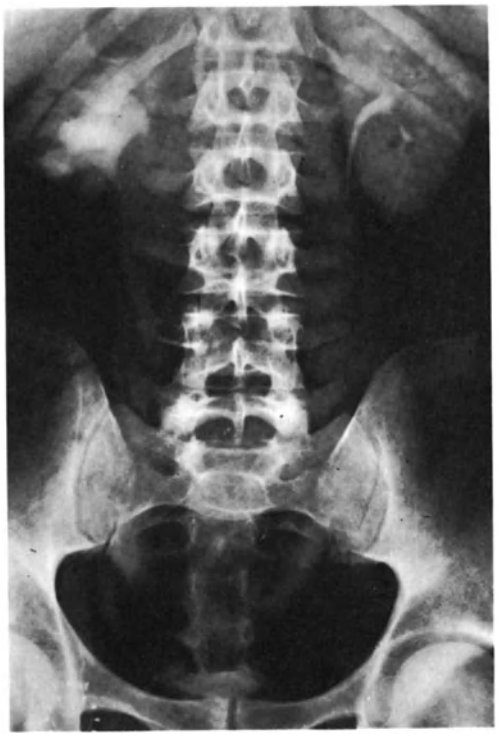

**Figure 13.** Excretory urogram of 34-year-old man showing urinary stasis on right side following pyeloplasty for subpelvic ureteral stenosis. Marked impairment of excretory function in right kidney; strong disparity between right and left renal vein renin activity during normal rest and exercise; patient has been treated medically to date (see Table 3, no. 8).

The results on blood pressure behavior postoperatively have clearly shown that, as in renovascular hypertension, surgical relief of hypertension is possible only if renin release is elevated in the involved kidney and suppressed in the contralateral kidney. Otherwise, correction of the urinary flow obstruction or nephrectomy is not curative with respect to hypertension[2,6,29,38,57,87,119,155,157,168,181] (Fig. 13).

## Hypertension due to Chronic Renal Failure

### Indication for Bilateral Nephrectomy

Patients with chronic renal failure who are treated by chronic hemodialysis can be divided into three groups with regard to their blood pressure:

1. *Normotensive patients.* In these patients the renal failure is based more on an involvement of tubular-interstitial structures than on arteriolo-glomerular structures. The plasma renin activity is low or immeasurable; it is never elevated.[23,139,182] The patients tend toward salt loss or show a reduced tendency toward salt and water retention.[63]
2. *Patients with controllable hypertension.* In the largest group of hypertensives with chronic renal failure undergoing hemodialysis, the blood pressure can be kept within normal limits solely by salt and water restriction.[8,24,128,177] Vertes et al. call this form *salt/water–dependent hypertension.*[177] Chronic glomerulonephritis occurs more frequently in this group than in the normotensive group; the plasma renin is within normal limits.[177,182]
3. *Patients with uncontrollable hypertension.* In this group the blood pressure remains at a malignant level despite salt and water restriction. An elevated renal renin content and elevated plasma renin activity can usually be demonstrated. Vertes et al. call this form *renin-dependent hypertension.*[177]

Morphologically, 86% of cases involve arteriolo-glomerular disease (nephrosclerosis, glomerulonephritis), while only 14% involve primary interstitial-tubular disease (chronic pyelonephritis, phenacetin kidneys).[182] It may be assumed that the renal disease has reached a state in which the combination of renal arterial and renal parenchymal disease is sufficient to trigger the same mechanism as in renovascular hypertension, i.e., hyperreninemia with secondary hyperaldosteronism.[24] This is also demonstrated by experiments with the "nonfiltering kidney" in dogs. Here the renal parenchyma is damaged to the point where the kidney has lost its excretory function but not its endocrine function. This permits the continued stimulation or suppression of renin release via the baroreceptors.[7]

After Kolff et al. demonstrated in 1964 that bilateral nephrectomy can lower the blood pressure in patients with chronic renal failure,[90] this procedure became a routine measure for several years. However, bilateral nephrectomy has several adverse side effects stemming from the loss of endocrine renal functions, such as disturbances of erythropoiesis with consequent anemia. As a result, this operation is now reserved for very specific indications, including uncontrollable renin-dependent hypertension in patients with chronic renal failure.

In addition to uncontrollable hypertension, these patients exhibit a very poor general state of health marked by anorexia, progressive weight loss, impairments of consciousness, and pathologic thirst.[24,98,182] Angiotensin is one of the strongest stimulants of thirst[55] and is considered to be the probable thirst

stimulus in these patients. The remaining symptoms are apparently associated with angiotensin-induced vasoconstriction and the resultant decrease in organ perfusion.

Following bilateral nephrectomy, the values for plasma renin activity, angiotensin II, and aldosterone fall within hours to normal or subnormal levels. Since elimination of the vasopressors creates a danger of hypotension, 3–6 liters of physiological saline is given parenterally immediately after the nephrectomy to correct the volume deficit. Besides a normalization of blood pressure, the patient exhibits an increase in energy, appetite, and weight and a decrease in thirst postoperatively.[24,98,182]

## Hypertension following Renal Transplantation

The incidence of hypertension in the first 2 to 12 months following renal transplantation is reported to be 30% to 80% and is thus very high.[30,32,100,130] Hypertension is observed more frequently in recipients whose kidneys were not extirpated prior to transplantation than in recipients who had a prior bilateral nephrectomy.[71,126] In recipients who undergo bilateral nephrectomy, the hypertension may stem from any of the following causes: rejection crisis, corticosteroid therapy, renal artery stenosis, parenchymal damage of varying origin, and, in the immediate postoperative period, surgery-related mechanical irritations at the graft.

Pathogenically, it must be considered that the denervated transplanted kidney possesses a normal responsiveness to renin stimuli;[140] i.e., diminished blood flow to the graft is associated with increased renin release and thus with hyperaldosteronism.[73,93,99,154] It must also be considered that the plasma renin activity is reduced in the intact graft, just as in otherwise intact individuals with a unilateral nephrectomy. Thus, a plasma renin activity within normal limits is considered to be elevated.

Increases in transient blood pressure in the immediate postoperative period which are not immunologically determined and are accompanied by hyperreninemia are attributable to a reversible decrease in blood flow due to manipulations of recipient and graft arteries during the transplantation, as well as to wound edema with resultant compression of the graft in the narrow iliac fossa.[73] This hypertension is different from that occurring in acute rejection crisis.[188] Acute *rejection crisis* occurs in about 30% of renal transplant recipients during the first 3 weeks postoperatively and in about 60% during the first 4 months. Before the appearance of histologic changes in the arteries and days before the onset of oliguria, a reduction of cortical blood flow, probably caused by preglomerular spasms,[11] could be detected by the radioxenon washout method.[172,173]

This reduction of blood flow is accompanied by an elevated plasma renin activity and hyperaldosteronism, which were shown to be related to the hypertension that follows renal transplantation.[73,105] If the blood pressure is normalized when immunosuppressive therapy is intensified, hypertension within the setting of acute rejection crisis is indicated. An opposite response of the blood pressure does not necessarily exclude a refractory rejection crisis, however.

The extent to which parenchymal damage resulting from infection, tubular necrosis, or urinary flow obstructions may cause a decrease in blood flow leading to hypertension is still unclear;[73] a recurrent glomerulonephritis in the graft must be considered in every case.

A clear connection has been established between hypertension and *corticosteroid medication,* which is one of the main causes of hypertension following transplantation. The medication does not alter the plasma renin but increases the production of aldosterone, which correlates with the level of the blood pressure and results from the transformation of prednisone to aldosterone. Replacing daily doses of prednisone with twice daily doses of methylprednisone or the administration of an aldosterone antagonist (spironolactone) leads to a normalization of blood pressure.[140]

Diffuse parenchymal damage can be differentiated from prerenal stenoses as a cause of posttransplant hypertension only by arteriography.[122,152,188] The typical signs of rejection crisis in the series angiogram are a narrowing and straightening of the intrarenal arterial branches with rarefaction of the parenchymal vessels, as well as organ enlargement with a diminished flow.

Arteriography is particularly useful in verifying *stenoses and occlusions of large and small arteries.* An incidence of 1% to 12% is reported for posttransplant arterial stenosis,[93,99,140] which is implicated in 50% of hypertension following renal transplantation.[32,46,120,152] Renal artery stenosis must be suspected as a cause of posttransplant hypertension whenever the hypertension is unresponsive to drug therapy, the function of the transplanted kidney deteriorates, or stenotic bruits are heard. This is accompanied by an increase in the plasma renin activity of the peripheral venous blood and an increased secretion of aldosterone.

Stenoses can be demonstrated both in the recipient arteries and in the arteries of the donor kidney.

Atherosclerotic changes are the cause of stenoses in the recipient arteries. Renal artery stenoses are located either immediately adjacent to the anastomosis or 0.5–2 cm distal to it. Stenoses affecting the entire renal artery and multiple stenoses are rare. "Kink" stenoses may occur as a result of faulty artery implantation, and stenoses in the suture line may result from an improper suture technique.

Reportedly, stenoses are more common after end-to-side anastomosis of the renal artery to the common iliac artery.[117] This is attributed to changes in the laminar blood flow, which have also been implicated in stenosis formation after end-to-end anastomosis of the renal artery to the internal iliac artery. Local rejection reactions have also been suggested as a causative factor. However, the most common cause of posttransplant renal artery stenosis is faulty technique during the removal and transplantation of the organ. Excessively fine dissection of the donor arteries may destroy their vasa vasorum, and tension on the artery during the dissection or improper use of the vascular clamp can cause endothelial lesions. However, the latter result mainly from excessive arterial dilatation during insertion of the perfusion cannula for hypothermal perfusion of the organ (Fig. 14); for this reason a proximal arterial cuff should be left in place after the perfusion.

Therapeutically, the only possibility is arterial reconstruction. The best results are achieved by resecting the stenosis and uniting the healthy arterial walls. This can relieve the hypertension as well as ameliorate or normalize renal function.

Thus, arteriography should always be performed if posttransplant hypertension develops and is accompanied by an audible stenotic bruit, if rejection crisis is suspected and drug therapy produces no hypertension relief or function improvement, if an initially controlled hypertension worsens, or if an intimal lesion is suspected as a result of a too-short renal artery which is damaged by the perfusion. Arteriographically demonstrated stenoses should be corrected even if the plasma renin is normal since, as mentioned, a plasma renin activity within normal limits is considered to be elevated, and arterial reconstruction will normalize the blood pressure.[93,99,144,152,154]

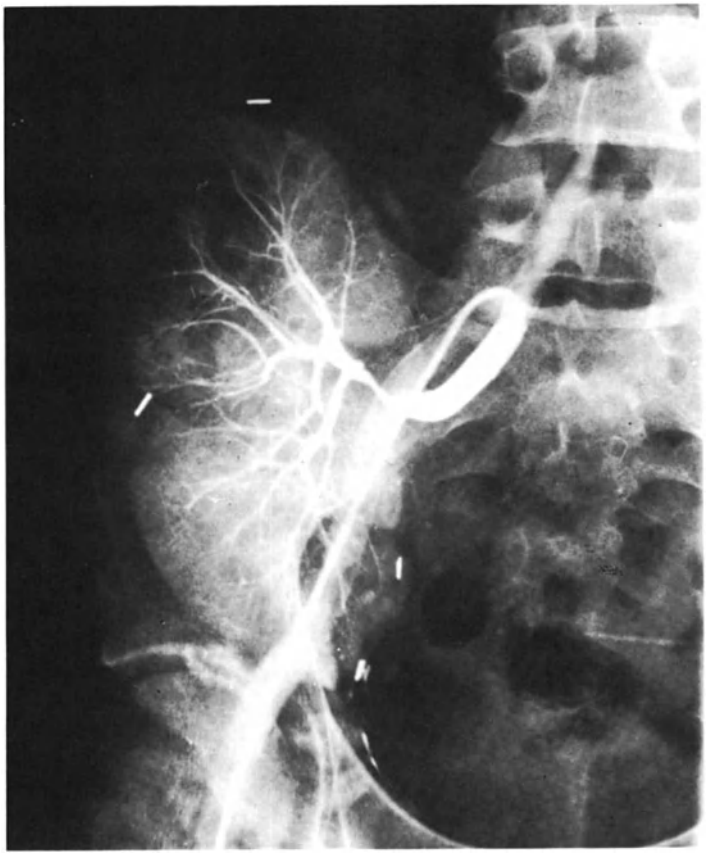

**Figure 14.** Arteriogram of transplanted kidney in 25-year-old man showing renal artery stenosis distal to anastomosis with right internal iliac artery; donor 9 years old; stenosis presumably caused by intimal lesions secondary to cannulation of narrow-lumened artery for hypothermal perfusion.

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# Central Hemodynamics and Cardiac Function in Hypertension

18

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## Central Hemodynamics

Despite the tremendous volume of information published on the mechanisms of hypertension, the details of the pathophysiologic relationships are not yet clearly understood. Many questions remain unanswered. In this article we shall attempt to review current knowledge on the dynamics of blood flow in the central region of the circulation, as well as on the dynamics of cardiac funtion.

Blood pressure and flow, as controlled variables in the circulatory system, undergo secondary changes in hypertension. Evidence indicates that this is probably true for the heart as well. Secondary cardiac involvement is well known and pronounced in the chronic course of hypertension. Hypertensive heart disease may result. Further problems arise when coronary heart disease occurs as a secondary complication. These complications will, in turn, have more or less pronounced hemodynamic repercussions on the peripheral circulation as a whole (v.i.).

Although the disturbances of hemodynamic function must be viewed as occurring secondarily to a primary mechanism localized elsewhere, they can in some circumstances acquire considerable significance as an individual component in the chain of reflex events. Thus, the elevated blood pressure itself—and not, for instance, the total peripheral vascular resistance—must be considered an essential variable which is closely and perhaps fundamentally linked with the primary process. This means that the rise of blood pressure, i.e., hypertension in itself, is the typical end result of the functional disturbance rather than, say, an increase in total peripheral resistance.

As far as the heart is concerned, doubt must be expressed concerning the assumption of a purely secondary involvement, at least for certain special forms of hypertension. Hyperdynamic and hypercontractile states are common in many, especially early, manifestations of the hypertensive process. They can be explained by increased sympathetic activity and an increased blood return to the heart. However, a hypertensive reflex was described recently which appears to have its afferent origin in the region of the proximal vascular section of the left coronary artery or its anterior interventricular branch.[30] This reflex is possibly responsible for the severe acute form of hypertension that may follow coronary bypass operations.

Despite the uncertainties that still exist in our present concept of the disturbance of central hemodynamics and cardiac function, it may nevertheless provide a basis for differential therapy. It is first necessary, however, that the varying hemodynamic patterns in hypertension be correctly identified diagnostically.

### Pathophysiology

#### Arterial pressure

The blood pressure, i.e., the mean arterial pressure (P), is a controlled variable, being determined by the cardiac output ($\dot{Q}$) and the total vascular resistance (R)

$$P = \dot{Q} \times R$$

The level of the blood pressure is maintained during both short-term (postural changes, blood loss)

and longer-term deviations (disturbances of water or fluid balance) by numerous, reflex-mediated control mechanisms. Some of these mechanisms act almost immediately, such as the baroreceptor reflex (response time 5 to 15 s). Others exhibit a slower but also more prolonged response, such as the renin-angiotensin-aldosterone system (hours to days) or renal mechanisms for regulating the fluid balance (days to weeks). In hypertension, one or more of these reflex mechanisms and associated control circuits appear to be set at an abnormally high level.

Mean blood pressure values above 105 to 110 mm Hg are regarded as hypertensive. The difficulties and problems of blood pressure measurement and identification of deviations from normal can not be discussed at this point, especially at the time of onset of hypertensive disease when the blood pressure undergoes strong fluctuations (single measurement, repeat measurement, charting of diurnal variations, measurements in the lying, sitting, and standing position, with or without physical or mental stress, etc.).

The systolic blood pressure is determined by the stroke volume of the heart as well as by the capacity and elasticity of the aorta and associated large arteries. This value increases with age,[23,32] rising from about 120 to 170 mm Hg from ages 20 to 70. The deviations from normal increase with age, owing in particular to atherosclerotic vascular changes. High values in the absence of aortic or aortic-valve changes (see below) can be considered a diagnostically useful sign of an increased stroke volume (bradycardia, hyperdynamic heart activity; see below).

The diastolic blood pressure is determined mainly by the total peripheral resistance, as long as the blood volume and thus the filling of the arterial vascular system is normal and the aortic valve intact, and no shunting exists between the aorta and low-pressure system (patent ductus arteriosus, aortic-sinus aneurysms, A-V fistulas, etc.). Values above 90 mm Hg can be considered a sign of increased total peripheral resistance and thus of hypertension. They preclude a normal or reduced peripheral resistance.

The configuration of the arterial pressure curve, as well as its progressive change in the arterial system with increasing distance from the aortic valve,[91] is related to the elastic and resonant properties of the arterial system but is probably not of diagnostic importance. The older method of Wezler and Böger for determining cardiac stroke volume was based on this principle. It has had historical importance, especially as employed by Wezler in the first recognition of hyperdynamic forms of hypertension.[85] Today it has largely been replaced by more accurate methods, although it may again achieve diagnostic significance as a useful noninvasive adjunct to ultrasonic diagnostics.

During physical stress (ergometric exercise test), the systolic blood pressure increases owing to a rise in stroke volume, at times enhanced by altered elastic properties of the central arterial system, while the diastolic value remains largely unchanged. Hypertensive individuals respond to stress in the same way as persons with a normal heart and circulation, in that the percentage increase is comparable in both situations. As in other types of stress (Valsalva maneuver, orthostasis),[17,36] the majority of hypertensives exhibit a normal response, but at a higher pressure level. There are exceptions, however: persons with borderline hypertension (early cases) may exhibit abnormal, diagnostically useful systolic and/or diastolic blood pressure increases during physical and/or mental stress. In advanced hypertension, coexisting cardiac disease (coronary disease with or without infarction, heart failure) may alter the stress test in a pathologic fashion.[1,32,43,44,48,56,57,79,80]

Abnormal blood pressure increases were described by Brod[5] during mental stress in essential hypertension, primarily in its early stage. Abnormalities in the orthostatic regulation of blood pressure occur in forms of hypertension with a reduced plasma volume, e.g., in advanced hypertension cases, during diuretic therapy,[17,37] or in cases of pheochromocytoma.

The level of the arterial blood pressure—i.e., the systolic, diastolic, and mean values—correlates with the prognosis in the absence of other cardiac and circulatory pathology, regardless of whether it is measured during the spontaneous course of the disease or under therapeutic control.

### Cardiac output

The cardiac output is determined primarily by the venous return to the heart according to the Frank-Straub-Starling mechanism, but also by contractility and pulse rate. The latter two factors are subject mainly to sympathetic control. Since the heart rate does not differ significantly from normal in most forms of hypertension or, if so, only temporarily, the cardiac output is the most important index for judging the performance of the heart and the flow rate in the overall circulation. For the analysis of cardiac function, derivative variables of the cardiac output are used, such as stroke volume, mean systolic ejection rate, and stroke work. The latter, as a combined index, includes pressure work of the heart (see p. 252).

For a long time it was assumed that hypertension resulted from an increase in the total peripheral vascular resistance, with a normal cardiac output and stroke volume. The persistence of this assumption,

which we now know to be false, is certainly due in part to the difficulties of measuring the cardiac output. Even today this cannot be considered part of routine diagnostics.

As Wezler proved several decades ago and many other authors have proved since, an abnormally high cardiac output with a normal or even reduced total peripheral resistance may lead to hypertension and is observed in 20% to 80% of cases.[3,6,13,33,57,77,80,85,86] The hemodynamic response varies from one form of hypertension to the next. Augmented cardiac output can be considered an early manifestation of most forms of clinical hypertension. However, it may also be seen later in the course of the disease.[18,56,85] Diagnostic differentiation from hyperkinetic heart syndrome is often difficult or impossible.

A prognostic evaluation of cardiac output changes has not yet been attempted.

### Total peripheral resistance

The total peripheral vascular resistance represents the sum of the organ-related arteriolar resistances localized in the various regions of the circulatory system. These resistances can vary over an extremely wide range, especially in hypertensive disease; they depend chiefly on $\alpha$-adrenergic innervation, which in turn is responsible for short-term changes of rapid onset and more or less limited duration. Angiotensin-mediated vasoconstriction shows a slower onset of action and longer persistence. In addition, the total peripheral resistance is determined by the mechanism of autoregulation,[25,91] which as a rule is confined to individual organs or organ systems.

In general, and particularly in the older literature, hypertension has been equated with an increase in the total peripheral resistance. As already mentioned above, however, we now know that the resistance can vary widely in hypertensive disease.[35] Most forms of hypertension show normal or even decreased resistance values at the onset of their natural course.[5,11,13,14,33,48,56,86] As the disease progresses there is usually an increase in the peripheral resistance. However, considerable variations in the behavior of arteriolar resistance can be observed even in different forms of hypertension. Even in certain cases of established hypertension, resistance may be low or normal. Here the adaptive mechanisms have longer response times (days to weeks), owing to the underlying process and/or related to the influence of therapeutic measures.

The object of this book is not to examine the conditions of vasoregulation in the various circulatory regions. However, it cannot be emphasized strongly enough how unhomogeneous and perhaps even misleading the concept of total peripheral resistance can be: It says nothing about the all-important behavior of the regional blood flows and very little about the reactivity of the vascular system. Nevertheless, the total peripheral resistance is an important factor in considerations of central hemodynamics and an important determinant of the development of secondary hypertensive cardiopathy and arteriopathy (see p. 252).

### Capacitance system

From 70% to 75% of the total circulating blood volume is contained in the venous vascular system.[91] Capacitance, venous tone, and extravenous conveyance mechanisms (respiration, muscle activity, posture) as well as the blood volume determine the quantity of blood returned to the heart.

The venous capacitance system represents the most significant factor in the control of the cardiac output. The variations in venous tone produced by $\alpha$-adrenergic innervation, which may be local in character and lead to a redistribution of the circulation blood volume, are capable of increasing the quantity of blood in the cardiopulmonary region, thereby altering the blood return to the heart and thus diastolic filling.

Tonal changes in the capacitance system during hypertension have been investigated by various authors.[3,6,17,20] While no uniform pattern has emerged,[19] it nevertheless appears that a regional redistribution of the circulating blood volume with a subsequent increase in the central blood volume is frequently produced in hypertension by a coordinated increase in venous tone. This probably occurs regularly in the early hypertensive phase.[5,6] The suggestion that this mechanism represents the primary disturbance in hypertension may or may not be true. It definitely underscores the importance of the capacitance system.

However, luminal changes in the peripheral venules together with tonal changes in the arterioles may very well be close to the mechanism that initiates hypertension, inasmuch as transcapillary filtration represents a crucial step in the distribution of the extracellular fluid volume.

### Blood volume

The blood volume has long been of interest as a determinant of cardiac and circulatory performance. With the plasma volume accounting for some 60% of the total blood volume, the blood represents a significant part of the extracellular space and extracellular fluid volume. This volume, which is controlled mainly by the kidneys, is considered the central variable in blood pressure regulation.[25,91] This assumption fits well with observations at the onset of hypertensive disease showing elevations of the cardiac

output which could be attributed to an increased blood delivery to the heart.

However, corresponding increases in the circulating blood volume have not been regularly found for the group of hypertensives as a whole.[79] This may relate to difficulties of blood volume determination in the older studies, as well as to the common but unreliable practice of grouping together different types and stages of hypertension. Finally, a hemodynamically active change in the blood volume could be so slight, both in absolute terms as well as in percentage of the total extracellular volume, that it escapes measurement.

In any event, an increase of at least the "central" blood volume associated with the aforementioned blood redistribution due to venoregulatory processes can indeed be found in the majority of early (borderline) hypertensives. Moreover, when the hypertension is classified according to stage, an inverse, albeit loose, correlation is found between the duration of the hypertension and the degree of increase in the total peripheral resistance.[14,20,28] The longer the hypertension persists and the higher the total peripheral resistance, the greater the decrease in circulating blood volume.

## Mechanism of Hypertension

Guyton has developed a concept for the pathogenetic mechanism of hypertension which takes into account numerous interrelated, mostly feedback mechanisms of blood pressure control.[25] The localization of the functional disturbance may vary in different forms of hypertension. Nevertheless, the Guyton concept is a generally valid one which is capable of explaining the majority of phenomena observed.

Briefly, the concept can be summarized as follows: Renal function, water balance, vasoregulation, central hemodynamics, and cardiac function are very closely interrelated. The time constant of the circulatory control mechanisms plays a decisive role: Short-term adaptive mechanisms such as the baroreceptor reflex are of considerably less importance than long-term processes such as the mechanisms governing the sodium and water balance and organ-specific blood flow (autoregulation).

Of central importance is the functional state of the kidneys and the mechanism of diuresis, which depends on the blood pressure. This sensitive mechanism regulates the sodium and water balance and is subject to influence by the renin-angiotensin-aldosterone system (RAAS), norepinephrine, i.e., the sympathetic activity, as well as many other factors. Disturbances may lead to a significant increase in the extracellular fluid volume even with very minor water retention. Alterations of this mechanism may be present, incidentally, even in the absence of the usual clinical criteria for renal dysfunction. Estimation of creatinine, urea, and uric acid, as well as conventional renal function, will not be capable of detecting a functional defect of the aforementioned nature and its pathogenetic significance.

Disturbance of the pressure diuresis mechanism leads to a transitory increase in blood volume, which parallels the change in extracellular fluid volume. This is followed by a considerable rise of the cardiac output. The baroreceptor reflex responds to the expected blood pressure increase with a concordant, transitory reduction of heart rate and of the total peripheral resistance. As a result, fluid leaves the vascular system (capillary filtration), and the original state is restored.

However, because the mechanism continues to act, the extracellular fluid volume continues to increase, and the functional chain remains intact. The result is a resetting of the baroreceptor reflex. In the long run, however, the mechanism of autoregulation becomes operative within the organ tissues. Within a period of days to weeks they respond to the increased perfusion ("overperfusion") with a rise of local vascular resistance in an effort to reduce the blood supply to a level normal for the parenchyma. If this occurs in a sufficient number of regions, the result is an increase in total peripheral resistance and venous tone. The latter factor, in turn, increases the blood delivery to the heart, thereby raising the cardiac output again.

The initially normotensive state is followed by a period of more or less mild hypertension due to an elevated cardiac output, with overperfusion of the body in a state of reduced peripheral resistance. Then blood pressure rises sharply, as cardiac output remains augmented and peripheral resistance begins to rise.[11]

In both of these phases of hypertension, in which the blood pressure values are often still borderline, the values for contractility and cardiac work are strongly increased.[10,43,44] Frequently signs of increased adrenergic activity are seen,[18,43] often accompanied by a decrease in parasympathetic tone.[34]

At this time the elevated cardiac output starts to return to the normal range, while the total peripheral resistance continues to rise. In the later course cardiac output may fall below normal, particularly if secondary disturbances of cardiac function supervene (e.g., myocardial infarction).

Of course this pattern is not typical of all forms of hypertension. An example is the pheochromocytoma. In this case adrenergic stimulation is predominant from the outset, and a decrease, rather than

increase, of blood volume is the rule. Even here, however, the central blood volume is not decreased to the same degree as the total blood volume and may even be increased in some cases.

## Forms of Hypertension

The different experimental and clinical forms of hypertension often show considerable differences in terms of the central hemodynamic response. Considerations of differential therapy make it necessary to outline the various patterns of findings that can be considered typical.

It is known that the most common cause of resistance to therapy in hypertension lies in an unrecognized increase in the extracellular fluid volume, the reduction of which restores responsiveness.

Hyperdynamic forms of hypertension respond well to $\beta$-receptor blockade or sympathetic inhibition with clonidine. These measures, however, may be ineffective in forms with normal or decreased cardiac output and high peripheral resistance. In the latter case, vasodilators are indicated. The two examples cited should not disguise the fact that we are still far from a treatment concept oriented toward the hemodynamic disturbance.[52] Nevertheless, we believe that such differential therapeutic considerations are important and indispensable.

### Experimental hypertension

In the Goldblatt model of hypertension as well as in perinephritic encapsulation, a rise of the cardiac output with an initially normal peripheral resistance is observed early in the development of the hypertension, usually within the first few days to a maximum of 4 weeks. For both experimental forms it has been shown that the high cardiac output results not from an increase in heart rate but from an increased stroke volume.[82] Evidence also suggests that a primary, sympathetic-mediated increase of contractility is not responsible. The plasma volume was found to be normal or slightly elevated, but the principal finding was a decreased distensibility of the veins, i.e., an increase in venous tone. The familiar increase in total peripheral resistance occurs only later in the course and is accompanied or followed by a return of the cardiac output to normal. Thus, both forms of experimental hypertension are in very good agreement with the concept described above and with the observations of clinical hypertension.

In experimental neurogenic hypertension with denervation of the aortic arch and carotid sinus, varying conditions are found. In some cases the cardiac output is elevated, in others the total peripheral resistance, and sometimes both. Hypertension following stellate ganglion stimulation and surgically induced brainstem lesions also generally exhibits varying degrees of increase in the cardiac output but results mainly from a rise in total peripheral resistance; the sodium and fluid balance is unchanged. The cardiac output increase is often only transitory, whereas the elevation of resistance tends to be persistent.

None of the experimentally induced forms of hypertension previously mentioned represents in a comprehensive way the model of clinical hypertension, particularly that form which is of greatest interest—essential hypertension. This syndrome is mimicked most closely by the genetic hypertension seen in the spontaneously hypertensive rats (SHR) of Okamoto-Aoki.[50] Observations have been made in this model which fit only in part with the mechanism described above: In young SHR, the cardiac output is somewhat higher than in normotensive controls, but because the heart rate is also higher, the stroke volume is normal. Probably as a result of this, contractility is also increased. Here, too, it appears that the cardiac output is elevated in the early phase, but that this is due more to increased adrenergic stimulation than to an increased fluid load on the heart caused by an expanded extracellular fluid volume. Of course it must be considered that fluid balance investigations under these conditions are very difficult and problematic.[19]

In any case, an increase in total peripheral resistance eventually develops which heralds sustained hypertension. But it appears that the development of the progressive peripheral resistance increase does not depend upon the elevated cardiac output in the offspring of these rats.

A decrease in extracellular fluid volume and plasma volume could even be demonstrated in one type of SHR (New Zealand), indicating that the chain of events described above cannot be held responsible for the development of hypertension. Again, under these circumstances, the progressive rise in peripheral resistance is seemingly independent of changes in central hemodynamics and cardiac activity.

### Clinical forms of hypertension

Studies employing different modes of investigation have consistently revealed a normal cardiac output and increased total peripheral resistance in the overall group of clinical hypertension cases. However, a reevaluation of these, for the most part, older studies is necessary in view of the fact that effects of drug therapy were often not fully accounted for, and that a differentiation according to the type and severity of the hypertension can often reveal marked differences.

***Borderline Hypertension.*** According to the criteria of the World Health Organization,[89] which are based mainly on the Framingham study,[37] borderline hypertension is present if (1) a diastolic blood pressure of more than 90 to 105 mm Hg is measured on at least two separate occasions, (2) values are normal during the interval between, and (3) there are no demonstrable secondary manifestations of the hypertension (e.g., ocular funduscopic changes, left ventricular hypertrophy).[39]

Clearly then, the syndrome of borderline hypertension encompasses a large number of early forms of essential hypertension. Although it cannot always be reliably differentiated from the "hyperkinetic heart syndrome," it nevertheless appears to constitute a rather uniform group.[3,5,33,35,48,57,77,86]

The changes in hemodynamics vary, but on the whole the findings can be described quite well: The heart rate is variable and often increased. The cardiac output is elevated, but is occasionally normal and in rare instances even decreased. When the cardiac output is elevated, this is usually associated with an increased stroke volume and often increased mean systolic ejection rate and is accompanied by an increase in myocardial contractility. The total peripheral resistance is normal and sometimes decreased; it increases only later in the course of the hypertension, while the cardiac output returns to normal.

Studies on the plasma volume in borderline hypertension have revealed normal or even reduced values. However, a redistribution in favor of the central (cardiopulmonary) blood volume has been found.[19] A marked decrease in plasma volume is seen in the later course.

In the search for causes of the elevated cardiac output, increased adrenergic tone and decreased parasympathetic innervation of the heart have been assumed. Indeed, the response to vagal blockade is reduced with atropine. Only after combined vagal and sympathetic blockade are both cardiac output and heart rate normalized.[18] The total peripheral resistance, which is generally within the normal range, was described by some authors as being inappropriately high in relation to the cardiac output.[20] The peripheral resistance also shows an abnormal response to stress conditions: The decrease in resistance with increasing stress and rising cardiac output is more gradual in borderline and essential hypertension than in normotensive persons. Only $\alpha$-adrenergic blockade lowers the "normal" peripheral resistance to an appropriate level, similar to its behavior under stress following $\beta$-blockade and atropine.

Patients with borderline hypertension who exhibit normal or low cardiac output values generally have decreased plasma volumes and elevated renin values.

***Essential Hypertension.*** The hemodynamic and cardiac responses in the early stages of essential hypertension are identical with those described for borderline hypertension (v.s.). Three stages can be distinguished during the course of the disease:[6,14,21,77]

1. The early, borderline stage is marked by the hemodynamic response and the changes of cardiac function described above. There are no morphologic signs of secondary vascular or organ damage at this point in time.
2. As the duration of the hypertension increases, there is a normalization of cardiac output and a progressive increase in total peripheral resistance. Now disturbances of cardiac function begin to emerge, although the cardiac work is still high and contractility may be increased. Initial morphologic organ changes are demonstrable in the heart and kidneys.
3. The total peripheral resistance is by now strongly increased, with considerable rise of blood pressure. The cardiac output is normal or decreased, as is stroke volume. The heart rate is usually normal but may be increased in patients developing heart failure. Accordingly, the myocardial contractility is normal or diminished (v.i.).

The plasma volume is decreased according to the duration and severity of the disease. There are distinct morphologic vascular changes which are evident, for example, in the ocular fundus. The hemodynamic changes which are characteristic of the three stages of essential hypertension are reviewed in Table 1.

***Renal Hypertension.*** The single term "renal" as a classification of hypertension may suggest a uniform picture, but in reality it encompasses a number of very different syndromes.[25,31] Nevertheless, all cases of renal hypertension, regardless of the respective etiology, are characterized by an early increase in the extracellular fluid and plasma volume. There is a very marked elevation of the cardiac output, stroke volume, and mean systolic ejection rate. Orthostatic hypertension indicates a hyperreactivity of the sympathetic nervous system. In addition, there is an early increase in the total peripheral resistance, which leads to severe degrees of hypertension. The effects of a combined increase in both the preload (increased blood return) and afterload (blood pressure)—volume and pressure load—may lead to relatively early incidence of cardiac failure (see below).

**Table 1.** Hemodynamic Changes during the Course of Hypertension*

| | Early Stage | Main Phase | Late Stage |
|---|---|---|---|
| Cardiac output | +/++ | Normal/− | −/−− |
| Stroke volume | Normal/+ | Normal/− | −/−− |
| Contractility | +/++ | Normal/+/− | −/−− |
| Cardiac work | ++ | Normal/+ | +/++ |
| Heart rate† | Normal/+ | Normal | Normal/+/++ |
| Total peripheral resistance | Normal/− | +/++ | ++ |
| Central blood volume | + | Normal/− | −/−− |
| Total plasma volume | Normal/− | −/−− | −− |
| Blood pressure | Borderline | ++ | +++ |

*The hemodynamic changes indicated are only rough generalizations (see text). In reality, the changes may vary substantially depending on the type of hypertension involved. The early stage is that in which blood pressure values are still labile (borderline). In the late stage, the picture is determined in large part by secondary complications (coronary disease, cardiac failure, etc.).
+, increased; −, decreased.
†Reflex bradycardia (baroreceptor reflex) is absent.

During the course of the disease the peripheral resistance increase soon dominates the hemodynamic pattern, although expansion of the extracellular fluid volume may remain very markedly elevated until the later stages of the disease. While the progressive decrease in plasma volume, which is typical of essential hypertension, is also present in renal hypertension, it has a delayed onset. In the early stages, increased fluid volume is present. Hypertension following acute glomerulonephritis is the prototype disease in terms of the hemodynamic pattern described.

In renal hypertension based on pyelonephritis, conditions are highly variable. This may have to do with the occurrence of sodium-loss syndromes, which can effect a variety of changes in the extracellular fluid volume. Thus, elevations of cardiac output are present only in some cases. The increase in peripheral resistance is the principal feature and dominates the development of hypertension.

In patients with chronic renal failure undergoing dialysis therapy, a distinctive pattern is observed. The blood pressure can, as a rule, be satisfactorily controlled by adjusting the fluid balance and plasma volume. If blood pressure elevations occur under dialysis, these are accompanied by an increase in cardiac output resulting not from a high stroke volume but rather from an increased heart rate. There is a concomitant increase in peripheral resistance; the mechanism for this is unclear. However, the rule still applies that the blood pressure can be adequately controlled by adjusting the extracellular fluid volume.

***Coarctation of the Aorta.*** The earlier theory that hypertension in coarctation of the aorta is caused by an increased resistance to ejection in the aortic segment proximal to the constriction is no longer tenable. Hemodynamic studies have revealed that the cardiac output is abnormally high, while the total peripheral resistance is within normal limits or even low. A renal pressor effect is probably involved. The cause of this is uncertain, but a reduction of renal blood flow prior to the development of sufficient collaterals may play a role. Neurohumoral factors are probably also involved.

Following surgical correction of the obstruction, the hypertension is relieved in only about 40% of cases, and even then usually only with the aid of drug therapy. Long-term antihypertensive therapy is necessary in more than 30% of cases. A satisfactory explanation for the mechanism of hypertension and hemodynamic changes in coarctation of the aorta has not yet been offered.

***Pheochromocytoma.*** Hypertension caused by the release of abnormal amounts of the sympathetic transmitter substances from pheochromocytomal tissue is characterized by a variety of findings, depending on the relative quantities of epinephrine and norepinephrine released. As a rule, the heart rate and total peripheral resistance are strongly increased. The cardiac output is usually normal. The positive inotropic stimulation in the face of a reduced plasma volume does not permit an increase in stroke volume or cardiac output. The result is a highly labile cardiac and circulatory situation in which even very mild external stimuli can evoke acute pressor responses. Cardiac and circulatory failure may easily supervene.

***Primary Hyperaldosteronism.*** The cause of hypertension in primary hyperaldosteronism rests with an increase of aldosterone secretion. The mech-

anism by which this substance produces hypertension is perhaps a model for the chain of events described earlier. Although only a few hemodynamic studies have been done to date on this relatively infrequent syndrome, it can be stated that early cases show high cardiac output and low resistance. In the chronic stage, hypertension is clearly due to an increase in peripheral resistance. Hemodynamic studies have shown that therapeutic aldosterone blockade with spironolactone leads within a period of days and weeks to a regression of the resistance increase, with a normalization of blood pressure.[11] Discontinuation of spironolactone therapy leads promptly to sodium retention and expansion of the extracellular fluid and plasma volume. This is accompanied by a rise of the cardiac output and stroke volume accounting for hypertension. There is no significant change in heart rate. *Before* any change occurs in total peripheral resistance, the blood pressure begins to rise. Only thereafter a progressive increase in peripheral resistance develops, with a further rise of blood pressure. Finally the elevated cardiac output gradually returns to normal. Restoration of the aldosterone blockade with spironolactone reverses the process.

In long-standing cases of hypertension associated with primary hyperaldosteronism, the heart, kidneys, and vessels undergo secondary changes typically seen in other types of hypertension as well.

### Summary

The changes in central hemodynamics that occur in arterial hypertension are, as a rule, secondary in nature. The principal regulatory change is a resetting of the arterial blood pressure at an abnormally high level, regardless of the etiologic mechanism. Meanwhile, normal adaptive mechanisms remain largely unchanged.

The blood pressure, as a controlled variable, is given by the product of cardiac output and total peripheral resistance. Each of these variables, in turn, undergoes characteristic changes during the course of hypertension.

Numerous reflex mechanisms have a modifying influence on blood pressure regulation. The short-term, quick-acting mechanisms include the baroreceptor reflex and regulation via the renin-angiotensin-aldosterone system. Both are capable of adaptation to various blood pressure levels. The principal long-term control mechanisms are those concerned with the regulation of sodium and water balance, again the RAAS and the renal pressure/diuresis mechanism, as well as the autoregulation of regional, organ-related blood flow, which is independent of sympathetic innervation and does not depend on the presence of angiotensin.

In most cases, the development of hypertension begins with an increase in the extracellular fluid and plasma volume. This results in a greater venous blood return to the heart, possibly reinforced by a simultaneous increase in venous tone and shifting of venous blood volume toward the central, cardiopulmonary region. The heart responds with an increase in stroke volume, and, hence, cardiac output. The reflex decrease in total peripheral resistance is offset in the long run by the mechanism of autoregulation, and an elevation of blood pressure results. The further course of the hypertension is marked by a progressive rise of the peripheral resistance. At the same time the venous tone increases, while the plasma volume declines. Finally, after the cardiac output returns to normal, the arterial pressure increase is maintained solely by the increased peripheral resistance. Later on, the hemodynamic pattern is further altered by the development of secondary organ changes (e.g., cardiac complications).

Typical hemodynamic patterns have been determined for a number of experimental forms of hypertension, as well as for most clinical forms. The mechanism described is considered to be valid for most cases. Other types of initiating mechanism and course occur in certain forms of renal hypertension, hypertension associated with pheochromocytoma, and certain special forms such as the severe acute hypertension that follows coronary bypass surgery.

Quantitative studies on the blood pressure response to changes in extracellular fluid volume according to the previously described mechanism of a chain of interlinked "control circuits" have revealed some striking relationships: Increasing the extracellular fluid volume by only 2% causes a 10% to 20% increase in the cardiac output, which can in turn lead to a persistent increase of 30% to 40% in total peripheral resistance, and thus to an arterial blood pressure elevation of 40% to 60%!

## Cardiac Function

Based on the cardiac manifestations of hypertension, a basic distinction is made between the severity of the hypertension;[22,61,77] the extent, localization, and severity of the resulting myocardial hypertrophy *(= myocardial factor);* and possible coronary manifestations *(= coronary factor).*[63] The myocardial and coronary factors can develop independently but almost always lead to reciprocal effects on ventricular mechanics and coronary circulation in the presence of significant hypertensive cardiac involvement (Fig. 1).

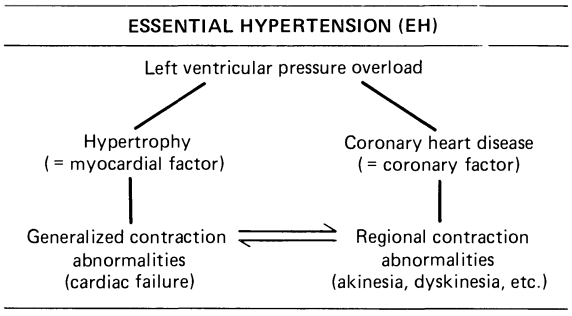


**Figure 1.** Schematic diagram of the cardiac complications of chronic arterial pressure overload of the left ventricle. The consequences of hypertrophy (myocardial factor) and coronary disease (coronary factor) lead to regional and generalized contraction abnormalities in the left ventricle. From Strauer, ref 72

It has proved useful from a clinical and pathophysiologic standpoint to describe central hemodynamics, ventricular function, and coronary circulation on the basis of a four-group classification of hypertensive heart disease which takes into account cardiac hypertrophy, dilatation, and failure as well as the coronary effects of arterial hypertension.[63,72]

Group I: compensated arterial hypertension without coronary stenosis
Group II: compensated essential hypertension with coronary stenosis
Group III: essential hypertension with regional abnormalities of wall contraction
Group IV: decompensated essential hypertension

## Ventricular Function

### Size of left ventricle

An accurate, standardized measurement of left ventricular size is of considerable practical importance for functional assessment and management of the hypertensive heart. Physical (percussion, palpation), electrocardiographic (and vectorcardiography!), radiologic (standard X-ray), and echocardiographic (M-mode and two-dimensional echocardiography) techniques are employed. ECG and VCG, as well as the standard chest X-ray, are considered useful and easy-to-perform routine procedures for semiquantitative estimation of ventricular hypertrophy and overall heart size and volume. Echocardiography furnishes direct measurements of wall thickness and allows approximate calculation of left ventricular mass, as well as cavity size. Owing to its simplicity, repeated application is possible, which is deemed of considerable value during follow-up.

In compensated essential hypertension with and without coronary stenosis (coronary heart disease, groups I and II), the radiologic size of the ventricle is usually normal even in the presence of severe left cardiac hypertrophy,[64] whereas the ECG is regularly abnormal indicating increased muscle mass. The normal overall heart size is due on the one hand to the normal or diminished end-diastolic volume of the left ventricle, which can cause the left ventricular silhouette to appear normal-sized despite a considerable mass increase owing to a reduction of the internal lumen. On the other hand, the left ventricular mass increment usually does not exceed 40% to 50% on the average in these hypertensive hearts (Fig. 2). The increased muscle mass results in a wall thickness gain of about 4 to 5 mm, which does not measurably alter the overall radiologic size of the left ventricle in most cases[45,46] but can easily be measured by echocardiography. However, the cardiac configuration still shows aortic and left-sided prominence in 87% of cases in group I and 84% of cases in group II, so that the left ventricular configuration on X-ray can provide some clinically useful etiologic information in the compensated hypertensive heart.[64]

### Ventricular mass and dimensions

Depending on the severity and duration of the hypertension, the hypertensive heart exhibits a compensatory myocardial growth which, according to Linzbach, is uniform up to a cardiac weight of about 500 g and a left ventricular weight of about 200 to 250 g, and which results from a thickness increase and growth of preexisting myofibrils and muscle fibers.[45,46] Only at higher cardiac and ventricular weights, i.e., in pathologic pressure hypertrophy, does a true increase in the number of muscle fibers occur. Macroscopically, compensated pressure hypertrophy is characterized by a thick ventricular wall, a thickened ventricular septum, a small internal chamber volume, and an elongated outflow tract. By contrast, large ventricles with high end-diastolic volume and eccentric dilatation will be seen in the decompensated stage.

The severity, type, and duration of the pressure load on the left ventricle are important factors in the development of hypertrophy. Volume overload, elevated heart rate, and increased sympathetic innervation, as seen to varying degrees in certain, especially early, forms of hypertension, will contribute to the process of hypertrophy and may influence the ratio of wall thickness and chamber volume. In longstanding established hypertension, the mass increase is greater than in borderline hypertension with its brief hypertensive period.[59] The ventricular mass also increases with the severity of the cardiac

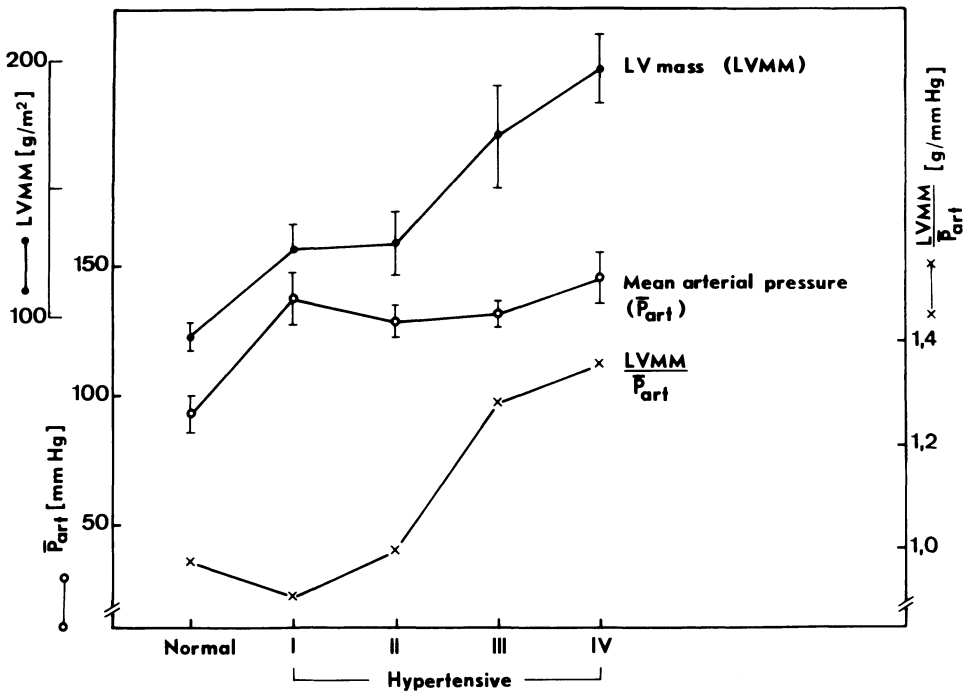


**Figure 2.** Left ventricular muscle mass (LVMM), mean arterial pressure, and left ventricular muscle mass per unit pressure load ($LVMM/\bar{P}_{art}$) in the normal group and the four hypertensive groups defined (see text). From Strauer, ref 72

manifestations of the hypertension. Thus, at comparable left ventricular pressure loads (50% increase in mean arterial pressure), the ventricular mass is 40% to 48% above normal in groups I and II, respectively, while it is 78% and 91% above normal, respectively, in groups III and IV (Fig. 2, Table 2). This means that coronary manifestations of hypertension (coronary artery stenosis >75%, group II), myocardial lesions based on impaired coronary blood flow (regional wall contraction abnormalities, group III), and congestive effects of hypertension (generalized contraction abnormalities, group IV) are accompanied by or may be the reason for a progressive increase in absolute ventricular mass from group I through group IV[75,76] (Fig. 2, Table 2). Also, the ventricular mass per unit developed pressure is considerably increased in groups III and IV, such that the mass increase is disproportionately high in relation to the pressure load (mean arterial pressure) as arterial hypertension progresses. Besides the level and duration of the blood pressure elevation, the manner in which the hypertension develops (abrupt/gradual, volume/pressure load), the heart rate and contractility (sympathetic influence), and genetic factors are also important with regard to the development of pressure-induced hypertrophy.

The end-diastolic pressure and end-diastolic volume of the left ventricle (filling volume) are markedly increased in arterial hypertension with coronary artery disease with or without regional as well as generalized contraction abnormalities (Fig. 3). The ratio of the muscle mass to the end-diastolic volume, called the mass-volume relation, is increased in compensated hypertensive patients (groups I to III) in favor of a considerable mass increase per unit volume. In decompensated hypertensives (group IV), on the other hand, the mass-volume relation tends to be numerically normal, owing to a disproportionate ventricular dilatation with a progressive mass increase (Table 2). This means that at least two inappropriate or disproportionate forms of hypertrophy can exist during the course of essential hypertension: (1) a mass increase which is disproportionately large relative to ventricular size in compensated hypertension, and (2) a mass increase which is not accompanied by progressive ventricular dilatation in the decompensated stage.[72]

### Pumping variables and contractility indices

The cardiac index, stroke index, and ejection fraction of the left ventricle are normal or elevated in compensated essential hypertension with and without coronary stenosis (groups I and II), and are significantly reduced in groups III and IV (regional as

**Table 2.** Mean Arterial Pressure ($\overline{P}_{art}$), Left Ventricular Muscle Mass (LVMM), Ratio of LVMM and $\overline{P}_{art}$, Left Ventricular End-Diastolic Pressure ($P_{LVED}$), End-Diastolic Volume (EDV), and Mass-Volume Relation (LVMM/EDV) in the Normal Group and the Four Hypertensive Groups Defined

| | $\overline{P}_{art}$ (mm Hg) | LVMM ($g/m^2$) | LVMM/$\overline{P}_{art}$ ($g/m^2 \cdot$mm Hg) | $P_{LVED}$ (mm Hg) | EDV ($ml/m^2$) | LVMM/EDV (g/ml) |
|---|---|---|---|---|---|---|
| Normal | 91 ± 9 | 92 ± 6 | 1.01 | 10 ± 1 | 81 ± 6 | 1.14 |
| Group I | 136 ± 9§ | 122 ± 11† | 0.90 | 12 ± 2 | 74 ± 6 | 1.65 |
| Group II | 128 ± 6§ | 129 ± 14‡ | 1.01 | 15 ± 4 | 80 ± 5 | 1.61 |
| Group III | 131 ± 3§ | 168 ± 16§ | 1.28 | 19 ± 7* | 112 ± 16 | 1.50 |
| Group IV | 146 ± 4§ | 192 ± 15§ | 1.32 | 23 ± 6† | 147 ± 17† | 1.31 |

*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.005$.
§$p < 0.001$.
From Strauer, ref 75 and 76.

well as generalized abnormalities of left ventricular contraction = congestive, decompensated essential hypertension). The maximal rate of rise of left ventricular pressure shows a pressure-dependent increase in all hypertensive groups (Fig. 4, Table 3).

The relation between end-diastolic volume and ejection fraction shows that the ejection fraction of the left ventricle can remain normal even in severe arterial hypertension with left ventricular hypertrophy, as long as there is no increase in end-diastolic volume (compensated arterial hypertension with and without coronary heart disease) (Fig. 5).[68] However, even incipient ventricular dilatation causes a marked decrease in the ejection fraction corresponding to a regression, as in patient groups with coronary heart disease and aortic stenosis (Fig. 5).[62]

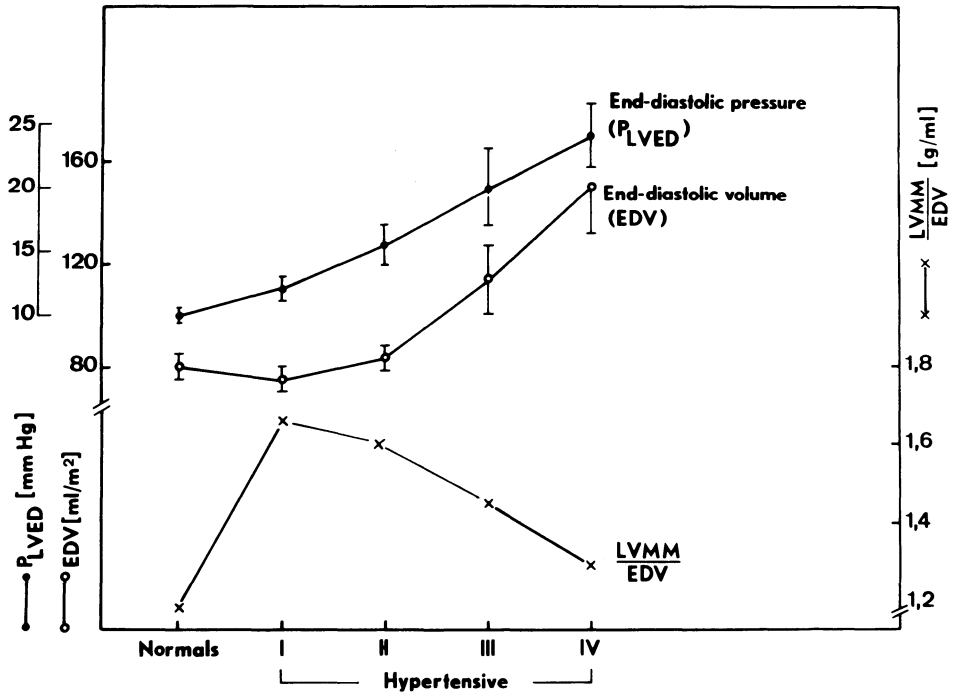


**Figure 3.** End-diastolic pressure, end-diastolic volume, and mass-volume relation (LVMM/EDV) in the normal group and the four hypertensive groups defined. Note the considerable increase in the mass-volume relation in the compensated hypertensives and the numerical normalization with increasing cardiac decompensation. From Strauer, ref 72

**Table 3.** Maximal Rate of Rise of Left Ventricular Pressure ($dp/dt_{max}$), Cardiac Index, Left Ventricular Ejection Fraction (EF), Mean Ejection Rate (MNSER), and Mean Velocity of Fiber Shortening ($V_{CF}$) in the Normal Group and the Four Hypertensive Groups Defined

| | $dp/dt_{max}$ (mm Hg/s) | Cardiac Index (liters/min · $m^2$) | EF (%) | MNSER (vol/s) | $V_{CF}$ (circ/s) |
|---|---|---|---|---|---|
| Normal | 1690 ± 90 | 3.82 ± 0.09 | 72 ± 2 | 2.52 ± 0.18 | 1.62 ± 0.13 |
| Group I | 2460 ± 110§ | 3.95 ± 0.08 | 78 ± 5 | 2.68 ± 0.21 | 1.71 ± 0.12 |
| Group II | 2400 ± 94§ | 3.93 ± 0.09 | 69 ± 5 | 2.50 ± 0.20 | 1.36 ± 0.11 |
| Group III | 2310 ± 88‡ | 3.22 ± 0.10‡ | 61 ± 6* | 1.98 ± 0.38 | 0.74 ± 0.14‡ |
| Group IV | 2190 ± 102† | 3.24 ± 0.11‡ | 40 ± 8† | 1.21 ± 0.44† | 0.44 ± 0.14‡ |

*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.005$.
§$p < 0.001$.
From Strauer, ref 64 and 72.

Thus, essential hypertension, together with aortic stenosis and coronary heart disease, is counted among the cardiac diseases which, with increasing left cardiac enlargement, are accompanied by a decline of ventricular pump function and contractility as measured by changes in the left ventricular ejection fraction. This behavior is quite marked and sensitive compared to conditions such as mitral and aortic regurgitation and ventricular septal defect.[60–62,66–68] Comparable relations are also seen between end-diastolic volume and mean velocity of fiber shortening (VCF) as well as the ejection rate normalized for ejection time (MNSER). Thus, a ventriculographically demonstrable increase in ventricular chamber size is a suitable criterion for recognition of depressed ventricular function in patients with essential hypertension.[63] Similarly, a change in cardiac volume or left ventricular size documented by standard chest X-ray should provide evidence of a clinically relevant alteration of ventricular function in essential hypertension.

Normal values for cardiac index, ejection fraction,

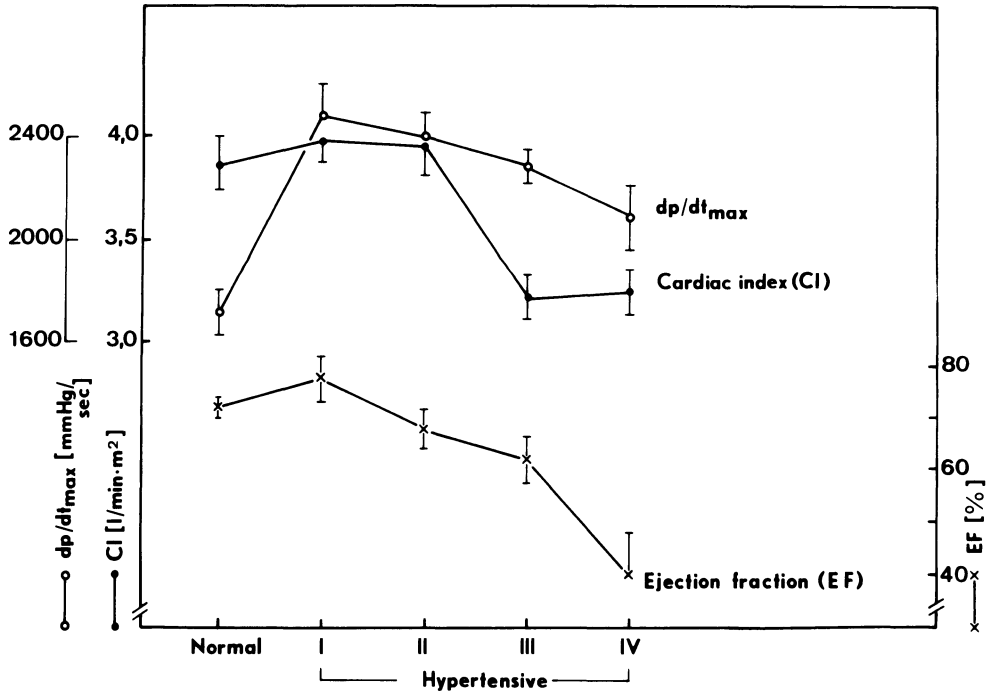


**Figure 4.** Maximal rate of pressure rise in the left ventricle ($dp/dt_{max}$), cardiac index, and ejection fraction of the left ventricle. From Strauer, ref 64

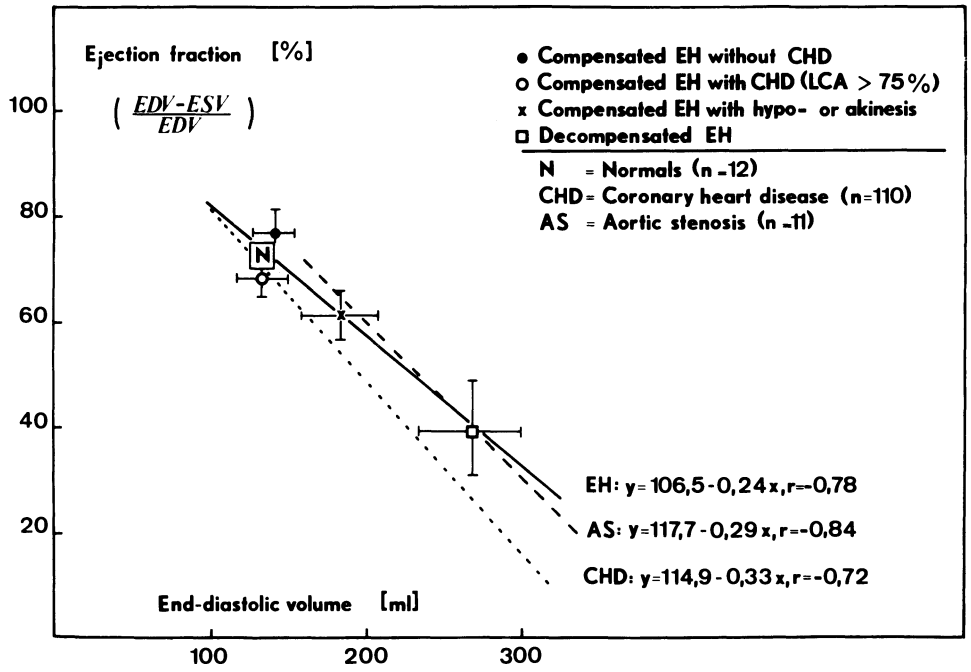


**Figure 5.** Relationship between end-diastolic volume and ejection fraction of the left ventricle in the defined hypertensive groups, the normal group, and in patient groups with aortic stenosis and coronary heart disease. From Strauer, ref 72

maximal rate of pressure rise, and auxotonous velocity and ejection parameters in hypertensive groups I and II indicate that despite considerable left ventricular hypertrophy with a 40% to 50% increase in muscle mass, ventricular function may be normal or even increased. This means that the pressure hypertrophy that occurs in compensated essential hypertension is not accompanied by a decline of ventricular function.[62-64] Thus, the hypertrophy in essential hypertension differs substantially from other forms of pressure hypertrophy, e.g., those due to aortic stenosis or coarctation of the aorta. Here a significant mass increase is generally accompanied by a decline of ventricular function and contractility even in the clinically compensated stage.[49,59] There is no correlation between left ventricular mass increase and diminished contractility in essential hypertension with pressure hypertrophy of the ventricle. Besides the forms of pressure hypertrophy that can be induced experimentally by hyperthyroidism and Goldblatt hypertension,[60,82] compensated essential hypertension thus represents a clinical disease which departs from the concept of diminished contractility resulting from pressure-induced ventricular hypertrophy.[49] The decisive factor could be that the patient with essential hypertension has a different hemodynamic history—i.e., type, duration, and severity of left ventricular pressure and volume load, and sympathetic stimulation are different from those of patients with other types of left ventricular pressure load. Thus, the general assumption of diminished contractility due to pressure hypertrophy is not justified.[9,10,62-64]

Assessment of ventricular function during physical exertion (ergometry in supine position with load of 1 W/kg) shows that in compensated hypertensive patients of comparable age with a normal coronary angiogram and different degrees of left ventricular hypertrophy (LV wall thickness = 0.69 cm/m$^2$ in group A, 0.86 cm/m$^2$ in group B), the variables of ventricular function are largely normal even with a very great increase in ventricular mass (Table 4).[64] Here the rise of left ventricular end-diastolic pressure is normal in group A and only slightly elevated in group B (from 12 to 17 mm Hg on the average). The cardiac index is above normal in moderate hypertension (group A) and is 90% of normal in the presence of severe left cardiac hypertrophy. Quantitatively similar findings are obtained for changes in stroke index and maximal rate of pressure rise. The relations between end-diastolic pressure and cardiac index or rate of pressure rise at rest and during exercise thus demonstrate a normal or increased stress reserve in group A with moderate left cardiac hypertrophy, while the hypertensives with severe left cardiac hypertrophy (group B) may exhibit a slight decrease in their stress reserve.[64]

As indicated by the tests performed during graded

**Table 4.** Left Ventricular End-Diastolic Pressure ($P_{LVED}$), Maximal Rate of Rise of Left Ventricular Pressure ($dp/dt_{max}$), Cardiac Index and Stroke Index at Rest and during Physical Exertion in a Normal Group and in Essential Hypertensives with Different Degrees of LV Hypertrophy

| | $P_{LVED}$ (mm Hg) | | $dp/dt_{max}$ (mm Hg/s) | | Cardiac Index (liters/min · $m^2$) | | Stroke Index (ml/stroke · $m^2$) | |
|---|---|---|---|---|---|---|---|---|
| | Rest | Exertion | Rest | Exertion | Rest | Exertion | Rest | Exertion |
| Normal | 9.5 | 12.5 | 1680 | 2590 | 4.02 | 8.6 | 51 | 68 |
| Essential hypertension | | | | | | | | |
| Group A* | 10 | 12 | 2190 | 3130 | 4.21 | 9.1 | 48 | 72 |
| Group B† | 11.5 | 16.5 | 2150 | 2990 | 3.88 | 8.2 | 49 | 69 |

*LV wall thickness = 0.69 $cm/m^2$.

†LV wall thickness = 0.86 $cm/m^2$; n = 14.

From Limbourg et al., ref 44; Strauer, ref 64 and 72.

exercise, the stress reserve of the hypertrophied left ventricle is generally normal and may even be supranormal[43] in compensated essential hypertension.[44,64] This means that cardiac output will be normal even under conditions of exertion and that significant pressure hypertrophy of the left ventricle need not imply exertional failure, though this is usually the case in the presence of coexisting coronary disease and more serious cardiac manifestations of hypertension (hemodynamically significant coronary stenoses, regional wall motion abnormalities, ventricular dilatation). One therapeutic implication is that measures with a positive inotropic action (e.g., digitalis glycosides) are not indicated in compensated essential hypertension with a view toward improving ventricular function and contractility, since there is no depression of the resting and exertional function of the left ventricle which would justify glycoside therapy. Whether the use of digitalis glycosides in compensated essential hypertension can delay the development of exertional failure is still unclear.

A clinically relevant impairment of ventricular function and contractility can occur in essential hypertension if any of the following are present:[44]

1. Coronary stenosis > 75%, with or without prior myocardial infarction
2. Regional wall motion abnormalities (hypokinesia, akinesia) as a result of coronary heart disease
3. Left ventricular dilatation resulting from a coronary or noncoronary complication of the essential hypertension[64,72]

Since the coronary manifestations of essential hypertension are responsible for ventricular dilatation and decline of ventricular function in the overwhelming majority of cases, the "coronary factor" is of considerable pathogenetic significance. However, hypertensive patients with significant coronary stenosis may exhibit normal ventricular function even in severe pressure hypertrophy, so that the existence of coronary stenosis alone need not be a limiting factor as far as ventricular function is concerned. The following constellations in essential hypertension are usually associated with a clinically manifest disturbance of ventricular function:

1. Coronary stenosis with prior myocardial infarction
2. Coronary stenosis with regional contraction abnormalities
3. Prior myocardial infarction and/or regional abnormalities with and without coronary stenoses

The presence of coexisting coronary disease appears to influence quantitatively function and contractile properties of the left ventricle in essential hypertension, as in normotensive heart disease.

The determination of cardiac and ventricular size provides a basis for assessment of the severity of cardiac involvement in essential hypertension and is helpful in drawing therapeutic conclusions, particularly by monitoring of changes. It must be borne in mind, however, that inclusion of cardiac size as a criterion also implies changes in cardiac and ventricular size of other etiology. Thus, cardiac enlargement in essential hypertension may be the result of ventricular hypertrophy with or without dilatation; regional wall motion abnormalities, especially due to coronary heart disease; or a generalized abnormality of left ventricular contraction with manifest resting or exertional failure. The abnormal pressure load with consequent ventricular hypertrophy (myocardial factor) and coronary heart disease (coronary factor) is a common coincidence with additive effect. Thus, an extensive regional contraction abnormality in essential hypertension with a subsequent increase in the akinetic segment could lead to an increase in ventricular size and a decrease in the ejection frac-

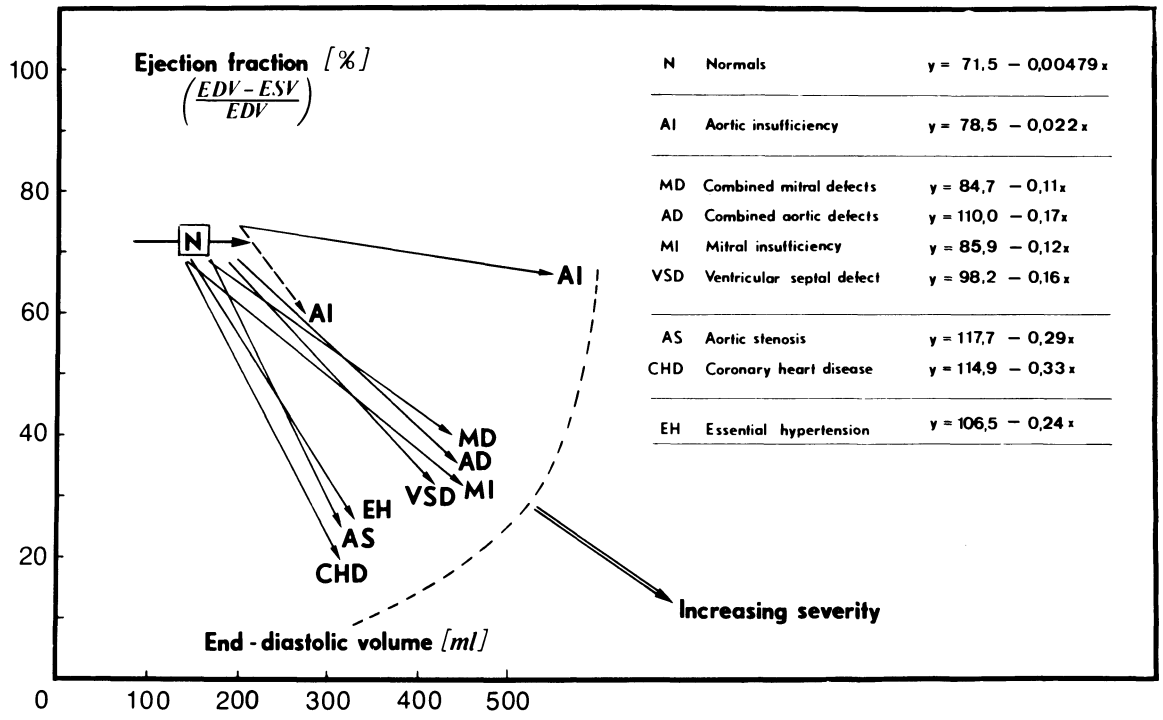


**Figure 6.** Spectrum of relationships between end-diastolic volume and ejection fraction of the left ventricle during left ventricular pressure and volume overload and in coronary heart disease. Note the marked differences depending on the nature of the underlying cardiac defect. From Strauer, ref 72

tion. The consequent decline of ventricular function is quantitatively comparable to hypertensive ventricular hypertrophy with ventricular dilatation without coronary heart disease. A decrease in ejection fraction with increasing ventricular dilatation can be demonstrated to an equal degree for normotensive coronary heart disease and for left ventricular pressure hypertrophy as a result of aortic stenosis (pure pressure load). The correlation between end-diastolic volume and ejection fraction shows a nearly identical course in essential hypertension as well, in contrast to valvular and shunt defects (Fig. 6). It is correct to conclude, therefore, that normotensive coronary heart disease, aortic stenosis without coronary heart disease, and essential hypertension with or without coronary heart disease exhibit a comparable, normal ejection fraction when the heart size is normal. They are accompanied by a sensitive decline of ejection fraction and ventricular function as the ventricular size increases. The determination of the relation between the two variables provides a sound basis for the functional and therapeutic assessment of ventricular contraction in these diseased states.[62–64,72,75,76]

### Left ventricular compliance

With increasing ventricular hypertrophy, changes occur in the shape of the diastolic pressure-volume curves (volume compliance). These are distinct from the changes that occur in myocardial compliance, as resulting from disturbances of myocardial function (e.g., ischemia) or structural alterations (e.g., necrosis, scarring).[22,24,66] In left ventricular hypertrophy associated with essential hypertension, the end-diastolic wall tension is within normal limits in the compensated hypertensive groups with and without coronary stenosis and regional contraction abnormalities. In contrast, the decompensated hypertensives demonstrate a marked increase in end-diastolic wall tension.[66,72] Thus, left ventricular compliance can be considered largely normal in compensated hypertensives with or without coronary stenosis. It is decreased in hypertensives with regional contraction abnormalities as well as in decompensated hypertensives. This means that despite significant left ventricular hypertrophy (compensated hypertensives with and without coronary stenosis), the myocardial compliance can be largely normal.[47] Significant decreases in compliance are observed in essential hypertension only in the presence of coexisting myocardial disease (hypokinesia, akinesia) and in the decompensated stage (Table 5). The myocardial structural changes that underlie coronary disease are etiologic, so that the diminished compliance in essential hypertensives with coronary heart disease (groups II and III) is deter-

**Table 5.** Indices of Left Ventricular Compliance in Normal Function and Arterial Hypertension

| | | Essential Hypertension | | | |
|---|---|---|---|---|---|
| | Normal | I | II | III | IV |
| $T_{diast}$ ($10^3$dyn/cm$^2$) | 26 ± 3 | 28 ± 2 | 31 ± 6 | 44 ± 6* | 68 ± 10† |
| dp/dV (mm Hg/ml) | 0.151 ± 0.008 | 0.162 ± 0.011 | 0.213 ± 0.016 | 0.326 ± 0.019 | 0.55 ± 0.032 |
| dV/dp (ml/mm Hg) | 6.78 ± 1.02 | 6.12 ± 0.92 | 4.8 ± 0.57 | 3.12 ± 0.21 | 1.81 ± 0.10* |
| dV/dp · V (liters/mm Hg) | 0.079 ± 0.009 | 0.077 ± 0.010 | 0.057 ± 0.006* | 0.029 ± 0.001† | 0.011 ± 0.001† |
| LMFS (rel. units)‡ | 508 ± 98 | 582 ± 72 | 623 ± 119 | 1120 ± 223† | 1610 ± 204† |

*$p < 0.01$.
†$p < 0.005$.
‡LMFS = $T_{diast}$.
From Strauer, ref 72.

mined primarily by the compliance change resulting from coronary manifestations. Again, the hypertrophic factor itself appears to be of minor importance.

Moreover, in patients with decompensated hypertension who exhibit a marked increase of end-diastolic pressure and volume, the preload can apparently play an active role. A preload-dependent decrease in compliance may be present. This is shown by the behavior of the wall tension and compliance indices, indicating a progressive increase of preload with increasing hemodynamic severity of essential hypertension. It must be considered, however, that a decrease in the mass-volume relation leads to an increase in end-diastolic wall tension purely for geometric reasons. A decrease in the mass-volume relation usually is also accompanied by ventricular dilatation. Therefore the increased ventricular radius and relative decrease in wall thickness always alter the compliance indices which figure into the equations defining these variables. In this respect these indices can provide only limited information on the true myocardial fiber stretch (preload), even if corresponding indices such as the LMFS or log dP/dV are used to estimate the myocardial compliance.[22,24]

## Ventricular Geometry and Degree of Hypertrophy

### Mass-volume relation

Essential hypertension leads to left ventricular hypertrophy as a result of arterial pressure overload. This is accompanied by a parallel mass increase with a change in ventricular dimensions. The radiologic heart and ventricular size can range from a normal configuration to a generalized cardiac dilatation, depending on the degree, duration, and intensity of the pressure load as well as on coexisting coronary and myocardial disease. For the same absolute left ventricular muscle mass, the left ventricle may be of normal size with a normal or decreased internal volume and greatly increased wall thickness, or it may be considerably enlarged with an increased volume and a normal or only slightly increased wall thickness. Thus, a quantitatively comparable increase in left ventricular mass resulting from arterial pressure overload may be accompanied by highly diverse ventricular dimensions in essential hypertension. The behavior and performance of the ventricle, in turn, are dependent on the absolute muscle mass, wall thickness, intraventricular pressure, and intraventricular volume (or radius).[26–29,40,45,67,68] If these geometric variables are changed, as from arterial and left ventricular pressure overload in essential hypertension, ventricular function will also change. Since these variables are a result of the left ventricular pressure overload, they are also the determinants of the degree of left ventricular hypertrophy. Accordingly, the degree of left ventricular hypertrophy can be defined as a result of the chronic left ventricular pressure overload, dependent upon the geometric variables of wall thickness, ventricular mass, intraventricular pressure, and intraventricular volume.[72,75,76]

The quantitative determination of the degree of hypertrophy, i.e., the relationship between mass, volume, pressure, and wall tension, permits an assessment of ventricular function in the hypertensive heart based on ventricular geometry, as well as a diagnostic classification of the hypertensive heart ac-

cording to the "degree of proportionality" of the hypertrophy. This concept is based on the fact that the ventricular hypertrophy in essential hypertension is considered to be proportional, regardless of the pressure-volume performance and muscle mass, as long as the wall tension remains normal. If wall tension increases, the hypertrophy is said to be *underproportionate.* If ventricular thickening is chronic and *overproportionate,* a decrease in wall tension occurs. Thus, left ventricular hypertrophy is determined qualitatively by the relationships between the pressure and wall thickness-radius relation, or the pressure and the mass-volume relation. It can be characterized by determining the intraventricular pressure, wall thickness, and radius, or the intraventricular pressure, muscle mass, and volume.[8,15,72]

The mass-volume relation of the left ventricle shows a marked correlation to the end-diastolic as well as peak systolic wall tension of the left ventricle (Fig. 7). As the mass-volume relation increases, the end-diastolic and peak systolic wall tensions decrease. Thus, hypertensives with a high mass-volume relation and normal or low diastolic or systolic wall tension can tend toward a comparison group with hypertrophic obstructive cardiopathy (closer to abscissa), while hypertensives with an approximately normal mass-volume relation and elevated diastolic and systolic wall tension tend toward a comparison group with decompensated aortic valve lesions (closer to ordinate). Starting from the normal range, the wall tensions may increase with either a rise or fall of the mass-volume relation; on the other hand, despite a comparable absolute left ventricular mass increase, wall tensions may be normal, decreased, or increased in essential hypertension as a result of a change in the ventricular cavity size, and thus the ventricular radius. Therefore, when judging the proportionality of hypertrophy in essential hypertension, one must take into account not only the muscle mass, but also the intraventricular volume and wall tension, which vary interindividually. Finally, the relation of muscle mass to chamber size is also dependent on the pressure and volume load, which vary in proportion. This problem can be particularly important in the hyperdynamic forms with an elevated cardiac output (see p. 245,248).

Assuming a proportional hypertrophy, the mass-volume relation will increase with increasing pressure load. The relationship between both variables, i.e., between the systolic pressure as a *measure* of the pressure load and the mass-volume relation as a

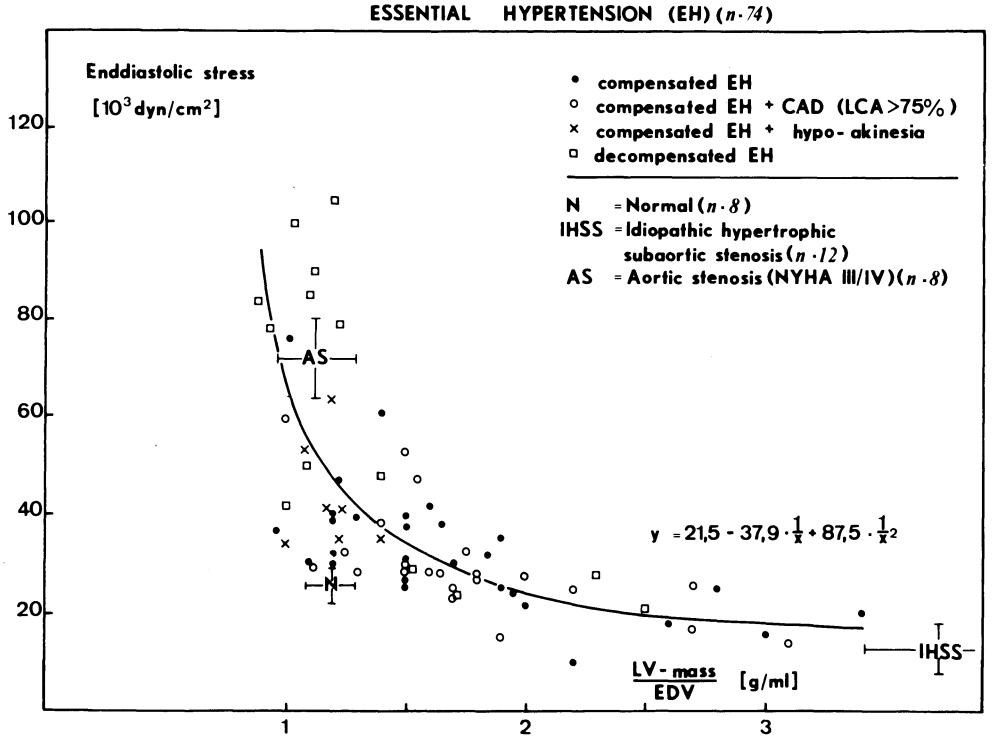


**Figure 7.** Relationship between the mass-volume relation (abscissa) and peak systolic wall tension of the left ventricle. From Strauer, ref 72

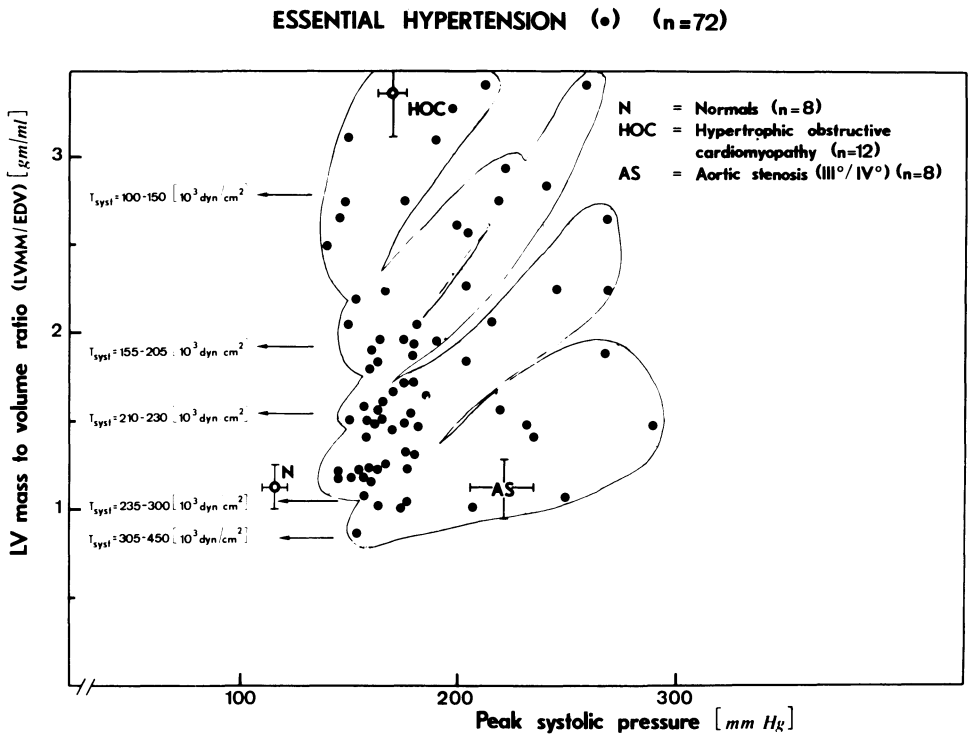


**Figure 8.** Relationship between the systolic pressure and mass-volume relation as a function of regions of approximately equal wall tension. The five isotension regions are based on nonoverlapping tension values. From Strauer, ref 72

*resultant* of the pressure load, reveals a firm relationship between the systolic pressure values on one hand and the mass-volume relation on the other when regions of equal tension ("isotension") are identified (Fig. 8). At a constant systolic pressure, the peak systolic wall tension decreases with increasing mass-volume relation. Conversely, at a constant mass-volume relation the peak systolic wall tension increases with increasing systolic pressure. On the other hand, the wall tension within an isotension region may remain unchanged despite an extreme pressure increase resulting from an increased mass-volume relation; it is necessary only that the relationship between pressure, volume, and muscle mass remains proportionate.[72] Presumably, coexisting myocardial disease, myocardial structural changes, severe dyskinesia, and acute drug interventions could cause shifts and overlaps to occur in these function curves determined for a chronic disease.

### Systolic wall-tension and contractility reserve

The contractility reserve of the pressure-loaded left ventricle is determined chiefly by its ability to develop and maintain a given systolic wall tension. Thus, the contractility reserve of the left ventricle is dependent on its systolic wall-tension reserve.[7,53] The latter, in turn, can be defined as the ratio of the maximum attainable systolic wall tension ($T_{max}$) to the instantaneous systolic wall tension ($T_{syst}$).[72] The maximum attainable systolic wall tension in the human heart is approximately 500 to 600 ($10^3$ dynes/cm$^2$), a value which corresponds to the maximal isometric tension developed by the isolated human myocardium at a maximal fiber length ($L_{max}$)[60] (Fig. 9).

As the systolic wall tension ($T_{syst}$) increases on the one hand, and/or the mass-volume relation decreases on the other, the wall-tension reserve of the pressure-hypertrophied left ventricle decreases by definition (Fig. 10). Thus, acute peak-pressure loads on the hypertensive heart lead to a decrease in the wall-tension reserve, depending on the instantaneous systolic tension ($T_{syst}$), with a ventriculodynamic predisposition toward pressure-induced myocardial failure. In chronic pressure overload with proportional (i.e., concentric and uniform) myocardial hypertrophy, the ventricular hypertrophy follows its respective isotension region. Thereby the wall-tension reserve can remain unaffected (Fig. 11). Thus, the initial state of ventricular dynamics, characterized by the wall-tension reserve and the sever-

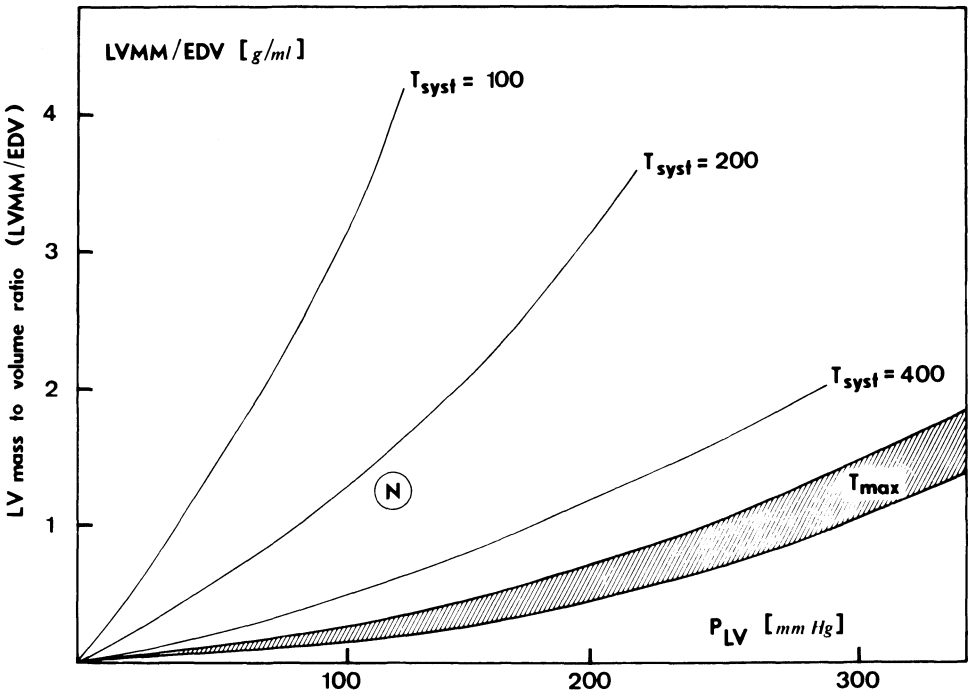


**Figure 9.** Schematic representation of the relationship between the pressure in the left ventricle and the mass-volume relation in various wall-tension ranges (isotension lines). The peak wall tension attainable by the left ventricle ($T_{max}$) is shaded. $P_{LV}$, systolic pressure in left ventricle; $T_{syst}$, systolic wall tension; $T_{max}$, maximum attainable systolic wall tension $\triangleq$ 5–6 g/mm$^2$. From Strauer, ref 72

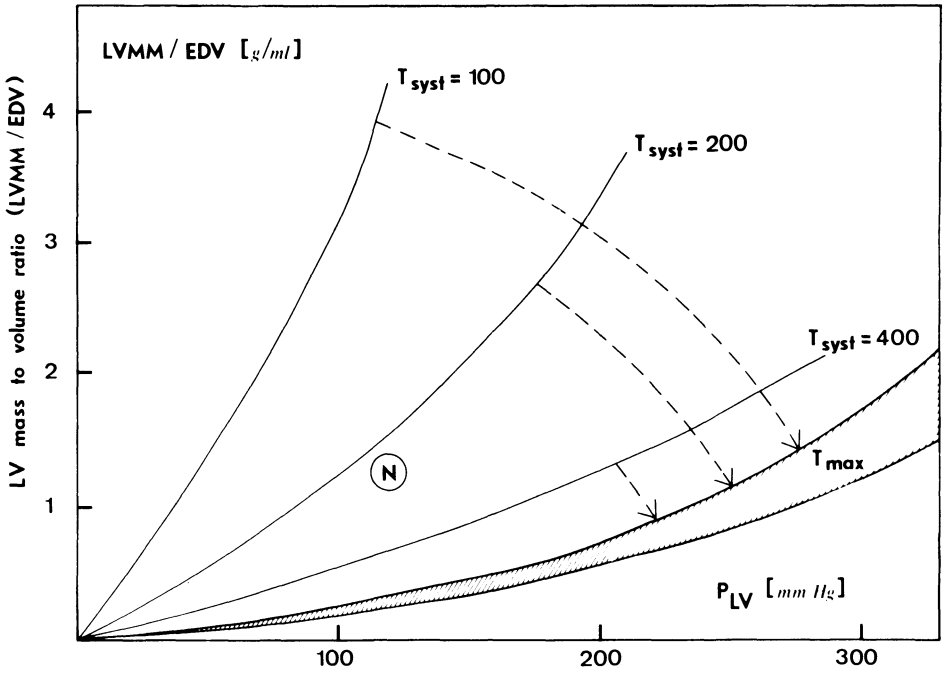


**Figure 10.** Schematic representation of the left ventricular wall-tension reserve, i.e., the ratio of the maximum attainable wall tension ($T_{max}$) to the instantaneous systolic wall tension ($T_{syst}$). Note that as the value of $T_{syst}$ increases, the wall-tension reserve and thus the contractility reserve of the left ventricle declines (N = normal range). From Strauer, ref 72

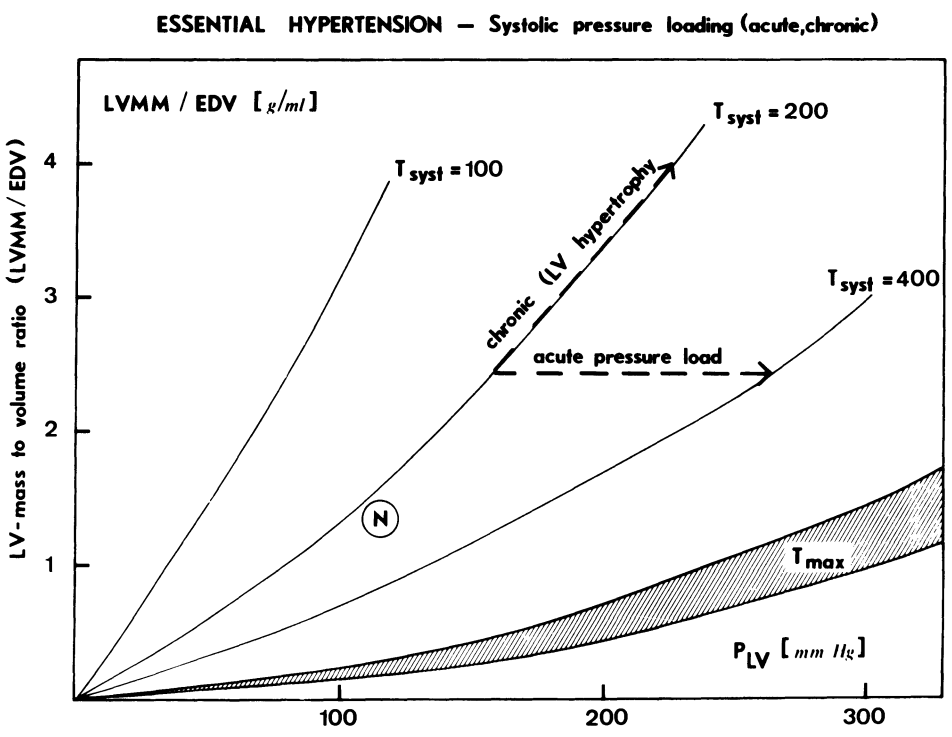


**Figure 11.** Effects of acute LV pressure load (hypertensive crisis) and chronic LV pressure load on the systolic wall tension. Note that the wall-tension reserve decreases with increasing wall tension in acute pressure loads, while the isotension region is preserved in the case of chronic, uniform hypertrophy. From Strauer, ref 72

ity of acute pressure loads, determines the function and contractility reserve of the left ventricle.[72] The systolic wall-tension reserve can be improved by positive inotropic interventions (to increase the maximum attainable systolic wall tension) or by a reduction of arterial pressure (Fig. 12). This enables the left ventricle to develop more wall tension from a particular initial dynamic state, or produce an equal increase of wall tension in progressive ventricular dilatation with a rise of $T_{syst}$. Thus, interventions with a positive inotropic action, such as digitalis glycoside therapy,[69] will produce an increase in the contractility reserve and functional capacity of the dilatated and hypertrophied left ventricle in hypertensive heart disease, while reduction of the arterial pressure, e.g., with vasodilators or $\beta$-receptor blocking drugs, will lower $T_{syst}$ and thereby increase the wall-tension reserve.[70–72]

### Regional ventricular wall hypertrophy

The increase of left ventricular muscle mass in essential hypertension is a useful measure of the severity of the hypertension and hypertrophy but provides limited information as to whether the hypertrophy of the entire left ventricle is proportionate or disproportionate relative to the pressure-volume performance, or whether the hypertrophy of the ventricular wall is regionally uniform or asymmetrical. The existence of a uniform or asymmetrical hypertrophy in essential hypertension can be demonstrated by regional wall-thickness determinations. By the analysis of the regional transmural wall thicknesses and end-diastolic to end-systolic wall-thickness changes along the long axis (apex) of the left ventricle and along five transverse axes perpendicular to it, it is found that the wall-thickness increase from end-diastole to end-systole is nearly twice the normal value in compensated hypertensives, amounting to 100% to 120% of the initial end-diastolic value in the ⅔ of the anterior wall opposite the base (normal = 40% to 50%) (Fig. 13). In the decompensated hypertensives, by contrast, the relative wall-thickness increase is much smaller. Thus, within these three hypertensive groups the regional wall-thickness increase is considerably greater in the two compensated groups (I and II) with a normal end-diastolic volume than in the decompensated group with a high end-diastolic volume. At the same time, the wall-thickness increase is more pronounced in compensated hypertension with coronary heart disease and no local contraction abnormalities than in the comparison group without

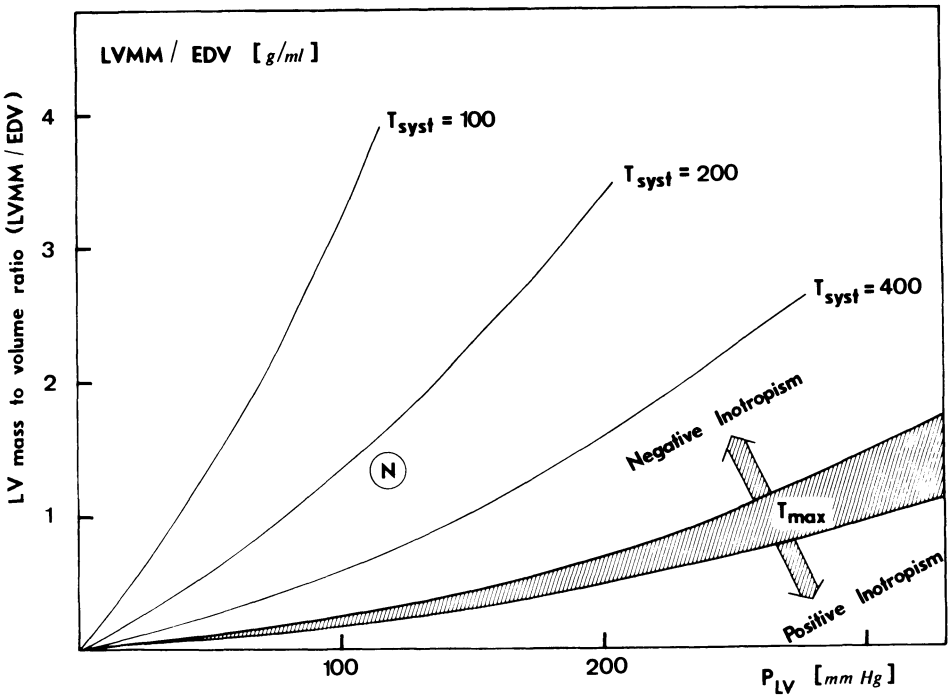


**Figure 12.** Schematic representation of the effects of inotropic changes on the left ventricular wall-tension reserve. From Strauer, ref 72

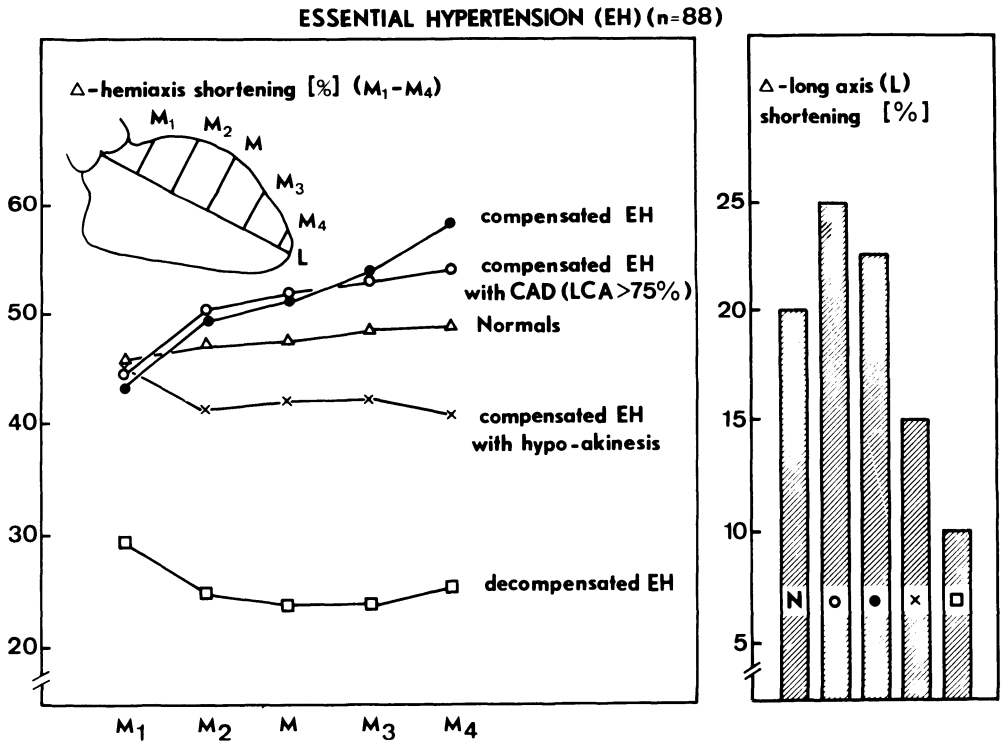


**Figure 13.** Wall thickness changes from end-diastole to end-systole (Δ wall thickness as percent of initial end-diastolic values) at five different transverse axes and at the cardiac apex in the normal group and the three hypertensive groups defined. From Strauer, ref 72

coronary disease. The wall-thickness change at the cardiac apex is considerably smaller on the whole than that in the left ventricular anterior wall, although here, too, the compensated hypertensives, especially those with coronary heart disease, show a systolic thickening which is about twice that in the normal group.

In 12 patients with essential hypertension and a normal end-diastolic volume (of the 92 patients studied), the regionally pronounced wall-thickness change led to ventriculographic findings similar to those in hypertrophic obstructive cardiomyopathy. Eight of these patients had significant coronary stenosis, and two also had extracranial carotid artery stenosis requiring operation; all the patients had a prior history of hypertension of more than 8 to 10 years' duration. In none of the 12 patients did provocative tests (Valsalva maneuver, amylnitrite inhalation, and postextrasystolic intraventricular and aortic pressure measurement) show evidence of a hemodynamically significant intraventricular obstruction or ventriculoarterial pressure gradient. Angiographic visualization of the right ventricle showed normal right ventricular contraction. Thus, excessive hypertrophy in essential hypertension can lead to systolic wall-thickness increases which usually cause a disproportionate thickening of the entire anterior wall as a result of generalized ventricular hypertrophy and are accompanied in about 14% of cases by asymmetric wall-thickness changes.

The prototype of an asymmetric or irregular ventricular wall hypertrophy is hypertrophic obstructive cardiomyopathy. The ventricular septum, subaortic outflow tract, or any other left ventricular segment may be affected with asymmetric hypertrophy in this disease.[42,61,87] The severity can range from mild forms with an hourglass-shaped left ventricle with no ventriculo-arterial pressure gradient and negative provocative tests to the most severe intraventricular obstruction with a high pressure gradient, positive provocative tests, and angina pectoris. However, arterial hypertension accompanies hypertrophic obstructive cardiomyopathy in only about 1% to 3% of cases.[16,87] A connection between the two diseases (essential hypertension and hypertrophic obstructive cardiomyopathy) appears unlikely. Conversely, no intraventricular obstruction was found in any of the hypertensive patients studied, despite a considerable irregularity of the ventricular hypertrophy. The provocative tests were negative. The right ventricle and right ventricular outflow tract were free. The left ventricular coronary reserve, which is generally normal in hypertrophic obstructive cardiomyopathy,[42,61] was reduced to about half normal. The majority of patients had significant stenoses of the left coronary artery. Thus, based on clinical and other findings, it is improbable that the irregular ventricular wall hypertrophy in essential hypertension represents simply an asymptomatic form of hypertrophic obstructive cardiomyopathy with essential hypertension. This would imply the existence of common etiologic features between the two diseases, yet there is no evidence of this. However, abnormal hypertrophy of the papillary muscles in arterial hypertension with the resulting ventriculographic features of irregular or asymmetric ventricular wall hypertrophy must be considered. It is more reasonable to assume that the irregular hypertrophy in essential hypertension develops in such a way that its ventriculogram resembles that in hypertrophic obstructive cardiomyopathy, without implying a necessary connection between the two syndromes.

### Diagnostic and therapeutic conclusions

Hypertensives with a diminished wall tension show, at comparable systolic pressures, an inappropriate ("overproportionate") hypertrophy in favor of an increase in the mass-volume relation. Hypertensives with a normal wall tension exhibit a proportionate hypertrophy over the entire range of arterial pressures and mass-volume relations. Hypertensives with an elevated wall tension show an inappropriate ("underproportionate") hypertrophy, which tends to decrease the mass-volume relation[75,76] (Fig. 14).

The relationships demonstrated are useful aids in the diagnostic classification and differential therapy of essential hypertension from the standpoint of ventricular function and coronary hemodynamics.[54] Hypertensives with a high wall tension and a normal or reduced mass-volume relation are at risk for cardiac disease. They have a depressed ventricular function and an increased myocardial oxygen consumption (Fig. 15). Hypertensives with a normal wall tension have normal ventricular function and normal myocardial oxygen consumption with proportionate hypertrophy. Hypertensives with a decreased wall tension and high mass-volume relation show a normal or increased ventricular function and a normal or decreased myocardial oxygen consumption. Thus, ventricular function and coronary hemodynamics in essential hypertension are determined primarily by the extent and proportionality of the hypertrophy.[75,76]

Besides their value in diagnostic and prognostic classification, the relationships between pressure, degree of hypertrophy, and wall tension provide information regarding the benefit to be derived from various forms of drug therapy in hypertensive heart disease. Decompensated hypertensives can achieve a shift in their abnormal function curves by two mechanisms in particular:

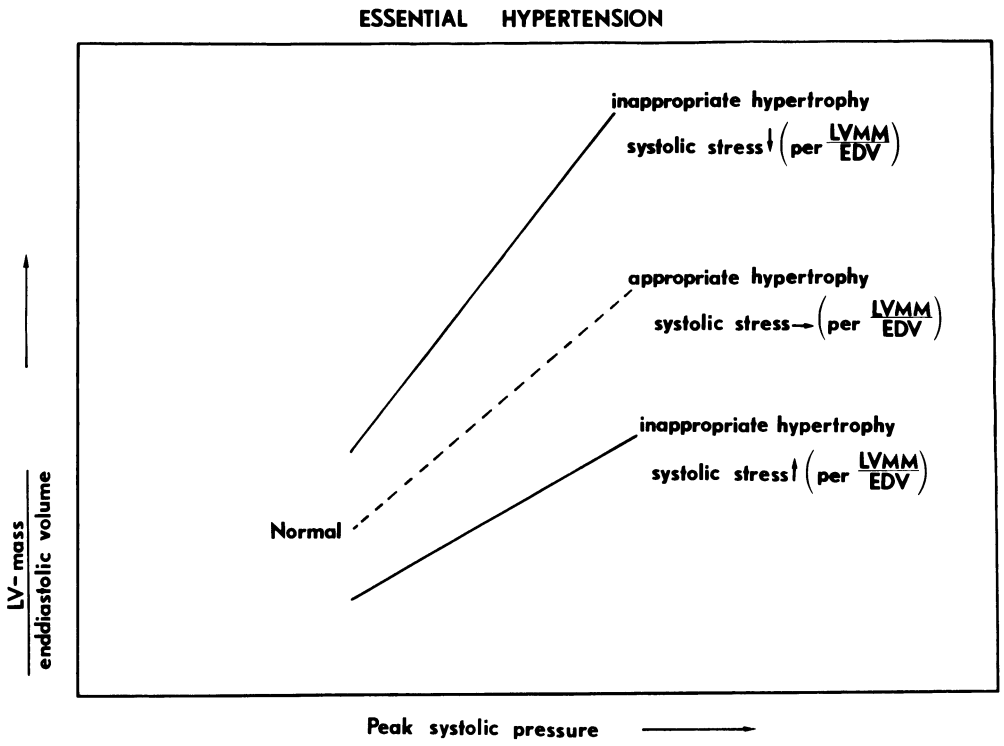


**Figure 14.** Relationship between left ventricular systolic pressure and mass-volume relation, taking into account the degree of proportionality of the hypertrophy. The isotension regions are shown schematically (cf. Figs. 8 and 9). From Strauer, ref 72

1. A pressure decrease and reduction of wall tension can be achieved by a reduction of arterial pressure, i.e., by the use of antihypertensive drugs which act by means other than negative inotropism (Fig. 16).[75,76]
2. The ejection fraction can be increased by positive inotropic measures, which effect a long-term reduction of cardiac size with a decrease in end-diastolic volume. Additionally, the abnormal mass-volume relation is increased by the reduction of end-diastolic volume (Fig. 17).[63]

Both types of therapy—pressure reduction and positive inotropism—can, when administered concurrently, exert additive effects. Therefore, a regimen consisting of digitalis glycosides plus antihypertensive drugs (preferably vasodilators) is indicated for decompensated hypertension.

The therapy for compensated hypertension and hypertension with overproportionate hypertrophy must rely mainly on mechanisms which normalize the abnormally high mass-volume relation. Since ventricular function is normal or increased, positive inotropic drugs are contraindicated.[69,70] The primary goal is a regression of the left ventricular muscle mass, which, in experiments on hypertensive as well as normotensive animals, can be achieved in varying degrees with $\beta$-receptor blocking agents.[81,84] The value of this concept in the long-term therapy of essential hypertension in man remains to be determined by long-term studies in essential hypertensive patients.

## Coronary Hemodynamics

### Preliminary remarks on pathophysiology

The coronary blood flow of the left ventricle is determined in part by the coronary perfusion pressure, the coronary resistance, and the blood viscosity.[2,4,47] In addition to the vascular control of coronary blood flow (vascular component of coronary resistance), which is normally dependent on arteriolar tone and thus on humoral, metabolic, and neural factors and is seriously impaired in the presence of structural coronary artery changes (e.g., coronary heart disease) owing to a loss of coronary dilating capacity, intraventricular and myocardial factors can lead to an impairment of coronary dilatation capacity and thus to an abnormally high coronary resistance and low coronary reserve (myocardial component of coronary resistance). This myocardial component of

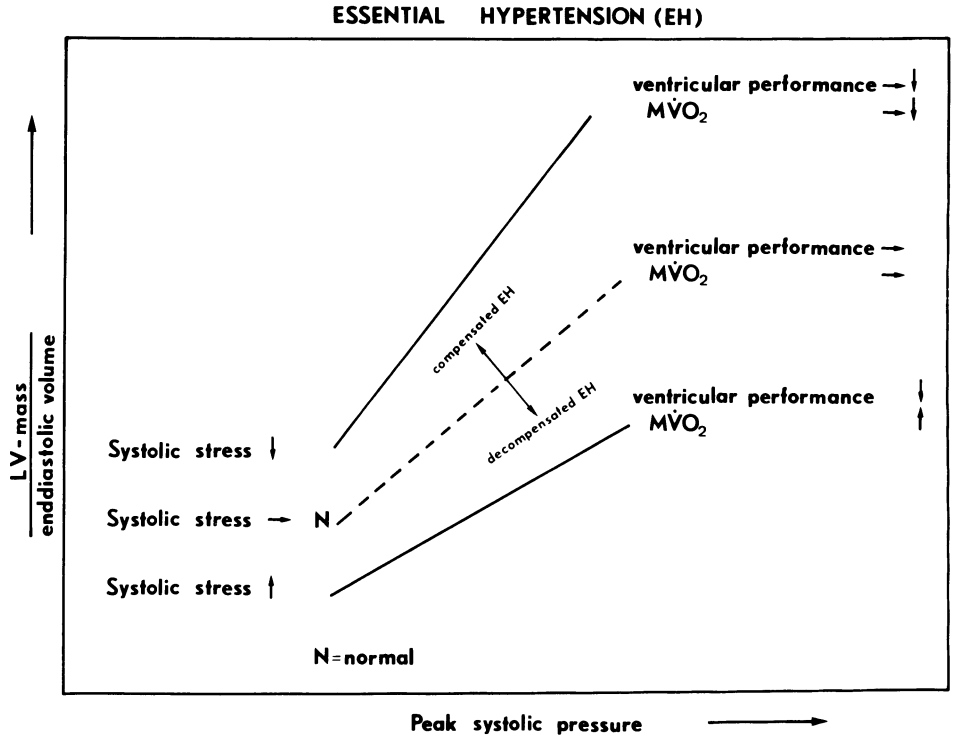


**Figure 15.** Relationship between left ventricular systolic pressure and mass-volume relation, taking into account the degree of hypertrophy, wall tension, ventricular function, and myocardial $O_2$ consumption. From Strauer, ref 72

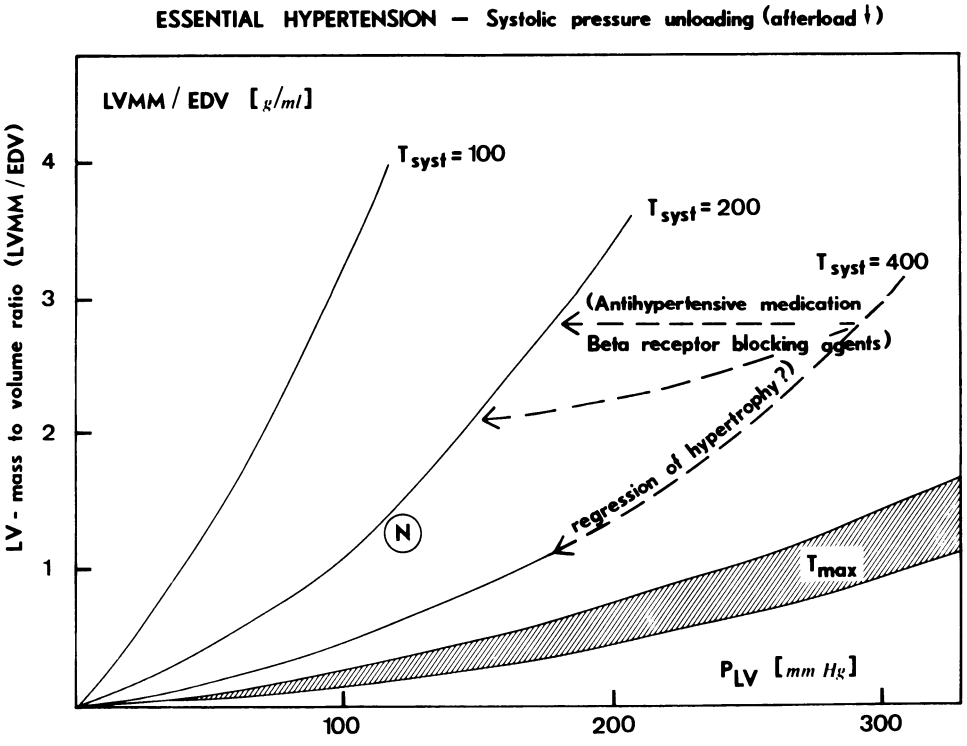


**Figure 16.** Effects of acute and chronic pressure reduction (LV pressure load relief) on instantaneous systolic wall tension ($T_{syst}$) and on the resulting wall-tension reserve. From Strauer, ref 72

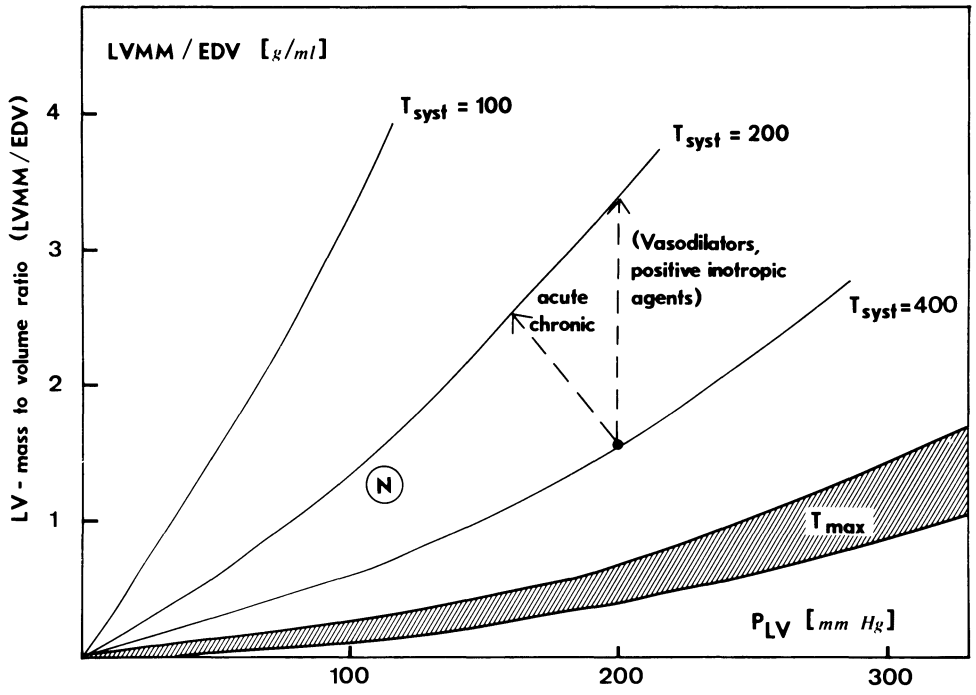


**Figure 17.** Effects of inotropic and vasodilating measures on the mass-volume relation and wall tension of the left ventricle. From Strauer, ref 72

the coronary resistance encompasses the effects on coronary resistance which are independent of the vascular component and are associated with the process of contraction and relaxation. It is most pronounced in the presence of abnormally high left ventricular end-diastolic pressures, abnormal myocardial hypertrophy with myocardial edema, tachycardia and inflammatory and fibrotic myocardial diseases, as well as hypertrophies of varying etiology.

The coronary reserve is defined as the ratio of the coronary resistance under initial conditions to the coronary resistance during maximal coronary dilatation. Thus, determination of the coronary resistance is of paramount importance in the clinical diagnosis of coronary function based on quantitative assessment of the coronary reserve. The definition of coronary reserve implies that this reserve is diminished if the coronary resistance is already decreased under initial conditions owing for example, to an increased myocardial energy demand. This results in a lower-than-normal ratio of the coronary resistance under initial conditions to the coronary resistance during maximal coronary dilatation. In this case the coronary reserve can be normalized by reducing the myocardial oxygen consumption. The coronary reserve thus defined takes into account the functional coronary and metabolic response range of the heart and largely disregards the absolute minimum of coronary resistance attainable during provocative testing. The coronary reserve determined from the coronary resistances has proved to be of significant value in the clinical setting.[4,41,71] To assess the absolute response range of the coronary flow, however, it is necessary to take into account the minimal coronary resistance as well.

The hypertrophied and dilatated hypertensive heart very often shows the clinical (symptoms, ECG) and morphologic (myocardial cell edema, mitochondrial swelling, and destruction) signs of coronary insufficiency. This has been attributed to several mechanisms: (1) to a cessation of growth of the aortic coronary ostial lumina during continued growth of the myocardial coronary arteries and their branches, (2) to a disproportion between the hypertrophied myocardial mass and the coronary artery system supplying it, (3) to a premature involvement of the small intramural arterioles, and (4) to an abnormal intramural pressure with a consequent increase in the myocardial component of the coronary resistance. Thus, both components of the coronary resistance—the vascular (large and small coronary arteries) and the myocardial component (the sum of all extravascular ventriculodynamic factors acting

**Table 6.** Variables of Coronary Function in Normal Patients, in Essential Hypertension (EH) and in Normotensive Coronary Heart Disease (CHD)

| | $P_{cor}$ (mm Hg) | $avDO_2$ (vol%) | $\dot{V}_{cor}$ (ml/min · 100 g) | $R_{cor}$ (mm Hg · min · 100 g · $ml^{-1}$) |
|---|---|---|---|---|
| Normal ($n$ = 12) | 82 ± 2 | 12.2 ± 0.1 | 71 ± 3 | 1.15 ± 0.04 |
| EH ($n$ = 63) | 129 ± 8‡ | 12.9 ± 0.2 | 83 ± 2† | 1.57 ± 0.06‡ |
| CHD ($n$ = 38) | 87 ± 5 | 12.8 ± 0.6 | 64 ± 3* | 1.36 ± 0.09 |

*$p < 0.02$.
†$p < 0.005$.
‡$p < 0.001$.
$P_{cor}$: coronary perfusion pressure; $avDO_2$: coronary arterio-venous oxygen difference; $V_{cor}$: coronary flow; $R_{cor}$: coronary vascular resistance; EH: essential hypertension; CHD: coronary heart disease.
From Strauer, ref 65.

on the coronary resistance)—contribute to the premature development of coronary insufficiency in the hypertensive heart.

### Coronary blood flow and coronary resistance

The coronary blood flow of the left ventricle at rest is elevated an average of 16% above normal in the overall group of hypertensive patients studied (Table 6). The coronary resistance is 38% above normal. The coronary perfusion pressure, i.e., the mean diastolic aortic pressure minus the mean diastolic pressure in the left ventricle, is elevated by 56% on the average. The coronary arteriovenous oxygen difference is slightly elevated (Table 6).

The increase in coronary blood flow per unit of left ventricular weight (100 g) demonstrated for the overall group of essential hypertensives studied shows that, with a largely normal coronary oxygen extraction, as indicated by the largely normal coronary arterio-venous oxygen difference, an increase in myocardial blood flow is necessary to maintain the myocardial oxygen balance of the left ventricle per unit weight. Essential hypertension thus represents a cardiac disease and form of hypertrophy which, unlike other forms, is caused, for example, by pressure and volume loads on the left ventricle (aortic defects, mitral defects, congenital heart defects, etc.). It produces an increase in myocardial and coronary blood flow and an increased myocardial oxygen consumption despite a significant rise in coronary resistance.[2,41,42,55,71-76] A change in the myocardial energy demand of the human heart is generally accomplished through a change in coronary blood flow, since the coronary arteriovenous oxygen extraction is complete, i.e., maximal or submaximal, and can for well-known physiologic reasons be increased only negligibly.[4,78] As a result, a state of increased myocardial oxygen consumption leads to a decrease in coronary resistance and an increase in coronary flow, thereby meeting the increased myocardial energy demand of the left ventricle. So far, no diseases of the human heart have been reported which are accompanied by an increase in coronary blood flow and myocardial oxygen consumption with a concurrent rise in coronary resistance, as in essential hypertension. It may be assumed, therefore, that the left ventricle and coronary vascular system in essential hypertension regulate the coronary blood flow and myocardial oxygen consumption so as to meet metabolic demands, doing so against an abnormally high coronary resistance. Numerous findings and discussions have been published on the possible causes of the increased vascular resistance in essential hypertension. Presumably, the metabolic "unloading" of the left ventricle, e.g., with antihypertensive or negative inotropic drugs, would provoke a further rise of coronary resistance, since such measures would counteract the decrease in coronary resistance induced metabolically.

### Coronary reserve of the left ventricle

Based on our own investigations,[65,75] the left ventricle coronary reserve as determined pharmacologically is reduced to 72% of normal in compensated hypertensives without coronary heart disease, and to 42% of normal in compensated hypertensives with coronary disease (Fig. 18). Thus, the coronary reserve in essential hypertension with coronary heart disease is comparable to that in coronary heart disease without essential hypertension, and it appears that the presence of a coronary factor in essential hypertension poses a risk of ischemia which is at least comparable to that in normotensive coronary heart disease as far as the coronary reserve is concerned.

It must be emphasized that the coronary reserve

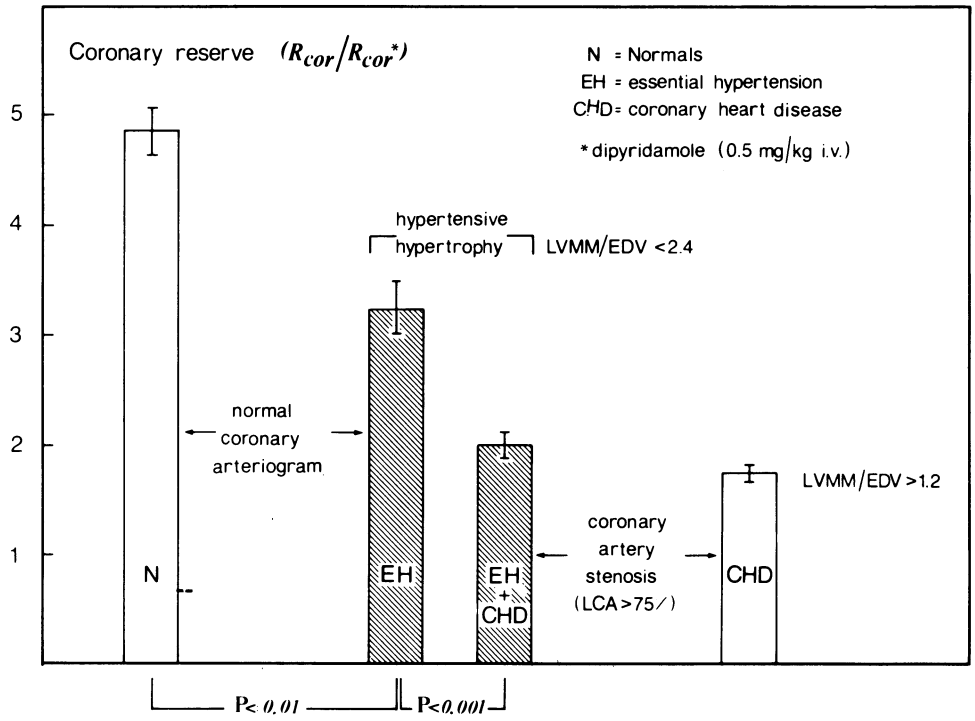


**Figure 18.** Left ventricular coronary reserve in a normal group, in EH with normal coronary angiogram, in EH with significant coronary stenosis, and in patients with normotensive coronary heart disease (CHD). From Strauer, ref 72

is markedly diminished even in compensated essential hypertension without coronary heart disease, i.e., with a normal coronary angiogram. No correlation exists between the reduction of coronary reserve and the end-diastolic pressure, end-diastolic volume, or end-diastolic wall tension. On the other hand, the coronary reserve is normal at a normal or decreased systolic wall tension (comparable to hypertrophic obstructive cardiomyopathy) and is decreased at an elevated systolic wall tension. At high systolic wall tension the myocardial oxygen consumption is augmented, so that a metabolically determined decrease in the initial coronary resistance contributes to the numerical decrease in the coronary reserve. No correlation is apparent between the coronary reserve of the left ventricle and its degree of hypertrophy as determined from the mass-volume relation.

The decrease in left ventricular coronary reserve seen in essential hypertension with angiographically significant stenosis (>75%) of the left coronary artery or its main branches is quantitatively comparable to that observed in normotensive coronary heart disease with a corresponding degree of stenosis. In this respect essential hypertension with coronary heart disease presents a coronary hemodynamic pattern which is similar to the diminished coronary reserve and coronary risk characteristic of normotensive coronary disease. This probably implies that the left ventricle is at greater risk for ischemia in essential hypertension with coronary artery stenosis than in normotensive coronary heart disease, since the condition essential for precipitating angina pectoris and coronary insufficiency, namely a disparity between oxygen supply and oxygen demand, is promoted by the underlying systolic pressure overload of the left ventricle. Thus, essential hypertension with coronary heart disease poses a high risk of ischemia.

Even compensated essential hypertension with no angiographic signs of coronary stenosis shows a marked decrease in left ventricular coronary reserve. Since the coronary factor cannot account for this on the basis of coronary angiographic findings, and since the myocardial factor, as determined from the degree of left ventricular hypertrophy, the mass-volume relation, and the end-diastolic and peak systolic wall tensions, shows no correlation with the decrease of coronary reserve in essential hypertension with a normal coronary angiogram, it is reasonable to conclude that this functional disturbance of coronary regulation may be based on a rise of coronary resistance due to disease of the small intramural coronary arteries. The assumption of a functional

coronary constriction is unnecessary, since histologic studies of the coronary vascular system in arterial hypertension have revealed structural thickening of the vascular walls, fibrosis, and luminal reductions of the small intramural arteries and arterioles in arterial hypertension.[30,38,50] Thus, the left ventricle in essential hypertension with a normal coronary angiogram must be considered at risk for ischemia solely from the standpoint of the range of coronary flow regulation.

The reduction of coronary reserve in these patients is consistent with the clinical observation that essential hypertensives or angina pectoris patients with essential hypertension may exhibit the clinical complaints and objective symptoms of coronary heart disease despite a normal coronary angiogram. It may further be assumed that continuous or intermittent blood pressure elevations and peaks cause increases in myocardial oxygen consumption which may lead to a critical myocardial oxygen supply. Both factors—the diminished range of coronary flow regulation and increased myocardial energy demand—thereby contribute to the pathogenesis of angina pectoris symptoms in essential hypertension with a normal coronary angiogram. Based on our own experience in patients with essential hypertension, left ventricular hypertrophy, and normal coronary angiogram, angina pectoris can be expected to occur in about 50% to 70% of cases. In severe left ventricular hypertrophy (mass-volume relation $>$ 2.0 to 2.2), this percentage increases to 80% to 90%.

### Myocardial oxygen consumption

The oxygen consumption of the left ventricle as a whole (ml $0_2$/min) is 62% above normal in the overall group of essential hypertensives. It shows a linear correlation with the left ventricular muscle mass ($r$ = 0.79), implying that increased oxygen consumption in essential hypertension develops as a function of ventricular hypertrophy and the underlying pressure load. At the same time, the oxygen consumption per 100 g of left ventricular weight (ml/min · 100 g) is 21% above normal. This means that a significant increase in myocardial oxygen consumption which is independent of the absolute ventricular mass takes place in essential hypertension. The slope of the line relating the two variables (left ventricular muscle mass vs. total oxygen consumption) varies considerably in the individual groups. No correlation exists between the increased oxygen consumption and aortic or left ventricular pressure values, isovolumetric velocity indices, and auxotonic pumping variables.

Hypertensives with a high mass-volume relation generally demonstrate a lower oxygen consumption than hypertensives with a low mass-volume relation resulting from ventricular dilatation. Thus, at comparable blood pressures, a connection would be expected to exist between oxygen consumption and the peak systolic wall tension and peak ventricular afterload. The relation shows a linear and significant correlation between both variables (Fig. 19). As the correlation further shows, oxygen consumption in essential hypertension may also be normal or diminished in comparison with the normotensive left ventricle. These cases involve an inappropriate hypertrophy with an increased mass-volume relation and diminished peak systolic wall tension, or an appropriate hypertrophy which can maintain a normal left ventricular peak systolic wall tension with a high systolic pressure owing to a proportionate increase in the mass-volume relation. Thus, the myocardial oxygen consumption is elevated, on the average, in essential hypertension and is determined primarily by the individual degree of hypertrophy, i.e., by the relationship between muscle mass, volume, and wall tension.

At a comparable arterial pressure elevation, increasing ventricular dilatation is accompanied by a pathologic decrease in the mass-volume relation and an increase in the peak systolic wall tension.[40,45] This results in a greater myocardial oxygen consumption. Thus, even with a normal coronary angiogram, conditions are such that myocardial ischemia and angina pectoris may be precipitated, because the degree of hypertrophy (myocardial factor) creates a disparity between oxygen supply and oxygen demand. We thus see that at a comparable arterial pressure load, a pathogenic correlation exists between the end-diastolic volume or left ventricular size and the change in myocardial energy demand as a result of pressure hypertrophy or dilatation in essential hypertension. Accordingly, the left ventricle is at increased risk for ischemia as ventricular dilatation progresses.

Therefore, essential hypertension with increasing cardiac enlargement, measurable by the change in cardiac size on the chest X-ray, must be considered a hypertensive heart disease that carries an increased ischemic risk. Of course a normal-sized or moderately enlarged left ventricle in essential hypertension may also be prone to ischemia or myocardial infarction if coexisting coronary artery stenosis is present. It is assumed that with increasing end-diastolic volume and mass-volume relation, i.e., with progressive left cardiac enlargement, the increase in myocardial oxygen consumption leads to a stronger reduction of the metabolic reserve. By applying therapeutic measures which effectively lower the blood pressure, reduce cardiac size, and increase the mass-volume relation, it is possible to improve ventricular function, lower the myocardial energy

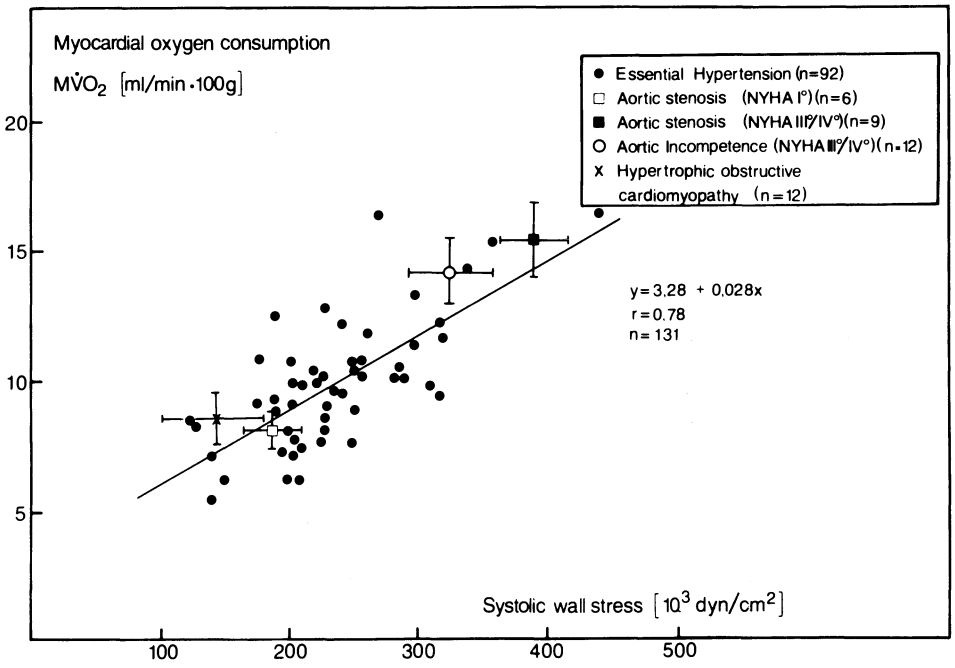


**Figure 19.** Relationship between peak systolic wall tension of left ventricle and myocardial oxygen consumption. Note the linear relationship between the two variables. From Strauer, ref 72

demand, and increase the mechanical and metabolic reserve of the left ventricle. Thus, cardiac size in essential hypertension not only represents a measure of ventricular function but is also a useful correlate of the level of the myocardial energy demand and the proneness of the left ventricle to ischemia.

## Summary

Arterial hypertension is the prototype disease for an increase in the left ventricular afterload. Its most serious cardiac complications relate to the development of left ventricular hypertrophy (myocardial factor) and coronary heart disease (coronary factor). Both factors promote the development of myocardial failure. The regional and overall function of the left ventricle are strongly dependent on the extent, duration, and secondary manifestations of hypertensive heart disease.

Compensated essential hypertension without coronary heart disease is characterized at rest and during exercise by a normal or increased ventricular function, even in the presence of severe left cardiac hypertrophy. Compensated essential hypertension with coronary heart disease may exhibit normal ventricular function as long as no regional abnormalities of wall contraction are present. If the end-diastolic volume becomes increased, or if regional contraction anomalies develop, the contractility of the entire left ventricle tends to be markedly impaired even at rest. Decompensated essential hypertension is present if the left ventricle is disproportionately enlarged relative to the degree of hypertrophy, resulting in a progressive decrease in the ejection fraction with increasing end-diastolic volume.

Coronary blood flow and myocardial oxygen consumption may be decreased, normal, or increased in essential hypertension, although overall there is an average increase of 16% to 21%, respectively. The oxygen consumption is strongly dependent on the peak systolic wall tension of the left ventricle, which is considered the main determinant of the myocardial energy demand. The coronary resistance is high—about 38% above normal. The left ventricular coronary reserve as determined pharmacologically is reduced to 81% of normal even in compensated essential hypertension without coronary stenosis, and to 43% of normal in essential hypertension with coronary heart disease. Thus, the hypertensive heart appears to be at high risk for ischemia from the standpoint of the coronary reserve.

Regional hypertrophy of the left ventricle is asymmetric in about 10% to 15% of essential hypertensives, producing ventriculographic features similar to these of hypertrophic obstructive cardio-

myopathy, but without intraventricular or outflow tract obstruction.

As arterial hypertension progresses and the cardiac consequences become more severe, there is a progressive increase in left ventricular mass. This mass increase is disproportionately large relative to the duration of the arterial pressure load. This means that besides the level of the arterial pressure, the duration of the arterial pressure elevation also determines the degree of ventricular hypertrophy. With progressive mass increase, there is an increase in end-diastolic volume and thus cardiac size. This is equivalent to a progressive dilatation of the ventricle. The result is a decrease or normalization of the mass-volume relation, which was considerably elevated in the initial stage of the essential hypertension.

A quantitative assessment of the degree of hypertrophy and determination of the cardiac risk of arterial hypertension is made possible by the relation between systolic pressure, wall thickness or muscle mass, and ventricular radius or volume. By determining the level of the systolic wall tension, the mass-volume relation is a major determinant of ventricular function. At a comparable left ventricular pressure load, the systolic wall tension, i.e., the systolic afterload, rises with decreasing mass-volume relation. Thus, hearts with concentric hypertrophy and a high mass-volume relation exhibit a low wall tension, while hypertensive hearts with dilatation and a low mass-volume relation have a high wall tension.

Increasing wall tension is accompanied by a depression of ventricular function as measured by changes in auxotonic pumping and contractility variables. Since there is a simultaneous increase in end-diastolic volume, we have a progressive ventricular dilatation based on the radiologic cardiac and left ventricular size, accompanied by a decline of function. At the same time, the myocardial oxygen demand increases since the systolic wall tension is an important determinant of left ventricular oxygen consumption. Thus, in the presence of significant coronary stenosis (coronary factor) or an abnormal increase in the myocardial component of the coronary resistance (myocardial factor), a chronic or acute pressure elevation with a rise of systolic wall tension leads to an increased myocardial oxygen demand, and to generalized or regional ischemia of the left ventricle with a consequent impairment of ventricular function.

The contractility reserve of the pressure-loaded left ventricle is determined mainly by its ability to develop and maintain the systolic wall tension. It thus depends upon the systolic wall-tension reserve of the left ventricle. The latter, in turn, can be defined as the ratio of the maximum attainable systolic wall tension ($T_{max}$) to the instantaneous systolic wall tension ($T_{syst}$). With increasing systolic wall tension ($T_{syst}$) and decreasing mass-volume relation, there is a decline in the wall-tension reserve of the pressure-hypertrophied left ventricle. Thus, acute peak-pressure loads in the hypertensive heart lead to myocardial insufficiency, depending on the value of $T_{syst}$. The initial ventriculo-dynamic state, characterized by the wall-tension reserve, and the severity of acute pressure load thus determine the function and contractility reserve of the left ventricle in hypertensive heart disease.

The systolic wall-tension reserve can be improved by measures with a positive inotropic action. These enable the left ventricle to develop more wall tension from a given initial dynamic state or maintain a given wall-tension increase in progressive ventricular dilatation. Digitalis glycosides and other inotropic measures provide a means of increasing the contractility reserve or performance of the dilatated and hypertrophied left ventricle in hypertensive heart disease.

Another means of improving depressed ventricular function besides the use of positive inotropic measures is given through changes of preload and afterload. This is equivalent to the treatment of myocardial insufficiency in hypertensive heart disease. A reduction of the *afterload* alone lowers the value of $T_{syst}$ and increases the wall-tension reserve ($T_{max}/T_{syst}$), thereby reducing the myocardial energy demand and improving ventricular function. A given reduction of pressure or wall tension is much more effective in achieving the desired afterload reduction at a high initial wall tension of the left ventricle than at a low initial wall tension. A reduction of the *preload* alone increases the mass-volume relation and alters ventricular geometry, even with no change in arterial or systolic pressure load. This results in a decrease in systolic wall tension. Thus, a combination of both measures, i.e., the use of preload- and of afterload-reducing substances, together with positive inotropic measures, represents an important strategy for the therapy of acute myocardial failure in decompensated pressure overload of the left ventricle.

## Recognition of Ventricular Hypertrophy

Cardiomegaly can clinically be detected by precordial palpation. Auscultation may add further information insofar as a left ventricular presystolic gallop appears with progression of myocardial hypertrophy and consequent alteration of compliance. It usually

indicates increased end-diastolic pressure, especially if accompanied by palpable presystolic expansion.

Cardiac enlargement can be quantified by chest X-ray. The information obtained can be improved by biplane estimation of cardiac volume, preferably in the supine position. Evaluation of the cardiac silhouette and calculation of volume is done according to Rohrer[53a] and Kahlstorf.[36a]

Although overall heart size increases with level and duration of hypertension, correlation with the extent of left ventricular hypertrophy has been unsatisfactory. More recent techniques, such as echocardiography, for estimation of wall thickness and chamber size have not been applied on a larger scale and are not yet available as routine tools in the diagnosis of left ventricular hypertrophy.

Electrocardiography (ECG) and vectorcardiography (VCG) have been the classical noninvasive tools for recognition of hypertrophy and of secondary changes of mechanical overload or nutritive myocardial imbalances ("strain"), as well as a sensitive means for the diagnosis of secondary complications, such as coronary artery disease. ECG and VCG have proved to be particularly useful for follow-up and in the recognition of progression of adaptive hypertrophy and secondary myocardial changes, and are valuable in prognostication. However, quantitative estimates of left ventricular muscle mass have not been possible with adequate accuracy, neither with ECG, nor with VCG. Only recently such attempts have been published, utilizing computer-assisted evaluation, which will be alluded to further on.

**Table 7.** Criteria for Diagnosis of Left Ventricular Hypertrophy from the Standard 12-Lead Electrocardiogram

| | Incidence (%) |
|---|---|
| Left atrial enlargement: | |
| P-vector shift counterclockwise | |
| P-wave duration increased (greater than 0.1 s) | |
| $P_{V1-2}$ diphasic, terminal component negative, greater than 0.05 s | |
| Ventricular hypertrophy: | |
| QRS-axis shift counterclockwise | |
| Horizontal axis | 25% |
| Left axis | 20% |
| QRS-T spatial angle 180° | 30% |
| QRS-T frontal plane angle in presence of left axis over 80° | |
| QRS duration increased over 0.08–0.11 s | 80% |
| Delayed intrinsicoid deflection in $V_{5-6}$ over 0.05 s | 20% |
| QRS voltage increased | 30% |
| $R_{V5}$ greater than 2.6 mV | |
| $R_{V5} + S_{V1-2}$ greater than 3.5 mV | |
| $R_{aVL}$ (horizontal or left axis) greater than 1.2 mV | |
| $R_{aVF}$ (vertical axis) greater than 2.0 mV | |
| $R_I$ or $S_{III}$ greater than 1.7 mV | |
| $R_I + S_{III}$ greater than 2.4 mV | |
| Ventricular "strain": | |
| QT interval increased (not necessarily "strain") | 45% |
| ST-T wave changes with ST vector opposite QRS vector | 70% |

## ECG

Numerous criteria for the recognition of left ventricular hypertrophy (LVH) have been proposed and tested. Table 7 gives a summary of the accepted and currently used criteria for the standard 12-lead ECG.

The diagnostically useful ECG changes can be grouped as follows:

***QRS Changes.*** LVH shifts the electrical forces posteriorly and to the left. This results in a counterclockwise motion of the mean QRS vector in the frontal plane toward horizontal or left axis deviation or left anterior hemiblock (approximately 10% of hypertensive individuals).

In the horizontal plane the increase in voltage is at first appreciated in $V_2$ with a deepening of $S_{V2}$ and augmentation of $R_{V4-6}$. With left-axis deviation beyond $-20°$ the QRS amplitude in the chest leads will decrease owing to vectorial reasons, especially in $V_{4-6}$, i.e., without actual loss of electrical potential.

The QRS axis also determines which lead in the frontal plane will be suitable for diagnosing LVH from amplitude criteria, aVL in left axis, aVF in vertical-axis conditions.[93] The fact that the mean axis in the frontal plane reflects only part of the electrical forces represented in the main direction of the spatial main vector, which for the most part develops posteriorly, that is vertically to the frontal plane, already emphasizes the limitations of the amplitude criteria in the frontal plane. It is obvious that the leads characterizing the horizontal plane will reflect the true increase in magnitude much more reliably. This effect is for the V leads further augmented through their proximity to the left ventricle. With more severe degrees of LVH, the prolongation of depolarization of the thickened left ventricular myocardium will become measurable in a delay of the upstroke of $R_{I,V5-6}$. The overall width of QRS will increase up to 0.11 s. Further prolongation of QRS is classified as left bundle branch block, thereby precluding the diagnosis of LVH from the standard ECG. If, however, a Q wave is maintained

in leads I, aVL, or $V_{4-6}$ and myocardial infarction can be excluded, then severe, advanced LVH resulting in the marked intraventricular conduction delay can be diagnosed.

The diagnosis of LVH in the presence of left bundle branch block may become possible with the use of orthogonal lead systems and computerized analysis as has been suggested by von Mengden et al.[99]

***P-Wave Changes.*** Alterations of the P-wave, termed "P sinistrocardiale," are secondary changes. They appear only after decreasing compliance of the hypertrophied ventricle has led to increased left ventricular end-diastolic pressure with subsequent augmentation of force of left atrial contraction. Left atrial hypertrophy and/or atrial myocardial damage with or without morphologic scar formation will result and is considered a substrate of the otherwise more nonspecific atrial conduction disturbance, called P sinistrokardiale. The recognition of atrial involvement is considered an important sign of LVH.[100,104]

***Repolarization Changes.*** Relatively early in the process of LVH, the spatial angle between the mean QRS vector and the T vector begins to widen.[94] This can be seen in the ECG at first, again in the horizontal plane: With increasing depth of $S_{V2}$ and height of $R_{V5}$ the amplitude of T in these leads changes in an opposite way. Similar developments can be seen in the leads of the frontal plane, where with increasing leftward shift of the mean axis the T vector moves in a clockwise fashion. Here, however, the respective changes are not as pronounced. In the early stages these changes are nonspecific or not yet diagnostic, except for the case of left anterior hemiblock with a QRS-T–vector angle wider than 70° to 80°. In the absence of coronary artery disease this sign can be considered a good indication of LVH.[94]

Widening of the spatial QRS-T–vector angle to or beyond 180° is not by itself considered evidence of left ventricular damage or "strain" in the proper sense. This diagnosis indicates compromise of oxygen and blood supply to the subendocardial layers of the myocardium in the absence of obstructive coronary artery disease. The condition is diagnosed when ST depression and/or T-wave inversion develops in I, aVL, $V_{4-6}$, i.e., the left ventricular leads, as evidence of an increasing magnitude of the ST vector opposite in direction to the mean QRS vector and concordant with the T vector. For formal details of the ST-T alterations in the so-called "strain pattern" of advanced LVH, the reader is referred to standard texts of electrocardiography.[97,102] With more severe degrees of "left ventricular strain" the ST-T alteration may become difficult to distinguish from subendocardial ischemia, as seen in coronary artery disease. This differential diagnosis can usually be solved only in the clinical context. Even exercise testing, if at all possible in the presence of hypertension, does not aid in differentiation.

The U-waves may become pronounced and increased in magnitude rather early in the development of hypertension and may already relate to the hyperkinetic circulatory disorder of early or borderline arterial hypertension. They are, unfortunately, rarely of any diagnostic usefulness.

***Factors Interfering with Reliability of ECG Criteria.*** Usefulness and reliability of the electrocardiographic signs of LVH are impaired through a variety of factors. In general, 15% to 20% of ECGs interpreted as showing LVH will in reality have no hypertrophy, i.e., be normal.[98] Over half of patients with LVH will show a normal, intermediate, or even vertical axis. QRS axis itself is always less indicative of LVH than an axis shift detected by serial ECGs.

QRS amplitude is a most unreliable index because it is subject to rather large influences, especially from extracardiac structures, for example, body size and build, configuration of the thorax, and thickness of the chest wall.[92]

In the presence of left bundle branch block, LVH cannot be diagnosed with the standard ECG.

The ST-T–wave changes are for the most part nonspecific and subject to influence of a host of factors, e.g., electrolyte disturbances, especially hypokalemia, so often present in hypertension with or without diuretic treatment. As is well known, the presence of digitalis glycosides obviates any interpretation of ST-T–wave changes, specifically in the hypertrophied heart.

## VCG

Orthogonal lead systems have been designed in order to compensate for the eccentric position of the heart in the thorax. This approach should be especially useful, where changes of spatial orientation and of amplitude are to be evaluated. The most widely used system is that devised by Frank. The hope, however, that more reliable estimates of LVH can be obtained by this technique has only partly been fulfilled (Table 8).

Although the scalar presentation of the Frank leads X, Y, and Z already yields highly informative amplitude criteria,[105] and the loop presentation furnishes even more information, namely spatial orientation of angles and polar vectors, the technique has for several reasons not found wider acceptance. Only recently a few centers began to incorporate the VCG into their diagnostic armamentarium. With

**Table 8.** Combined Indices for Left Ventricular Hypertrophy

| |
|---|
| Lewis index: |
| $(R_I + S_{III}) - (R_{III} + S_I)$ greater than 1.7 mV |
| Gubner and Ungerleider: |
| $R_I + S_{III}$ greater than 2.5 mV |
| $ST_I$ greater than −0.05 mV |
| $T_I$ less than 0.1 mV (36% autopsy positive) |
| Goldberger |
| $R_{aVL}$ greater than 1.3 mV |
| $R_{aVF}$ greater than 2.0 mV |
| LV strain with wide QRS-T angle (68% autopsy positive) |
| Sokolow and Lyon |
| $R/T_{V5-6}$ greater than 10 |
| $R/S_{V5}$ divided by $R/S_{V1}$ greater than 100 |
| $R_{V5-6} + S_{V1-2}$ greater than 3.5 mV (64% autopsy positive; 36% false negative) |
| Noth, Myers, and Klein |
| QR greater than 0.05 s |
| R duration in $V_5$ or $V_6$ greater than 0.04 s |

**Table 9.** Correlation Coefficients for Several ECG and VCG Parameters Predicting Left Ventricular Muscle Mass and Angiocardiographic Estimation of Left Ventricular Myocardial Weight

| | *r* |
|---|---|
| Sokolow-Lyon index (standard ECG) | 0.69 |
| Max. magnitude of QRS vector $H_{max}$ | 0.80 |
| Max. magnitude of spatial QRS vector | 0.79 |
| Magnitude of QRS polarvector | 0.62 |
| First maximum of QRS velocity vector | 0.61 |
| Second maximum of QRS velocity vector | 0.50 |
| $R_x + R_z$ | 0.78 |
| $H_{max} + F_{max} + S_{max}$ | 0.75 |
| $R_{max}T$ | 0.72 |
| QRS duration | 0.59 |
| Max. magnitude of spatial T vector | 0.55 |
| Magnitude of T polarvector | 0.52 |

From Hain et al., ref 96.

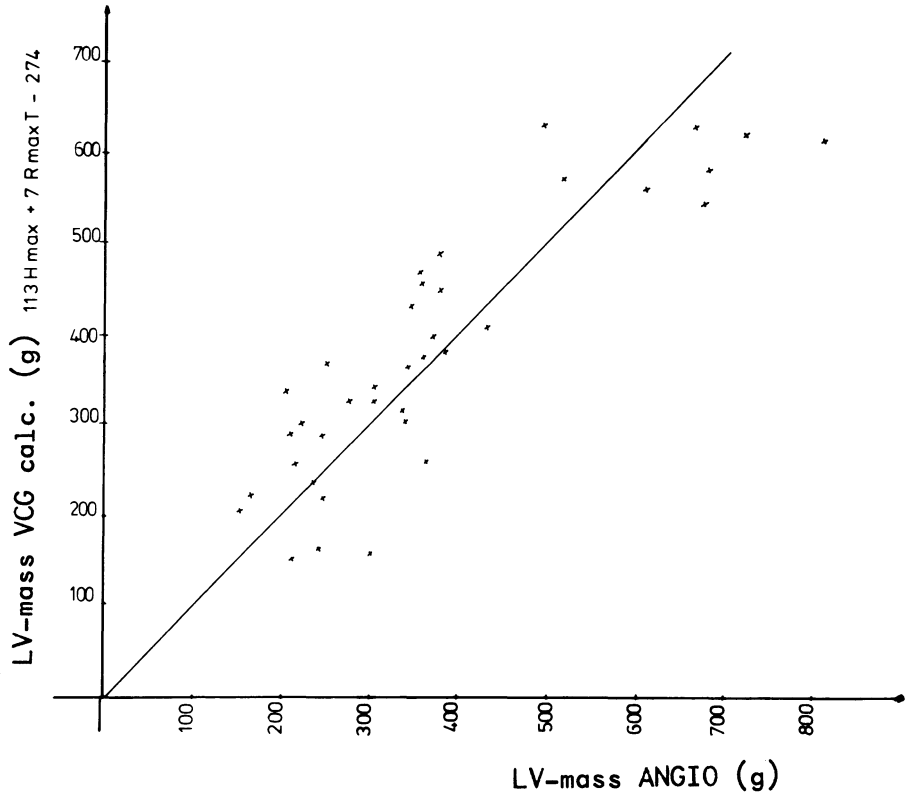


**Figure 20.** Correlation between angiocardiographically determined and vectorcardiographically estimated left ventricular mass in 36 patients with left ventricular hypertrophy. The formula for estimation of left ventricular mass utilizes two vectorcardiographic parameters, namely $H_{max}$ and $R_{max}T$ (see text). Angiocardiographic mass values are given on the abscissa (LV-mass ANGIO), vectorcardiographic estimates on the ordinate (LV-mass VCG calc.) together with the formula used. It can be seen, that the correlation is very good; the regression line is nearly identical with the line of identity of the two populations. Hain et al, ref 96

the aid of computer analysis, methods for prediction of left ventricular mass have been developed.[96]

According to Wikstrand et al.[105] evidence of LVH is detected four times as frequently by VCG (scalar leads) than by standard ECG. Therefore, the VCG should be able to detect LVH earlier, not only more reliably. LVH is diagnosed from scalar leads by amplitude criteria if $R_X$ or $R_Z$ is greater than 1.8 mV, $R_X + S_Y$ is greater than 1.9 mV, or $R_Z$ greater than 1.3 mV.

***Prediction of Left Ventricular Mass.*** Using computer analysis of the Frank VCG in patients with LVH of varying degree, a method for prediction of the left ventricular muscle mass can be developed through comparison by statistical means with left ventricular mass as estimated by quantitative angiocardiography.[96] Table 9 shows correlation coefficients for several single VCG parameters and the Sokolow-Lyon index from the standard ECG. It can be seen that the correlation is unsatisfactory in each case.

With the use of combined parameters, however, the result can be improved rather markedly. Through statistical search methodology, a correction factor can be introduced which further enhances the predictive power.

The following formula has been derived:

$$\text{Left ventricular mass (g)} = 113 \times H_{max}(\text{mV}) + 7 \times R_{max}T\ (\text{ms}) - 274$$

Application of this formula yields a very satisfactory correlation between calculated and angiocardiographically estimated left ventricular muscle mass (Fig. 20).

The example shows very clearly that the diagnosis of LVH by standard ECG or by VCG remains uncertain if single parameters are considered, but can be improved greatly with a comprehensive view of the different parameters, signs, and indices, thereby transforming the qualitative surface ECG into a semiquantitative method.

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# Essential Hypertension

# 19

M. P. Sambhi

## Historical Background

Essential hypertension was so named by Frank in 1911[1] and termed *hypertensive cardiovascular disease* by Janeway in 1913.[2] There is evidence that the disease existed in ancient times. "Hard and bounding pulse" is described variously as an important manifestation of disease in the ancient systems of medicine in China and India; bloodletting was recommended as therapy to lower the tension.[3] It is, of course, not surprising that for centuries, in the era preceding the development of modern concepts on blood circulation and blood pressure, the descriptions of hypertension as a disease are traceable only as references to its dire complications or terminal events. Through the centuries hypertension presumably was recognized as "apoplexy." Early Greco-Roman concepts on "apoplexy and paralysis" were summarized in the 5th century A.D. by Caelius Aurelianus.[4] Sclerosis of the kidneys in the absence of pain, oliguria, hematuria, and dropsy was described by Aetios in the 6th century A.D.

Much later, in 1761, Morgagni, in autopsies of some of his cases, recorded an association of enlarged heart with hardening of the arteries.[3] Richard Bright's synthesis of a syndrome with a variable combination of enlarged heart, albuminous urine, hardness and fullness of the pulse, dropsy, apoplexy, and hardening of the kidney and an increase in blood urea created the impression that hypertension and nephritis were inseparably linked to each other.[5] Subsequent investigators of the same century sought to separate the entity of primary hypertension from renal disease. Akbar Mahomed in 1874 wrote on the "prealbuminuric stage of Bright's disease."[6] Von Basch in 1880 reported on cases of "latent arteriosclerosis" with renal involvement.[7]

The etiologic concepts of primary hypertension passed through another phase of similar guilt by association, this time with arteriosclerosis. Clifford Allbutt in 1895 had already started the second process of emancipation when in the first Hunterian Society Lecture he articulated his views on high arterial pressure in elderly persons (or senile plethora), which could occur without arteriosclerosis.[8]

## Problems of Definition

An intense search for the cause of hypertension over the last half century has produced one of the most active and fascinating chapters in the annals of investigative medicine. Impressive strides have been made in defining the often curable types of hypertensive disease secondary to renal or adrenal cause. The secondary types of hypertensive disease amount to approximately 10% of the total. In the majority of patients, the fundamental cause continues to be unknown, and the diagnosis of essential hypertension remains a diagnosis of exclusion.

It is uncertain whether all cases that today fall by exclusion into this diagnosis of idiopathic hypertension necessarily belong to a single entity. Although the natural history of the disease appears to express a classic core pattern when a large number of patients are surveyed, the disease is apt to exhibit a wide variation in individual patients. This fact has sustained the attractive anticipation that the diagnosis of essential hypertension represents today

merely a mixture of undiscovered subentities. It has also aided in the formulation of certain well-known, albeit controversial, theories. Pickering proposed that essential hypertension may represent a quantitative rather than a qualitative deviation from the norm, acquired through multifactorial inheritance and modified by environmental factors.[9] Page has supported the concept that essential hypertension is a disorder of cardiovascular regulation originating in an altered interplay of a mosaic of factors rather than in a single cause.[10]

## Natural History

Both genetic and environmental factors appear to play a prominent role in the development of hypertension, but their relative contribution is debated. Although elevated blood pressure due to any cause may follow a similar pattern, the course can be modified by several factors, some of which are well known, some controversial, and still others unidentified.

The asymptomatic stage of the disease before the target organ damage is clinically apparent has often been called the benign stage of the disease. The term *benign* should not be used interchangeably with essential hypertension; there is nothing benign about the eventual course of essential hypertension. A more appropriate classification of essential hypertension is into mild, moderate, and severe, depending upon the level of blood pressure and the extent of clinically detectable target organ damage to the heart, fundi, kidney, and brain. The accelerated or malignant phase of hypertension is by no means the mandatory end result in all cases, yet the malignant phase has been known to supervene in all types of preexisting hypertensive disease. The inciting mechanisms initiating the malignant phase remain to be fully defined.

### The Course of Untreated Essential Hypertension

Our knowledge of the life history of essential hypertension is limited to the studies performed before the advent of modern antihypertensive therapy. Recent studies have established the favorable effects of long-term treatment on the course of the disease and have thus precluded on ethical grounds future controlled studies of the course of the untreated disease. The following review includes selected studies of large size only.

Janeway published in 1913 a retrospective survey of 870 patients who had attended his private clinic over the years.[2] Hypertension for the purpose of this survey was defined as systolic pressure about 165 mm Hg; the diastolic blood pressure was ignored. The patients belonged to a select socioeconomic class in New York, were not hospitalized, and no data were available from necropsy examinations.

Bechgaard reported in 1946 on 1038 subjects with hypertension attending an outpatient clinic with a follow-up period of 4 to 11 years.[11] The initial acceptance in the study was based on a single casually recorded blood pressure. The patient was included in the study if the blood pressure exceeded 160/90 or if the systolic blood pressure alone exceeded 180 mm Hg. The range of blood pressures included in the study was therefore very wide, varying from 190/60 to 300/190 mm Hg. Patients with associated diseases such as diabetes mellitus and atherosclerosis were included in the study, although an attempt was made to assess separately their relative contribution to the course of hypertensive cardiovascular disease.

This critique on these two major investigative efforts of that time is presented not as a criticism but rather to highlight the tremendous pitfalls and problems involved in the performance of studies of this type. Both studies followed patients starting from a random point in the natural history of the disease, and both included systolic hypertension and atherosclerosis in the study population, a sanction that is not in accord with the present-day definition of essential hypertension (see below).

A subsequent study free from many of the objections raised above was reported by Perera in 1955.[12] Hypertension was said to exist if repeated recordings of casual diastolic blood pressure yielded values of 90 mm Hg or above. Patients with discernible secondary causes for hypertension or existing complications were excluded. A total of 500 patients with untreated hypertension were followed until death; 150 of these were followed starting from before the onset of hypertension, and the remaining 350 were followed starting from a random point during the uncomplicated phase of essential hypertension. The appearance of complication in this population is listed in Table 1.

The cause of death in this series was less clearly defined. In 43% of the cases the cause was listed as undetermined sudden death. Death was attributed to congestive heart failure in 22%, to uremia in 10%, to cerebrovascular accidents in 9%, to myocardial infarction in 6%, and to rupture of an aneurysm in 2%; mixed multiple factors claimed the remainder. Other reports in the literature estimate that one-third to two-thirds of patients with untreated essential hypertension die of cardiac disease, 15% to 40% die of strokes, 5% to 15% die of renal failure, and the remainder succumb to a complicat-

**Table 1.** Complication Rate in 500 Patients with Essential Hypertension

| | % |
|---|---|
| Cardiac hypertrophy | 74 |
| Congestive heart failure | 50 |
| Angina pectoris | 16 |
| Myocardial infarction | 8 |
| Proteinuria | 42 |
| Azotemia | 18 |
| Malignant hypertension | 7 |
| Retinopathy | |
| Grade II | 32 |
| Grade III | 14 |
| Grade IV | 7 |

Data from Perera GA, ref 12.

ing disease. In Perera's study the mean survival was 20 years; three-fourths of this period was the average duration of the uncomplicated (benign) phase of essential hypertension.

In sharp contrast to the variable course of essential hypertension, the course of the untreated malignant phase is strikingly uniform. Schottstaedt and Sokolow in 1953 found the average survival to be 8.4 months in 86 patients.[13] Rapidly progressive renal failure is the cause of death in the majority. Hemorrhagic strokes and blindness may occur. In recent years a point of view maintains that a primary variant of malignant nephrosclerosis accompanied by microangiopathic hemolytic anemia and uremia may appear as a cause of severe hypertension rather than as its result.[14] In the American black, malignant hypertension is described with musculomucoid intimal hyperplasia of intrarenal arteries in the absence of its classic pathologic hallmark, namely fibrinoid necrosis.[15]

## Factors Altering the Course of Essential Hypertension

### Antihypertensive Treatment

The degree to which the natural history of hypertension is apt to be altered by treatment appears to depend upon the severity of the hypertensive disease, the efficacy of blood pressure lowering by drugs and, in case of long-term treatment, the side effects of the particular pharmacologic agent administered. The earliest available effective antihypertensive agents, such as ganglionic blockers, were too toxic for prolonged use in asymptomatic hypertension, but their contribution to prolonged survival of patients with malignant hypertension was dramatic and undisputed.[16,17] With the availability of antihypertensive drugs better tolerated for prolonged periods, beneficial effects of treatment on the course of moderate to severe hypertension were reported.[18] It was noted that the protection afforded by treatment reduced the incidence of renal failure, heart failure, and cerebrovascular accidents but did not seem to alter the incidence of myocardial infarction.[19] Reasons for this change are incompletely understood, but it has been suggested that certain of the complications of hypertension (such as hypertensive left heart failure, hemorrhagic strokes, and vascular damage) are more directly pressure-dependent, and their amelioration by antihypertensive therapy allows a relatively greater expression of those complications such as myocardial infarction with multiple risk factors, some of which are independent of hypertension.

The benefits of long-term treatment in moderate to severe diastolic hypertension were clearly established in the Veterans Administration cooperative study.[20] Treatment improved survival and reduced the incidence of complications.[21] The protection afforded by the treatment was further shown to be proportional to the blood pressure lowering achieved by therapy.[22] In case of mild hypertension (diastolic $<104$ mm Hg) the results of the treatment were equivocal. Several large-scale prospective trials, in Europe as well as in America, have been organized to investigate whether the course of mild hypertension (diastolic pressure 90 to 109 mm Hg) is favorably altered by drug treatment.[23] Most of these trials are still ongoing; at this time results are available only of the U.S. Public Health Service hospitals cooperative study, in which 389 subjects with diastolic pressure between 90 and 115 mm Hg were prospectively studied for 7 to 10 years and randomly assigned to either a placebo group or to the treatment group receiving a diuretic and reserpine. The incidence of major endpoints of death, myocardial infarction, and stroke was equal in the two groups despite effective lowering of blood pressure in the treatment group.[24] In a recently completed and unpublished study of 56 patients with uncomplicated essential hypertension treated with diuretics alone (see below), we find that the subjects with mild hypertension (150/104 or lower) constituted the bulk of the nonresponders to therapy.[25]

In view of the above findings, it may be asked whether fundamental mechanisms of hypertension during its mild phase are sufficiently different from those operative during the subsequent established phase, thus explaining the relative lack of response to diuretics and the influence of antihypertensive therapy on the incidence of morbid events. An answer is not available at this time. The possibility

cannot be excluded that long-term effects, hitherto unrecognized, of the particular drugs used partly contribute to the observed results,[26] and more innocuous pharmacologic agents of the future will confirm the favorable effects of blood pressure lowering even in mild hypertension, compatible with actuarial data indicating that cardiovascular morbidity and mortality are inversely related to the levels of blood pressure included in the range defined as mild hypertension.[27]

### Individual Characteristics

The special association of atherosclerosis and diabetes mellitus with hypertension and their aggravating influence on its course and prognosis are well known. A discussion of atherosclerosis is presented elsewhere in this volume. The influence of the superimposition of atherosclerosis on existing essential hypertension is discussed later in the chapter.

The influence of age, race, sex, body weight, heredity, and environmental factors on the course of hypertension is also discussed separately in this volume. Only selected comments are made here on recent work. The influence of heredity is being uncovered by blood pressure studies on children,[28] and the relative importance of environmental factors is being studied on genetically homogeneous populations transplanted to a higher-risk environment.[29] In the United States, hypertension is almost twice as prevalent among blacks as whites.[30] This greater incidence in blacks becomes apparent during the teenage years,[31,32] A recent survey revealed that mortality attributable to hypertension is almost four times higher in blacks than in whites.[33] A recently completed survey by the National Institutes of Health in the United States indicates a highly interesting inverse relationship of the level of education and the prevalence of hypertension in both blacks and whites. The prevalence of hypertension was almost 50% lower in college graduates than in those with less than 10 years of formal schooling.[34] Weight reduction, independent of salt restriction, has been shown to lead to a significant lowering of blood pressure in patients with uncomplicated essential hypertension.[35]

### Biochemical Markers

A vast literature, much of it controversial, had developed in recent years on the question of whether "low renin essential hypertension" is a distinct variant of the disease which runs a more benign course than usual, and whether renin is vasculotoxic and an important determinant of target organ damage in hypertension.[36] The question is still unresolved and will be briefly discussed later on.

An inverse relationship of urinary kallikrein concentration with blood pressure in 601 children was reported by Kass.[37] This study further showed that the urinary concentration of kallikrein exhibited a significant familial aggregation parallel with the familial aggregation of blood pressure. Black children excreted significantly lower kallikrein levels than did white children for comparable levels of blood pressure and urinary electrolytes. The significance of these data is speculative at this time. Future standardization of these measurements and extension of these observations shall be awaited with interest.

## Target Organ Damage in Hypertension

Physical effects of chronically elevated blood pressure in the past have been considered adequate to explain the main features of organ damage and complications of essential hypertension. In recent years involvement of other factors, particularly those with possible etiological relationship with hypertension, has been sought in the development of target organ damage.

### Heart

Cardiac hypertrophy is observed in three-fourths of the patients with essential hypertension (see above), yet the quantitative relationship between the degree of hypertrophy and the level of blood pressure does not always hold.[38] It has been suggested that differences in cardiac sympathetic drive among hypertensive subjects may partly account for this discrepancy.[39] Sen et al. observed increased heart weight in spontaneously hypertensive rats during the prehypertensive stage.[40] The same authors also proposed that the renin-angiotensin system may promote cardiac hypertrophy through its stimulatory action on protein synthesis. However, clinically low renin hypertension, including primary aldosteronism, does not exhibit a lower propensity for cardiac hypertrophy.[41] Marked increase in the myocardial hydroxyproline content of the hypertrophied heart in hypertension is probably an index of the increased fibrous tissue that presumably accounts for the predominant decrease in ventricular compliance. Congestive heart failure, on the other hand, appears to be a complication more directly related to blood pressure and as much to systolic as to diastolic levels. The Framingham study showed that congestive heart failure developed six times more frequently in hypertensive than in normotensive subjects and that

the survival rate was 50% after 5 years of the development of this complication.[42] Hypertension was present in 75% of all subjects with heart failure.

The risks of even mild hypertension in potentiating the incidence of coronary artery disease and myocardial infarction are well accepted and were reported by Paul in a 10-year prospective study of 6640 males.[43] As pointed out earlier in our discussion, however, antihypertensive therapy does not appear to afford the same protection from coronary artery disease as from other complications of hypertension.

## Kidney

The incidence of so-called "shrunken kidney" of benign nephrosclerosis has been grossly overestimated.[44] Zollinger reported 13 cases in a series of 10,000 necropsy examinations.[45] Castleman reported on 500 renal biopsies taken by Smithwick during the splanchnicectomy operations.[46] In 45% of the cases the renal vascular disease was classified as none to mild; in 44% the disease was termed moderate, and in the remaining 11% the renal vascular changes were called severe. In the mild and severe cases of renal vascular disease there was a close correspondence with the clinical grade of retinopathy in the same patients; in the moderate classification there was no correlation between the extent of vascular damage in the kidney and the retina. The development of proteinuria and azotemia in patients with only mild to moderate hypertension in the absence of severe or malignant hypertension is, therefore, generally regarded as a clue to the presence of primary chronic renal disease.

It should be remembered that stenotic lesions of renal arteries from atherosclerosis and from fibromuscular dysplasia may develop during the advanced course of essential hypertension. The possibility should be considered in all patients who may for no discernible reason exhibit a greater severity of hypertensive disease and a resistance to previously effective therapy.

In mild hypertension, in the absence of detectable anatomic change in the kidney, renal function studies usually show an increase in filtration fraction presumably due to a reduction in renal plasma flow.

## Brain

Prineas and Marshall reviewed angiographic data on 135 patients with the clinical diagnosis of cerebral thrombosis with infarction and found that in patients with hypertension (diastolic blood pressure >110 mm Hg) the lesions were smaller, with a deep location in the cerebral hemisphere and without demonstrable stenotic or occlusive disease of larger vessels.[47] These findings were contrasted with those observed in subjects with diastolic pressure less than 110 mm Hg who had a high incidence of cortical or subcortical infarction associated with demonstrable atherosclerotic disease in the larger intracranial or extracranial vessels. The Framingham study provided evidence for a direct contribution of blood pressure to the incidence of cerebral infarction.[48]

Hemorrhagic stroke is visualized, however, as a more characteristic lesion in the hypertensive brain than cerebral infarction. Pickering has offered evidence in favor of the somewhat controversial entity of small aneurysms described by Charcot and Bouchard in 1868 as the anatomical basis for intracerebral bleeding in the hypertensive patient.[17] Fisher has described a variety of other vascular lesions and miliary aneurysms in the brains of hypertensive patients, proposing that fibrinoid necrosis underlies all as the key pathogenic lesion.[49]

Cerebral hemorrhage is a major cause of death among patients with hypertension in Japan. Population studies and animal experiments have indicated that a low-protein and high-salt diet have a potentiating effect,[50] and a high-protein diet has a protective effect on the incidence of stroke.

There are important and significant functional effects of sustained high blood pressure on the cerebral circulation. There are adaptive structural alterations leadig to a thickening of arteriolar walls.[51] As a result, the limits of the pressure range, both upper and lower, across which cerebral blood flow can be effectively autoregulated are shifted upward.[52,53] Elevation of the upper limits of pressure autoregulation in the hypertensive subjects may be viewed as a protective phenomenon against the development of encephalopathy at high pressures; on the other hand, the elevation of the lower limit causes a fall in blood pressure to be less well tolerated and may be partly responsible for the hypotensive symptoms associated with sudden changes in posture.

The changes in retinal blood vessels that can be observed by ophthalmoscopic examination have long been used in the assessment of the severity of hypertensive disease. Extreme degrees of change, such as the differences between groups I and II vs. groups III and IV as described by Keith et al.,[54] are readily apparent and so is their significance. Beyond this assessment the information afforded by routine examination of retinal vessels is limited because of the limited patterns of reaction to stimuli and injury exhibited by these vessels. Retinal vessels differ from other systemic vessels of comparable size in certain fundamental respects and perhaps are similar to intracerebral blood vessels in the same respects. The vessels presumably lack sympathetic in-

nervation,[55,56] and autoregulatory response to higher intravascular pressure is exhibited as narrowing and constriction of the vessel wall. Furthermore, the endothelium in these blood vessels is normally impermeable, exudates and hemorrhages occur only when a vessel wall has been injured beyond the limits of autoregulatory response.

## Presumed Variants of Essential Hypertension

### Systolic Hypertension

The fundamental hemodynamic abnormality in essential hypertension is elevated peripheral resistance. In the presence of a normally compliant and elastic arterial system, elevation of peripheral resistance leads to an elevation of mean pressure, with systolic and diastolic blood pressures rising proportionately, and the changes in pulse pressure are insignificant.

Elevation of systolic blood pressure disproportionate to the level of diastolic blood pressure (and hence resulting in a widened pulse pressure) is termed *systolic hypertension.* It can occur under the following conditions:

1. In subjects of young age with normal compliance of the arterial tree, high cardiac output states, such as hyperthyroidism and arteriovenous fistula, may lead to a selective elevation of systolic blood pressure with a subnormal diastolic pressure and a subnormal total peripheral resistance. These conditions should not be classified under essential hypertension. The therapeutic approach calls for the management of the specific cause.
2. The syndrome of the so-called hyperfunction of beta-adrenergic system in young subjects[57] can be classified under the category of selective or isolated hypertension if increased stroke volume and rate exist with a normal peripheral resistance. The syndrome, however, can occur in the presence of mild and labile elevations of diastolic pressure and is therefore more appropriately classified under borderline hypertension (see below).
3. In the presence of a rigid and noncompliant arterial system secondary to arteriosclerosis in elderly subjects, systolic hypertension occurs in two varieties. Although not always possible, clear distinction between the two varieties should be attempted because the therapeutic approach, prognostic significance, and probably the fundamental pathogenic mechanisms in the two types are very different. Elevation of systolic blood pressure is attributable in both varieties to the rigidity and the loss of compliance in the large arteries. The distinction rests entirely on whether the mean blood pressure and peripheral resistance are normal or elevated.

#### Selective or isolated systolic hypertension

If the peripheral resistance, the cardiac output, and the mean blood pressure remain essentially unchanged, a superimposed increased rigidity of the larger arteries causes mainly a redistribution of systolic and diastolic efflux from the arterial system, increasing the systolic and decreasing the diastolic runoff and blood pressure. This picture is observed in the isolated systolic hypertension of the elderly. There is ample evidence in favor of the view that elevations of systolic blood pressure alone are not innocuous.

Actuarial studies have shown that, at any level of diastolic blood pressure, the calculated risk for the cardiovascular mortality and morbidity rises in direct proportion to the level of systolic blood pressure.[27] The Framingham study data indicated that males as well as females with near-normal diastolic but elevated systolic blood pressures showed increased cardiovascular risk.[48] Data from the Chicago Peoples' Gas Company study[58] and from the Chicago Heart Association Detection Project in Industry extending over 100 firms in greater Chicago[59] indicated that systolic hypertension (systolic pressure $>160$ mm Hg, diastolic pressure $<95$ mm Hg) was associated with a considerably higher prevalence of cardiovascular abnormalities in subjects 40 to 65 years of age than that observed for age-matched controls with blood pressure in the normal range. A retrospective study selected 72 subjects with systolic hypertension (systolic blood pressure $>160$ mm Hg, diastolic $<90$ mm Hg) from a retirement community of 10,500 at Leisure World in Seal Beach, California, and compared them with an equal number of age-matched normotensive controls; cardiovascular morbidity and mortality were higher in the group with systolic hypertension.[60]

The increase in total cardiac work in hypertension is nearly proportional to the elevation of systolic pressure and relatively much greater than with the elevation of mean or diastolic pressure.[61] The well-known studies of Sarnoff and colleagues proposed that the increased pressure generation during systole (afterload) was much more demanding for the heart in terms of energy requirements than the increased filling pressure during diastole (preload).[62] The mean ventricular systolic pressure generated during the systole is a direct index of the tension

developed in the ventricular wall, which is a significant determinant of myocardial oxygen consumption along with ventricular volume (Laplace law).

These observations have forced a reconsideration of therapeutic goals and attitudes regarding this entity (see below).

### Dominant or disproportionate systolic hypertension

In this case the elevation of systolic blood pressure is disproportionate to the elevation of diastolic blood pressure. The distinguishing feature, however, is a wide pulse pressure existing with an elevated mean blood pressure and elevated peripheral resistance. This category can be further subdivided into two: fixed and labile.

1. *Fixed dominant systolic hypertension* is observed in elderly subjects with rigid, inelastic large arteries and an accompanying increase in mean blood pressure and peripheral resistance. Systolic elevation is dominant; the diastolic elevation is generally milder. In the presence of grossly elevated systolic blood pressure, for the mean blood pressure to be normal as observed in selective systolic hypertension (see below), the diastolic blood pressure has to be subnormal. Conversely, a mildly elevated or even a normal diastolic pressure in the presence of dominant systolic hypertension signifies an increased mean blood pressure and an increased peripheral resistance, provided the stroke volume is normal. A therapeutic vasodilation of the arterioles usually lowers diastolic pressure, but the systolic pressure either shows only minor parallel changes or remains relatively fixed as long as the cardiac output stays normal.
2. *Labile dominant systolic hypertension* is observed in patients generally with moderate to severe diastolic hypertension with a wide pulse pressure that increases in proportion to the severity of diastolic hypertension and decreases with its therapeutic amelioration. Loss of arterial compliance in these cases should be viewed as functional to the extent it is responsive to antihypertensive measures. This loss of distensibility of the entire arterial wall is pressure-dependent and in addition is partly due to a reactive increase in smooth-muscle contraction (see below).

## Factors Decreasing Volume Elasticity Coefficient of Large Vessels in Hypertension

The nature of the diminished elasticity of large arteries in hypertension is due to factors that may be (1) structural and fixed or (2) functional and reversible.

Structural and relatively fixed increase in arterial rigidity is attributable to arteriosclerosis and to the alterations in the nature of elastic tissue commonly observed with advancing age. Similar changes are potentiated by long-standing hypertension.

There are functional factors in hypertension that lead to a loss of elasticity and increased rigidity and are more or less reversible through antihypertensive therapy. Accordingly, in clinical hypertension it is an erroneous oversimplification to accept the existing levels of pulse pressure as an index exclusively of arteriosclerotic rigidity of large vessels as opposed to the increased vasoconstriction of smaller arterioles reflecting the existing level of diastolic blood pressure. These functional factors can be listed as follows.

*Raised mean arterial pressure.* The distensibility of arteries decreases progressively as the intra-arterial pressure is elevated. At higher pressures, therefore, large and medium-sized arteries act as rigid and noncompliant tubes. Hence, pulse pressure widens progressively in hypertension as higher levels of pressures are attained, quite apart from the influence of structural alterations in the vessel wall.

*Increased turgidity of the vessel wall.* The following factors, frequently operative in hypertensive disease, lead to a less compliant and stiffened arterial wall:

1. Increased salt and water content of the vessel wall
2. Neurogenic and/or humoral vasoconstriction
3. Reactive increase in contraction of the vascular smooth muscle (Bayliss effect)

These factors are operative to a variable degree in hypertension of different etiologies. Their effects are reversible in direct proportion to the success of the antihypertensive treatment. The so-called waterlogging effect of salt retention is generalized in the entire arterial system and leads to a decreased distensibility of the larger vessels. This mechanism can be assumed to predominate in the mineralocorticoid excess type of hypertension. Muscular contraction in the vascular wall of the hypertensive subject, mediated neurogenically, humorally, or through a physical reaction to excessively increased transmural pressures, not only serves to increase the peripheral resistance at the level of smaller muscular arterioles but also affects the larger arteries. The effect on the larger arteries may not narrow the lumen and may, indeed, depending upon the anatomic arrangement of the layers of vascular smooth muscle, cause an increase in the lumen of larger ar-

teries (e.g., the aorta), but the effect on the compliance of the vessel wall is uniformly reflected as an increase in rigidity. These effects are reversible to the extent that structural changes have not developed in response to long-standing hypertension.

## Approach to the Management of Systolic Hypertension

A clear distinction has not always been made in the literature between the pure and disproportionate varieties of systolic hypertension recording separately either their respective prevalance or the associated cardiovascular mortality and morbidity. A correlation of the systolic levels of blood pressure with increased cardiovascular mortality and morbidity, in the presence of elevated mean and diastolic blood pressure (dominant or disproportionate type), indicates that in hypertensive subjects superimposition of a loss of arterial compliance, mediated through either structural or functional factors, significantly adds to the cardiovascular morbidity and mortality in comparison with those showing an elevation of peripheral resistance in the presence of normally compliant arteries. This is hardly surprising. However, the therapeutic implications are not directly applicable to the isolated pure variety of hypertension.

The data from the Veterans Administration Cooperative Study on Antihypertensive Agents indicated that treatment of mild hypertension (defined as diastolic blood pressure 90 to 104 mm Hg) afforded a significant protection against cardiovascular morbid events if patients above 60 years of age (with elevated systolic levels) were separately considered.[63] There was no significant difference among the treated and placebo groups in patients less than 60 years of age. There is little reason, therefore, for diffidence in recommending appropriate antihypertensive therapy in the disproportionate variety of systolic hypertension. There is, on the one hand, justification for being more or less aggressive in the aims of the antihypertensive therapy for subjects in this category; as previously discussed, the functional component responsible for a decrease in arterial compliance should respond well to antihypertensive therapy. Drug treatment, on the other hand, is apt to be less successful in reducing systolic levels of pressure, without concomitantly lowering cardiac output, in those patients in whom a fixed and structural basis exists for increased rigidity of larger arteries. The conventional therapeutic goal of lowering diastolic blood pressure levels to normal or somewhat below normal should, however, suffice for both types of cases. Contrary to some recent implied recommendations, it is prudent in the latter group not to take the systolic levels as the primary index of the optimal therapeutic response and not to be aggressive in lowering it to normal, provided diastolic pressure can be maintained somewhat below normal.

In the case of the isolated or pure variety of systolic hypertension, there is room for a legitimate difference of opinion regarding the therapeutic approach. The evidence is irrefutable, indicating that pure systolic hypertension is also associated with increased cardiovascular mortality and morbidity. However, there is no proof to indicate a cause-and-effect relationship with systolic elevation per se. Systolic elevation may represent merely a marker for other associated factors responsible for cardiovascular damage.[64]

Arguments in favor of not subjecting patients with isolated systolic hypertension to the unpleasant and sometimes serious side effects of antihypertensive drugs can be offered as follows:

1. There are no controlled studies available to indicate that antihypertensive therapy can, in fact, reduce the cardiovascular mortality and morbidity in this group of patients.
2. The isolated systolic hypertension in the elderly responds poorly to drug therapy because, first, elderly subjects are more prone to the side effects of almost all antihypertensive agents; second, significant reduction of systolic blood pressure in these patients can be achieved only at the cost of lowering the stroke volume and running the risk of compromising the perfusion of vital organs.

On the other hand, a compelling rationale can be mustered in favor of considering drug treatment in addition to the nonpharmacologic modes of therapy on the isolated variety of systolic hypertension in the elderly subject:

1. The height of the systolic blood pressure represents the peak pressure during the cardiac cycle and represents the peak intravascular strain as well as the peak wall tension generated by the left ventricle. Elevated systolic pressure requires a greater myocardial $O_2$ consumption even if mean blood pressure is normal. Elevations of systolic pressure accordingly correlate well with the occurrence of pressure-dependent complications of hypertension, such as rupture of blood vessels and left ventricular failure. It should be prudent to lower the systolic pressure in these patients as much as feasible without inviting serious or troublesome side effects of drug therapy.
2. Loss of elasticity in the arterial tree deprives it of another one of its important functions, that of accommodating extra blood during acute changes

in stroke volume or cardiac output due to exercise, sudden change in posture, or change in emotional state. This limitation is often reflected as wide fluctuations in blood pressure with systolic elevations to levels that may threaten the integrity of intracerebral blood vessels as well as the performance of the left ventricle. Drug treatment designed to prevent undue blood pressure fluctuation is strongly indicated.

Specific recommendations on therapy are not warranted at this time. We personally have had good results with the use of small doses, at least half normal, of clonidine or metolazone or of a combination of the two drugs.[65] The decision of whether to treat or not should be based not only on the resting levels of blood pressure but also on the response of the blood pressure in the elderly subject to the demands of increased cardiac output.

The importance as well as the dilemma and the difficulty in always making a clear distinction between so-called systolic hypertension and essential hypertension are apparent from the above discussion. If isolated systolic hypertension in the elderly has its pathogenesis originating from arteriosclerosis, and the pathogenesis of sustained essential hypertension is mediated principally through arteriolar vasoconstriction and an elevation of peripheral resistance, the two should be regarded as separate disease entities. The fact that arteriosclerosis and hypertension share certain risk factors and seem to potentiate the severity of each other should not be used as a sanction to obliterate the discernible distinctions between the two entities for the purpose either of therapeutic approach or of etiological investigation. In this regard it is unfortunate that epidemiologic surveys have in the past and in some cases still continue to include age-related elevations of systolic blood pressure in the study of the natural history of essential hypertension in different population groups.

## Borderline Hypertension

The term *borderline hypertension* in preference to *labile hypertension* was coined by Conway and associates at the University of Michigan, Ann Arbor, in 1968[66] to describe subjects in whom the diastolic blood pressure was sometimes below and sometimes above 90 mm Hg. The term *early hypertension* is also used to describe the same entity. It is tacitly assumed that borderline hypertension represents a pathogenetic forerunner of sustained hypertension.

The prevalence of borderline hypertension increases with age from approximately 10% below 30 years of age to 25% or more in later years. Similar estimates have been provided by surveys conducted in the United States,[67] Germany,[68,69] and Belgium.[70] The development of later sustained hypertension among the borderline hypertensives has been reported to vary from 8% to 26% in recent studies.[71]

A variable proportion of subjects with borderline hypertension show an elevation of cardiac output and heart rate.[71] It has not been established whether this increased beta-adrenergic function represents a primary increase in sympathetic drive to the heart or if the autonomic nervous activity is secondary to the circulatory abnormality. Careful hemodynamic measurements have shown, however, that for a given level of cardiac output during rest, exercise, tilting, or volume expansion, peripheral resistance is always elevated. An increase in cardiac output, therefore, does not appear to be essential for the maintenance of borderline hypertension.[72]

Studies by Safar et al. demonstrated an increase in cardiopulmonary (central) blood volume relative to the total blood volume in borderline hypertension in comparison with normotensive and sustained hypertensive subjects.[73] The authors further suggested that enhanced venous tone and venous return secondary to increased sympathetic activity were involved in the redistribution of blood volume and the elevated cardiac output observed in borderline hypertension.

Esler et al. classified patients with borderline hypertension into low-, normal-, and high-renin groups on the basis of a plasma renin and urinary sodium normogram.[74] In high- and normal-renin groups, blood pressure was elevated because of increased total peripheral resistance, neurogenically mediated, that could be normalized in the high-renin group by total autonomic blockade. In low-renin subjects, on the other hand, the total peripheral resistance was normal, while central blood volume and stroke volume were elevated; it was suggested that the blood pressure elevation was volume-mediated and renin activity was suppressed via cardiopulmonary volume receptors.

Our recent studies on patients with uncomplicated essential hypertension (see above) treated with diuretics alone have attempted to characterize determinants of antihypertensive response. The nonresponders to thiazide diuretics achieving no significant fall in blood pressure after 3 months of therapy had significantly lower blood pressures during the pretherapy period than did the responders. Many of the nonresponders could be classified as borderline hypertensives on the basis of blood pressures recorded during the control period before therapy (Fig. 1). The nonresponders also exhibited a tendency toward higher plasma aldosterone and angiotensin II levels and higher rates of in vitro an-

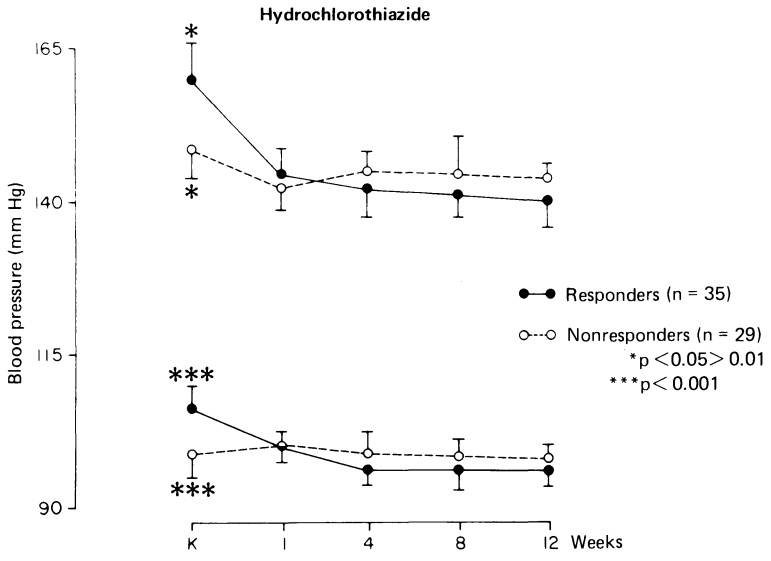


**Figure 1.** Systolic *(upper panel)* and diastolic *(lower panel)* blood pressures in 64 patients with uncomplicated essential hypertension are shown during a control period (following a period of no therapy for at least 4 weeks) and during treatment with hydrochlorothiazide 50 mg twice daily at 1, 4, 8, and 12 weeks. The subjects were classified as nonresponders if the difference between the control mean blood pressure (diastolic blood pressure plus one-third pulse pressure) and the average of mean blood pressure during all treatment periods was less than 5 mm Hg. At each time period systolic and diastolic blood pressure values are shown as mean ± S.E.M. of the two groups. From Sambhi et al., ref 25

giotensin generation in plasma. Significance of these findings in relation to the pathophysiologic mechanisms underlying mild and borderline hypertension remains to be elucidated. A caution is warranted, however, against the common recommendation for the use of a diuretic agent in subjects with mild and borderline hypertension. Julius has discussed recommendations for selective use of drug therapy in borderline hypertension.[71]

## Low-Renin Hypertension

Approximately 25% of patients with essential hypertension show suppressed values of plasma renin activity. Renin is relatively unresponsive to the usual stimuli, and in certain respects these subjects behave similarly to those with mineralocorticoid excess. On the basis of retrospective studies it has been proposed that patients with low-renin hypertension have a negligible incidence of cardiovascular complication such as strokes and myocardial infarctions.[75,76] Opinions are sharply divided among various investigators on the two questions: does low-renin hypertension represent a distinct variant and a separate entity, or is it merely a nonobligatory phase that can occur during one or more periods in the natural history of essential hypertension? Is the circulatory level of renin (activity) an important enough determinant of cardiovascular damage secondary to hypertension, so that for prolonged periods lower levels, spontaneous or induced, confer a significant protection and conversely higher levels, spontaneous or induced, increase the risk of hypertensive cardiovascular complications? A vast amount of literature has accumulated in recent years on these questions and on the pathophysiologic characterization of low-renin hypertension. Notable recent reviews and surveys should be consulted for details.[36,77,78] A brief summary of selected aspects only is presented here. A well-known major problem appreciated by every critic and ignored by every investigator has been the practice of using differing methodology to define the low-renin group and of accepting small, skewed samples of subpopulations for study to represent the total as essential hypertension. This practice has seriously retarded a better characterization of the entity.

### Pathophysiology

The weight of evidence indicates a lack of detectable increase in the total blood volume and exchangeable sodium space in patients with low-renin hypertension.[79–81] In low-renin subjects categorized as borderline hypertensives, an increase in central blood volume and, therefore, in the ratio of central to total blood volume has been reported.[74] Inhibition of renin via stimulation of cardiopulmonary receptors is proposed as the mechanism of renin suppression. It is not established whether the proposed mechanism can account for renin suppression in all or a significant proportion of cases with low-renin hypertension. The expansion of central blood volume has been reported by other investigators to be a feature of all unselected subjects with borderline hypertension, presumably regardless of their renin status.[73] Furthermore, low-renin state is undoubtedly ob-

served in sustained or permanent hypertension, sometimes with moderately high diastolic blood pressure.

The question of mineralocorticoid excess as the mechanism for low-renin hypertension, failing to qualify as a serious contender, has nevertheless managed to keep alive. A recent symposium held at the Mayo Clinic summarizes the state of the art.[82] Genest presents a convincing synthesis of arguments supported by data from his group, showing that a relative state of aldosterone excess demonstrated by somewhat higher plasma aldosterone levels and a lower metabolic clearance rate is characteristic of most cases of uncomplicated essential hypertension regardless of their renin status.[83] Similarly, an excess of adrenal secretion of 18-hydroxy-11-desoxycorticosterone (18-OH-DOC), a very weak mineralocorticoid, but with a potential of producing experimental hypertension in the rat, occurs in a small proportion of patients (10%) with low- or normal-renin essential hypertension. Melby and Dale reported that the synthesis of a metabolite of 18-OH-DOC (16 $\alpha$, 18-diOH-DOC) is greatly accelerated by the adrenal tissue of patients with low renin.[84] This metabolite lacks mineralocorticoid activity by itself but is capable of greatly potentiating the sodium-retaining action of aldosterone. The Vanderbilt group retracted their previous observations on C-19 mineralocorticoids (16 $\beta$-OH-DHEA) regarding their excess presence in low-renin patients as well as their ability to produce hypertension in rats.[85] Instead, suggestive evidence was presented favoring the role of an unknown mineralocorticoid in the blood pressure elevation of patients with low-renin hypertension. A blocker of the adrenosteroid biosynthetic pathway in the early steps (aminoglutethimide) reduced aldosterone secretion as well as blood pressure in low-renin hypertension. A distal blocker (metyrapone) likewise reduced aldosterone but did not reduce blood pressure. New and Levine presented case histories of two patients in whom hypertension was not related to any of the known mineralocorticoids but behaved as if it were dependent upon an adrenocorticotropic (ACTH) stimulable unknown steroidal hormone.[86] It may be concluded that mineralocorticoid excess attributable to unknown mechanisms may be responsible for the hypertension in some cases, but probably only in a very small proportion of patients with low-renin hypertension.

A diminished sympathetic tone has been proposed as a mechanism for suppressed renin in patients with low-renin hypertension. Esler and Nestel related high and low levels of plasma renin at rest and during head-up tilting to a corresponding level of urinary norepinephrine.[87] We have recently reported that chronic administration of clonidine in patients with low-renin hypertension leads to a significant renin stimulation, whereas plasma renin levels are unchanged in patients who have normal renins to start with.[88] These findings have been interpreted in favor of the view that the prevailing adrenergic tone is different in patients with low-renin hypertension from that in the normal renin group. It is unknown, however, whether the observed deviations in the tone of the autonomic nervous activity in low-renin hypertension are primary, or whether they are secondary to unidentified factors.

Another hypothesis proposed by our group attributed the renin suppression in patients with essential hypertension to a feedback suppression of renin by increased instantaneous local generation of angiotensin in close vicinity of juxtaglomerular receptor sites.[89,90] The proposed schema leading to renin suppression is shown in Figure 2. It was proposed that a substance other than renin and its substrate circulates in the plasma of hypertensive subjects and acts as a renin activator to accelerate the rate of angiotensin generation. As it has not been possible to isolate or identify the proposed renin activator from hypertensive plasma, the hypothesis remains plausible but unsubstantiated. More recently, the enzyme renin has been described as occurring in various molecular weight species and in forms with greater and lesser enzyme activity.[91] The physiopathologic significance of the so-called active and inactive renin forms remains to be explored.

It appears, therefore, that low-renin hypertension is not a separate, distinct entity, but rather that suppressed renin observed in a proportion of patients with essential hypertension is attributable to several mechanisms and can occur in early or borderline hy-

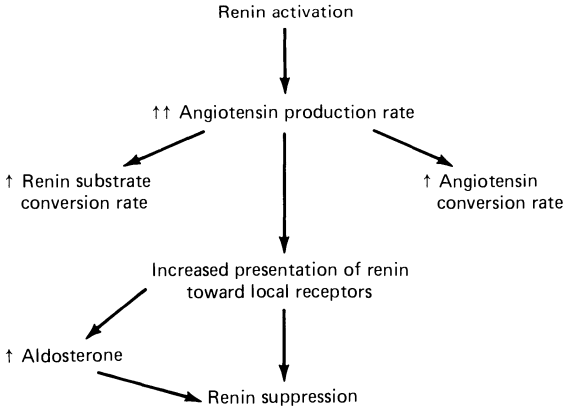


**Figure 2.** Chain of events proposed as the mechanism originating from the presence of a "renin activator" leading to renin suppression in the kidney. From Sambhi et al., ref 89, p 36

pertension as well as in association with long-standing sustained diastolic hypertension. The small proportion of cases that demonstrate mineralocorticoid excess may preferentially respond to aldosterone antagonists, but most of the patients do not show this selectivity. The controversy concerning the influence of renin levels on the incidence of the complications of hypertension can be resolved only by careful prospective studies. For the present, there is no evidence to claim that, if a group of patients with hypertension characterized today as low renin were to be followed, they would be destined to have a lower complication rate in the future, or that the rate or type of progression of hypertensive disease is predictable in these patients. On the other hand, retrospective evidence from some, but not all, studies indicates that the extent of cardiovascular damage is small during the time renin remains suppressed in patients with hypertension.[92] When significant damage is present, renin is high. Therefore, although a cause-and-effect relationship is unproved, renin appears to be one of the indicators of cardiovascular damage.

Another area of active controversy and conflicting opinions is the question of whether, or to what extent, plasma renin activity determines the antihypertensive response to drugs. Several studies reported that aldosterone antagonists were capable of achieving a greater fall in blood pressure in patients with low-renin hypertension.[93–95] Other studies have considered beta blockers to be relatively ineffective in low-renin hypertension.[96] These studies have demonstrated correlations between the pretreatment levels of plasma renin activity and the magnitude of fall in blood pressure achieved with the use of spironolactone or propranolol. These correlations have been interpreted to indicate a cause-and-effect relationship between the two parameters and to provide support for the vasoconstriction volume hypothesis proposed by Laragh.[97] A greater body of evidence, including carefully controlled reinvestigations, has, however, failed to confirm a significant relationship between plasma renin and the antihypertensive effects of spironolactone[98,99] as well as propranolol.[100–104] It should be made clear that the preceding remarks on therapy are limited to low-renin hypertension and do not address themselves to the so-called high-renin hypertension or to the broader subject of the relationship of drug treatment and plasma renin, which is outside the scope of the present discussion. In the case of low-renin hypertension it may be concluded that there is no convincing evidence available at this time in favor of the view that measurement of plasma renin or the identification of the "low-renin status" in a given patient with hypertension is a useful aid in planning the antihypertensive treatment.

## The Nature of the Abnormality

The kidney, the heart, and the brain have each been proposed as the seat of the primary abnormality. The seat of the elevated resistance to blood flow lies predominantly in the small muscular arterioles. The initiating mechanism for this increased resistance is controversial. Humoral or neural vasoconstriction has been considered likely. Increased flow in the initial stages resulting in structural thickening of the small arterioles, the so-called resistance, has been proposed as an equally plausible alternative.[51] The vascular constriction or the narrowing of the lumen by wall thickening is not uniform in the regional circulations and is probably critical in the splanchnic area. Other regions may participate in this process but do not appear to be essential to the increase in the "total" or "effective" increase in peripheral resistance.[105] Loss of one or more of the limbs does not result in hypertension. Potent vasodilation selectively of limb vessels in a subject with hypertension does not lead to a reduction of blood pressure.

In recent years an increasing body of evidence has accumulated to show the central nervous system involvement in blood pressure regulation and in hypertension.[106] The role of the autonomic nervous system in the development of experimental hypertension is ably reviewed by deChamplain.[107] Since the demonstration that certain centrally acting drugs such as clonidine reduce blood pressure through the stimulation of subhypothalamic and medullary centers, resulting in a reduced peripheral sympathetic discharge, it has been proposed that a defective excitation of these inhibitory centers as a primary cause of essential hypertension is an attractive hypothesis deserving attention of future investigators. Such a hypothesis is not subject to proof in the hypertensive patient by means of present-day methods, nor is the unresolved question of whether the role of the nervous system is limited to a permissive one in the expression of hypertensive disease or is more than that.

Increased cardiac output, as discussed earlier, is frequently observed in patients with early labile or borderline hypertension. Increased cardiac output presumably originating from an elevated beta-adrenergic tone may, over a period of time, induce structural resetting of resistance vessels, as proposed by Folkow.[51] With the development of sustained hypertension, cardiac output is visualized as returning to normal *pari passu* with the elevation of total peripheral vascular resistance. According to Guyton, the mechanism by itself lacks a propensity for self-perpetuation, as the phenomenon of pressure diuresis will counteract the establishment of raised arterial pressure.[108,109]

It has come to be generally recognized that central

to any self-sustaining mechanism for the maintenance of elevated arterial pressure is its altered relationship to the sodium excretion by the kidney, so that a higher perfusion pressure is required to excrete the amount of sodium optimal for the maintenance of sodium and volume balance. The question remains as to what triggers this altered relationship in primary hypertension.[110,111] The abnormality in the kidney can presumably be transmitted genetically in Dahl's salt-sensitive strain of rats[112] and by transplantation of a kidney from the Milan strain of spontaneously hypertensive rat to a normotensive rat.[113] The central and pivotal role of the kidney in the genesis of hypertension cannot be refuted.

In the uncomplicated early stage of essential hypertension, plasma renin activity, plasma and extracellular fluid volumes, and exchangeable sodium are not increased. Renal blood flow is generally decreased; glomerular filtration fraction is increased. Plasma renin may be suppressed. The reduction in renal blood flow occurs preferentially in the outer cortical region of the kidney, with a redistribution of blood flow to the inner juxtamedullary and medullary regions. The well-known phenomenon of exaggerated natriuresis in response to volume expansion is present.[114]

A full discussion of various theories proposed as the "fundamental renal abnormality" in essential hypertension is outside the scope of this chapter. The interested reader is referred to a recent treatise on hypertension.[115] Folkow has supported the fundamentals of Guyton's hypothesis and suggests that a neurogenically mediated increase in preglomerular resistance may be responsible for resetting the relationship of sodium excretion to increased arterial pressure.[116] Experimental support for this hypothesis has been provided by Folkow and associates.[117] Birkenhäger and Schalekamp[118] and Brown et al.[119] have proposed that autonomic nervous overactivity over a period of time, by working through its effect on the heart and blood vessels, leads to a reversible resetting of pressure natriuresis, which in time may become irreversible through the development of renal vascular changes. The time required for the development of the renal abnormality is variable, and the term *renal transformation time* was coined to denote this variability. Susceptible individuals are said to have a short renal transformation time. Renal transformation is presumably mediated through an increased renal vascular resistance and an increased filtration fraction leading to an increased sodium reabsorption, owing partly to a rise in the oncotic pressure and partly to a reduction in hydrostatic pressure in the peritubular capillaries. Blood pressure rises in order to maintain sodium balance in the face of these changes.

The above hypothesis (with minor variations) seems to represent the core pattern of many viewpoints on the mechanism of hypertension. It would be out of character for the ego of a full-time hyperpiesiologist to resist the temptation to express a personal bias; that bias is to keep looking for a single dominant cause within this plausible scheme of self-perpetuating chain of events, a cause that can be transmitted genetically as well as through transplantation of the kidney with the "fault." Our further bias is not to exclude the renin-angiotensin system from this scheme, because plasma renin is usually suppressed or normal during the uncomplicated phase of essential hypertension. It is our view, at the time of writing this, that the suppression of renin content in the kidney and consequent changes in the renin content of the renal vasculature trigger the establishment of elevated renal vascular resistance, leading to an increase in systemic arterial pressure. The fundamental cause remains unknown.

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# Hypertension in Pregnancy

# 20

Ch. Lauritzen

## Definition

In pregnancy a blood pressure of 140/90 is considered to be borderline. Higher readings are regarded as pathologic. Though the disadvantages of blood pressure measurement with the usual sphygmomanometers are well known, most investigations are based on this method. There are also studies on the direct measurement of intra-arterial blood pressure,[33] but the authors found a relatively close correspondence to the usual, simpler methods of measurement. No correlation was found between blood pressure levels and arm circumference or skin-fold thickness in this area.

## Causes of Hypertension in Pregnancy

A distinction must be made between causes preceding pregnancy and those leading to an elevation of blood pressure during pregnancy itself. The former group includes glomerulonephritis, renal artery stenosis, coarctation of the aorta, pheochromocytoma, pyelonephritis, and essential hypertension. However, preexisting diseases relatively seldom cause hypertension of pregnancy. The most frequent cause is the elevation of blood pressure brought about by the pregnancy itself. It occurs in the last trimester and is usually due to toxemia. The causes of toxemia and hypertension are not well understood. Nevertheless, it is known that endogenous pressor peptides formed in the placenta play a crucial role. There is evidence that pregnant women who develop hypertension in late pregnancy respond excessively to the stimulation of the renin-angiotensin system by salt depletion in early pregnancy.[15] Generalized vascular spasms occur, first with functional, then with morphologic changes in the sensitive organs. Intravascular coagulation and specific glomerular renal lesions are the typical morphologic substrate in the development of hypertension, with albuminuria and edema present up to the stage of preeclampsia.

## Role of Enzymes in the Etiology

It has been conjectured that there is a correlation between the deficiency of monamine oxidase in the placenta and hypertension of pregnancy as well as hypertension in toxemia. It has been assumed that the deficiency of this enzyme might underlie the production of hypertensinogenic amines, particularly since it is known that the vessels of the human placenta respond very sensitively to 5-hydroxytryptamine. This, in turn, would mean vasoconstriction, anoxia, and a further reduction of monamine oxidase activity. There are no studies available at present on the influence of the kallikrein-kinin system on hypertension in toxemia.

## Renin-Angiotensin System

Renin is normally produced by myometrial and endometrial cells. Its role in the normal pregnancy has not yet been fully elucidated. It probably takes part in the regulation of the uteroplacental blood flow. A reduction of blood flow induces a rise in renin secre-

tion and in the levels of circulating or local angiotensin, whereupon blood flow is again increased via beta-adrenergic stimulation.[9]

The induction of hypertension by pressor substances formed by the ischemic placenta might follow a course analogous to that known for the ischemic kidney. Again, the enzyme which plays the key pathogenic role is renin. It is produced by the renal juxtaglomerular cells and is found in the kidneys, blood, uterus, placenta (chorion), and amniotic fluid. As far as is known, the physiologic effects of renin are again mediated by angiotensin, i.e., the inactive decapeptide angiotensin I and the vasopressor octapeptide angiotensin II. The main effects are a systemic influence on blood pressure, the release of epinephrine, the stimulation of autonomic ganglia, the production of aldosterone, and the alteration of sodium excretion. Owing to the high estrogen levels, aldosterone is increasingly bound to plasma protein. This results in a decrease of free aldosterone and a concentration of sodium in the serum. Progesterone causes increased reabsorption in the distal tubule and thus leads to a stimulation of renin secretion.[19] In normal pregnant women a rise of plasma renin, renin substrate, and angiotensin II ensues. In patients with hypertension of pregnancy and severe forms of toxemia, values for renin, renin substrate, and angiotensin II are reduced.[4,8,15,17,20,39] In hypertensive patients with hydatidiform mole and hydrops fetalis the values are markedly elevated, as in diabetes. In normal pregnancy, sensitivity to angiotensin is reduced, but in hypertensive women it is heightened.[5] Possibly the lack of a decrease in the renin-angiotensin-aldosterone levels which are elevated in normal pregnancy predisposes to hypertension and toxemia. The suppression of the renin-angiotensin-aldosterone system in late hypertensive toxemia might well be an adaptation to the increase of previously unidentified pressor peptides or mineralocorticoids in the blood.

## Incidence of Hypertension in Pregnancy

About 20% of all women become hypertensive during their first pregnancy. In later pregnancies the incidence of this complication tends to be lower, but it increases again with age. It varies greatly from country to country and at different times. In about 30% of cases the rise of blood pressure is due to essential hypertension; in 10% it is due to nephritic toxemia. About 2% may be attributed to renal diseases not caused by pregnancy but arising during pregnancy. The remaining 60% of all cases of hypertension in pregnancy are due to the presence of toxemia. About one-third are monosymptomatic toxemias with hypertension only (H-toxemias), without edema or proteinuria. The variety of symptoms increases with the duration and severity of the disease.

## Risk Factors

It has been demonstrated in large population surveys[35] that apparently there is no relation to diet, especially to the protein, fat, or carbohydrate content of food. However, the incidence of hypertension in toxemia increases with age. Primigravidas are at greater risk for toxemia and hypertension. Familial factors play an additional role. The incidence of toxemias with elevated blood pressure increases to 40% in the sisters and daughters of women who themselves experienced toxemia in pregnancy.[1,7] The weight gain in pregnancy has no prognostic significance in terms of predicting whether a patient will develop hypertensive toxemia or not. However, a rise of blood pressure combined with weight gain and albuminuria strongly indicates an increased risk of toxemia-induced premature delivery and perinatal mortality. Women who develop hypertension toward the end of their pregnancy have larger children than normotensive mothers. This is presumably due to the fact that hypertensive women also experience a greater weight gain than normotensive women.[25]

## Toxemia of Pregnancy (Preeclampsia, Gestosis)

The three main symptoms of toxemia of pregnancy are hypertension, edema, and proteinuria, of which hypertension is the most striking and most frequently demonstrable. Because the blood pressure may rise quite gradually, other symptoms have to be relied upon for definition and early diagnosis of toxemia. The presence of edema is of no major clinical significance. Proteinuria, however, is less frequent and is a clear pathologic sign.[24] It usually occurs when the blood pressure exceeds 90 mm Hg diastolic or 140 mm Hg systolic.

Nephritic toxemia can occur in patients who have a chronic renal disease before becoming pregnant. It is often accompanied by very serious complications. If the hypertensive toxemia is caused by pregnancy alone, it is called *hypertension of pregnancy*. If only an elevation of blood pressure is present, it is called *monosymptomatic toxemia* or *H-toxemia*. If the hypertension is combined with edema and proteinuria, EPH-toxemia is present.

### Kidneys

In the kidneys, i.e., in the endothelial cytoplasm of the glomerular capillaries, a marked endothelial swelling is found which contributes to the narrowing of the capillary lumen. Apparently this general vascular reaction is produced by substances, presumably polypeptides, which are synthesized in the placenta. The described changes are very similar to those seen in rejection of a renal transplant. It has been assumed, therefore, that an antigen-antibody reaction may be the etiologic factor.

### Optic Fundus

The retina and its vessels provide a means of directly observing vascular events that take place in hypertensive toxemia. The pathologic changes in the retinal vessels increase markedly with the severity of the disease. More pronounced, irregular reflex bands are observed on the retinal arterioles, as well as a generalized narrowing of the arterioles. These initially functional changes of the fundus may progress in the severe forms of the disease to retinal edema, hemorrhage, exudations, and eventually to retinal detachment.

Diminished perfusion and its consequences are also found in the liver and brain. Jaundice, headache, and finally eclamptic convulsions may follow.

### Hormones

In hypertension of pregnancy, the levels of estrogens, HCG, and HPL in plasma and urine are normal. In cases of secondary placental insufficiency, the estrogens and HPL fall, while the HCG rises. Aldosterone values are usually lowered. Aldosterone secretion in pregnancy responds very sensitively to changes in sodium intake. If it decreases, the aldosterone level rises.

## Early Diagnosis of the Development of Hypertension in Pregnancy

The potassium/creatinine ratio in the 36th week is lower in pregnant women who later develop hypertensive toxemia.[15] This finding, however, is not highly reliable. According to investigations by Gant et al., women who show a rise of 20 mm Hg diastolic when changing from the lateral to supine position between the 28th and 32nd weeks of pregnancy are at very high risk for developing acute hypertension in later pregnancy (93% certainty).[12] These women also show increased sensitivity to the intravenous infusion of angiotensin II. Indeed, the probability that hypertension will develop is greater than 90% when the infusion of less than 8 ng/kg/min of angiotensin II induces a rise of diastolic pressure of at least 20 mm Hg during the 28th to 32nd weeks of pregnancy.

The metabolic clearance rate (MCR) of the adrenal estrogen precursor hormone dehydroepiandrosterone sulfate shows a marked decrease about 4 to 5 weeks prior to the clinical appearance of hypertension. Though MCR is the sum of several possible factors in the plasma clearance of the hormone, it mainly represents a kinetic measurement of placental function. Apparently placental function is depressed as early as 4 to 5 weeks prior to the development of a late hypertensive toxemia.

## Effects of EPH Toxemia on the Child

Perinatal morbidity is higher in pregnancies with toxemias, especially in the presence of proteinuria and elevated blood pressure. The high infant mortality is mainly a problem of premature delivery, since 30% of the babies born to preeclamptic women have a birthweight less than 2500 g. The low birthweight cannot be attributed only to the frequently reduced duration of pregnancy, but also to the presence of placental insufficiency with retardation of fetal growth. Primigravidas with hypertension alone do not have a higher perinatal mortality than normotensive women. The birthweight is generally lower in toxemia combined with hypertension and other symptoms than in toxemia with hypertension alone.

## Treatment

The therapy of hypertension during or after pregnancy consists of lowering the blood pressure in order to avoid the occurrence of placental insufficiency with its increased fetal morbidity and mortality, as well as to prevent premature placental separation and eclampsia. The most important treatment is bed rest, in order to improve placental perfusion and increase plasma renin activity and concentration.[37] The diet should be rich in proteins and low in fats and carbohydrates. Salt intake should not exceed 2 to 3 g daily. Diuretics are disadvantageous as they tend to exacerbate salt loss. In any case, thiazides do not significantly lower the

blood pressure in toxemia of pregnancy.[28,30] In severe hypertension of pregnancy, treatment with antihypertensive drugs may be required. This mainly improves the prognosis for the mother, less so for the fetus. Suitable drugs include reserpine, dihydralazine, and clonidine. An excessively rapid and forceful lowering of the blood pressure may jeopardize the life of the fetus by an insufficient blood supply. If the maternal hypertension is intractable and rapidly progressive, the pregnancy must be terminated in the interest of the mother (and the child).

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# Hypertension in Childhood with Special Reference to Cardiovascular and Renal Causes

21

H. C. Kallfelz, G. Offner

## Introduction

Until 10 years ago persistent hypertension in infants and children was considered an extreme rarity. However, in recent years much evidence has accumulated that primary hypertension in the young age groups is much more prevalent than was previously conceived.[42,60,66,67,72,83,113,129,130] Earlier, when an elevated blood pressure was discovered in a child, there was often a tendency by physicians to discount the significance of the finding, relating it to the anxiety of the child. Moreover, there were few facilities available for differential diagnosis and proper treatment applicable to children. If hypertension was secondary to coarctation of the aorta, it could be relieved by resection, and surgery was also successful in the rare cases of renal tumors or neoplasms with endocrine activity. With improved diagnostic methods, nowadays applicable even to infants, such as arteriography, isotope renogram, renal scan, renal biopsy, and renin assay, and with the introduction of new, safe drugs to control hypertension not amenable to surgery, the hitherto nihilistic attitude to diagnosis and treatment has considerably changed. In most cases now precise differential diagnosis is possible and consequently in the majority adequate therapy can be accomplished.[13,43,73,96]

The latest phase of interest in childhood hypertension is prevention. If we are able to detect and control hypertension in its early stages, we might prevent much chronic illness in later life as well as early deaths; so systemic hypertension to a great extent is a challenge to the pediatrician. This chapter will deal only with those aspects of hypertension specific to the pediatric age group. For details regarding physiopathology and diagnostic and therapeutic measures pertinent to all age groups, please refer to the special chapters.

## Techniques of Blood Pressure Measurements in Infants and Children

Reliable indirect blood pressure measurements in infants and young children are often difficult to obtain. This may be the reason that many studies have to be undertaken to evaluate and to compare various methods and instruments.[11,25,41,59,87,88,103,119] It is now agreed that certain precautions relative to equipment and its use as well as to the present status of the patient to be examined and his or her environment have to be taken into account in order to avoid errors (Table 1). The most important factor intrinsic to the pediatric patient is anxiety, which leads to falsely high measurements. Thus an infant or young child crying may demonstrate a systolic pressure 30 to 50 mm Hg higher than under quiet or basal conditions. A relaxed and unhurried atmosphere is therefore important, and a well-trained nurse is often preferable as a blood pressure examiner. The usual method for taking blood pressure in children is by using an arm cuff and auscultation. The cuff size is especially important when measuring blood pressure in children. An inappropriate cuff size can falsely elevate or lower arterial blood pressure readings.[70,76,88,89,117] The American Heart Association recommends that the width of the inflatable cuff be two-thirds of the upper arm length and in children of adult size be about 20% greater than the diameter of the arm.[53] The inflatable bladder should be at least long enough to halfway encircle the limb, with

**Table 1.** Possible Sources of Error in Measuring Blood Pressure in Children

| |
|---|
| *Equipment* |
| Defective sphygmomanometer, tubing, cuff, stethoscope |
| *Use of equipment* |
| Improper cuff size |
| Instrument not at heart level |
| Inflation too slow, deflation too rapid |
| Mercury column not at eye level |
| *Examiner* |
| Imperfect knowledge of technique |
| Hearing deficiency |
| *Variations in condition of subject* |
| Sitting or supine position |
| Anxiety |
| Presence of pain |
| Postexercise |
| Postprandial |
| Bladder distension |
| Infection |
| Fever |
| Drug therapy |
| *Environment* |
| Diurnal variation |
| High or low ambient temperature |
| Noise pollution |
| Mass screening versus individual examination |

care taken to apply the bladder directly over the artery and to fix it snugly. Since the length and diameter of the limbs increase with age, a variety of cuff sizes must be available. The following recommendation may be taken only as a guideline for the proper cuff size:

| Age Group | Appropriate Cuff Width (cm) |
|---|---|
| Premature and newborn infants | 2.5–3 |
| 1–12 months | 4–5 |
| 1–3 years | 5–6 |
| 4–8 years | 8–9 |
| 9–12 years | 12 |
| Over 12 years | 12–14 |

In practice the appropriate size of cuff is selected according to the size of the child. It is generally agreed that phase I of Korotkoff is the index of systolic pressure. The index of diastolic pressure is less certain. There has been controversy about whether the muffling offsounds, or phase IV, is a better signal than the disappearance of sounds. Muffling tends to give readings which are too high, and cessation of sounds tends to give results which are too low.[53] Thus it is advisable to follow the recommendations of the American Heart Association that the point of muffling and of disappearance of sounds both be recorded, e.g., 100/70/55 or, if muffling does not occur, 100/55/55.

Three alternative methods are useful in infants or small children if the arterial sounds for any reasons cannot be heard. When the flush method is used,[1] the cuff is placed above the wrist or ankle and a compression bandage is wrapped around the extremity distal to the cuff. The cuff is inflated to 200 mm Hg, the compression bandage removed, and the cuff slowly deflated. The pressure is read when the first flushing distal to the cuff appears, and this pressure will approximate the mean blood pressure. For accurate results the procedure requires two observers.[87]

Visual or electric oscillometers[2] are still widely used for indirect blood pressure measurements, mainly in newborns and young infants.[47,59,91] Systolic pressure can be obtained as precisely as by the auscultatory method. However, the diastolic pressure is difficult to assess accurately.

The Doppler ultrasonic method[3] introduced into pediatrics in 1970[110] has proved to be most reliable even in low-birth-weight babies. Various investigators have determined simultaneously direct intra-arterial blood pressure and pressures recorded by the Doppler ultrasonic technique. A good correlation between the two methods for systolic and diastolic pressure could be demonstrated. The method is quite simple and can be used by well-trained nurses for routine blood pressure determination in all pediatric age groups.[97a] The main drawback to its widespread use is cost. Nevertheless, this type of equipment should be used in all pediatric intensive care and newborn wards as well as in pediatric operating theaters.

## Definition of Normal Blood Pressure in Children

Tables giving normal ranges of blood pressure through infancy and childhood differ significantly in the mean systolic and diastolic values, depending mainly on conditions of testing ("basal," office, hospital, home, school) and whether phase IV or V of Korotkoff was used for the diastolic pressures. Figure 1 clearly demonstrates the wide range of normal values. The difference between the highest and lowest systolic and diastolic mean measurements approximated 10 to 15 mm Hg in all age groups. It may

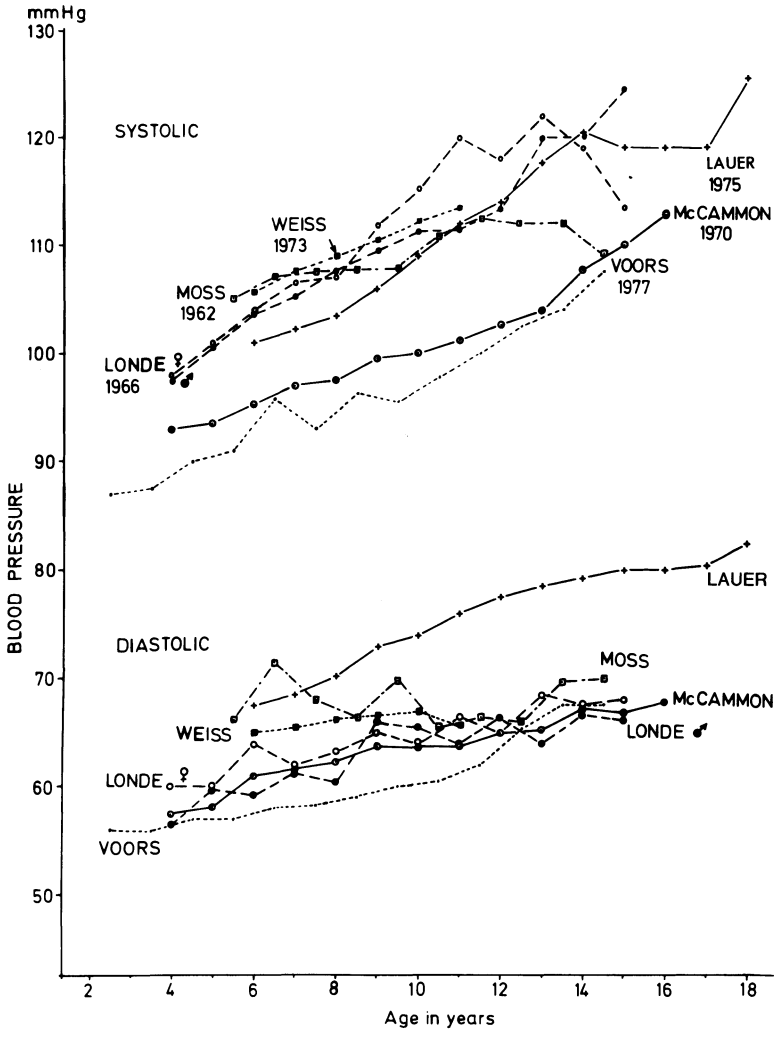


**Figure 1.** Comparison of indirect blood pressure measurements of children and adolescents from six selected studies in the literature.[60,70,82,88,119,122] Londe et al. used phase 5 of Korotkoff for determining diastolic blood pressure. The other studies used either phase 4 or a combination of phases 4 and 5.

be assumed that the lower systolic values reflect basal conditions,[88,120] whereas the high measurements in the other studies cited are probably influenced by some extrinsic factors. Thus the data from Londe[70] are established as "normal" standards for office practice in a supine position. The children examined by Lauer et al.[60] all had their blood pressure taken in a seated position, which may account for the higher measurements.

Up to the age of about 10 years most of the studies show no significantly different systolic and diastolic pressure values in boys and girls. During adolescence, however, there seem to be significant sex differences either in systolic or diastolic pressures.[48,74,97,130] On the other hand, there is no evidence that puberty leads to hypertensive pressure levels.[75] However, Londe et al.[74] recently demonstrated that significant systolic or diastolic pressure differences between black and white children ($n$ = 2481) from 3 to 14 years of age do not exist. In contrast to this, the Bogalusa study[118] ($n$ = 3720, ages 5 to 15 years) showed the blood pressure to be significantly higher in black children from the age of 9 years on.

Few studies have been published on the blood pressure in normal infants and young children up to the age of 4 years. The data available (Table 2) need further confirmation.

## Definition of Hypertension in Children

There is still some uncertainty as to what constitutes an adequate definition of hypertension because large numbers of children followed for many years with blood pressure measurements recorded by a single observer under standardized conditions

**Table 2.** Blood Pressure (mm Hg) in Infants in Three Studies

| | Mean Arterial Blood Pressure* | | Arterial Blood Pressure | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Systolic | | Diastolic | | Systolic | | Diastolic | |
| Age | $\bar{X}$ | Sx | $\bar{X}$ | Sx | $\bar{X}$ | Sx | $\bar{X}$ | Sx | $\bar{X}$ | Sx |
| Newborn period | 41 | ±8 | 70–80 | ±5 | 40–50 | ±6 | | | | |
| 1–3 mo | 67 | ±11 | 74 | ±4 | 51 | ±4 | | | | |
| 4–6 mo | 73 | ±9.5 | 85 | ±2 | 64 | ±7 | 92.6 | ±7.4 | 52.7 | ±5.8 |
| 7–9 mo | 76 | ±9 | 86 | ±2 | 63 | ±1 | 96.7 | ±6.4 | 55.0 | ±5.3 |
| 10–12 mo | 76 | ±14 | 89 | | 68 | | 97.5 | ±5.4 | 54.9 | ±5.1 |

*Flush method.
Left data from Moss AJ, Adams FH, ref 88: center data from Kirschsieper KM, Rutenfranz J, ref 52; right data from Fredebohm, ref 27a.

are unavailable. The recommendation of the World Health Organization for adults (values of 140–160/90–95 mm Hg = borderline hypertension; any values over 160/95 mm Hg = definite hypertension) cannot be valid for the pediatric age group because of the normal changes of blood pressure with age. Also, the arbitrary values of 130/85 to 140/85–90 mm Hg recommended by some as upper limits for normal blood pressure in children of all ages[36,60,66] cannot be accepted, because pressures above these

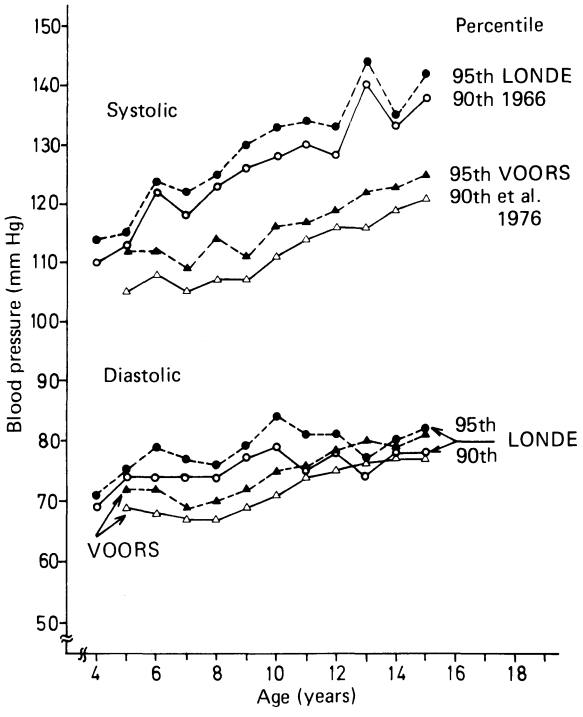


**Figure 2.** Spread between lowest and highest 90th and 95th percentile values for systolic and diastolic blood pressures in two reliable studies (boys and girls together).

readings would represent severe degrees of hypertension for children under the age of 10 years. In addition, hypertensive patients of this age group would be eliminated from consideration although their blood pressure may be lower than these values.

Londe et al.[70,74] adopted the suggestions of Master et al.[81] in their study of adults and classified children as hypertensive if their blood pressure was occasionally above the 95th percentile or consistently above the 90th percentile for age. Even those limits, however, are subject to considerable variability, as illustrated by the range between the lowest and highest 95th percentiles for systolic and diastolic pressure in some of the studies (Fig. 2) It should be kept in mind that a single high blood pressure recording in a child does not confirm hypertension. It is important to rule out first all sources of error, in particular from equipment and environment. Repeated measurements are mandatory before the presence of hypertension can be established. One has to be careful not to label a child as chronically ill unless there is sufficient proof. If, on the other hand, a child has mildly elevated blood pressure with a family history of hypertension and is obese, there is a strong likelihood that this is the beginning of essential hypertension.

In summary, the approach of Londe et al. to the problems of defining hypertension in childhood seems logical. Their data (Table 3) should serve as a guideline for evaluating blood pressure levels in children and adolescents. The pressure levels for defining or suspecting hypertension in the pediatric age group given by Liebermann et al.[64] and Mitchell et al.[85] are probably too high. If, however, Londe's rule is applied to the data of Voors et al.[118] the number of children being classified as probably hypertensive would increase considerably, because these blood pressure data are far lower than in all other studies.

**Table 3.** Blood Pressure Levels Suspicious of Hypertension in Children and Adolescents According to Data of Anglo-American Authors*

| | | Age (Years) | | | | | |
|---|---|---|---|---|---|---|---|
| Author, Year | Criteria | 3–6 | 7–9 | 10–13 | 14 | 15 | 16–18 |
| Londe et al., 1977 | Supine | 110/70 | 120/75 | 130/80 | m133/82 | 137/85 | 140/87 |
| | 90th percentile | | | | f128/83 | 128/83 | 128/38 |
| Lauer et al., 1975 | Seated | 118/82 | 122/83 | 139/91 | 143/93 | 142/93 | 144/93 |
| | 95th percentile | | | | | | |
| Mitchell et al., 1975 | Supine | 115/84 | 130/92 | m140/80 | | 138/95 | |
| | 95th percentile | | | | | | |
| Liebermann, 1974 | Supine | 120/70 | 130/75 | f140/80 | 140/85 | | |
| | ? | | | | | | |
| Voors et al., 1976 | Seated | | | | | | |
| | 90th percentile | 105/69 | 107/67 | 116/74 | 119/77 | 121/77 | |
| | 95th percentile | 112/72 | 114/70 | 119/78 | 123/79 | 125/81 | |

*Systolic and diastolic blood pressures in mm Hg.

## Incidence and Epidemiology of Primary and Secondary Hypertension in Children

The actual incidence of hypertension in children is not yet known. The data in Table 4 from six different screening studies indicate that approximately 1% to 12% of children and adolescents have high blood pressure. Interpretation of the data, however, is difficult for various reasons, including the following: different definition of hypertension,[1] different position and environment of the subjects when blood pressure was recorded,[2] different instrumentation used,[3] and different definition for the diastolic pressure (fourth or fifth Korotkoff sound). Moreover, in the majority of the studies the prevalence of hypertension in the population screened by age, sex, and race is not indicated.

A precise distribution of the age at which hypertension was first documented in 131 children was given by Londe and Goldring[73] (Fig. 3). Thirty percent had normal pressure before they became hypertensive, and 76 (58%) of the hypertensive children were below 10 years of age. Lauer et al.,[60] applying different criteria for hypertension in the younger age group, found virtual absence of hypertensive levels in children aged 6 to 9 years. In the highly selected group of 100 hypertensive children from Gill et al. (only 1% essential hypertension) 28% of the patients presented before age 5.[29] From all these data, no clear conclusions regarding percentage of hypertensive children in a population and onset of hypertension may be drawn.

Many factors have been implicated as playing a role in the epidemiology of essential hypertension. It is unequivocal that both genetic and environmental factors are important in determining blood pressure. For some time it has been accepted that *familial aggregation* of blood pressure occurs.[64,95,130] It could, however, only recently be shown[10,40] that the correlation of blood pressure scores between parents and natural children was highly significant, whereas the correlation between parents and adopted children was not significant. The conclusion, therefore, is that heredity explains most of the familial resemblance of blood pressure in children.

Moreover, several longitudinal studies have definitely proved the so-called tracking phenomenon: a low blood pressure remains low through many years of observation; on the contrary, high pressure readings stay in the upper percentile range as a rule.[15,64,74,130] These findings point also to a strong in-

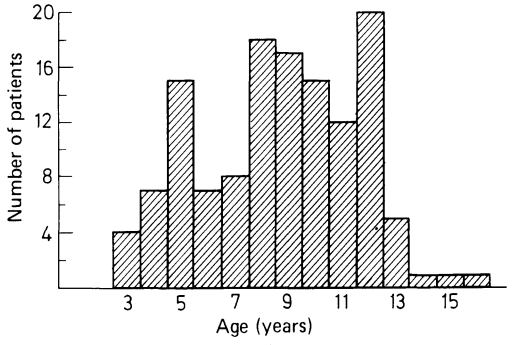


**Figure 3.** Age at which hypertension was first documented in 131 children under practice office conditions. Reprinted from Londe S, and Goldring D, ref 73, with permission

**Table 4.** Incidence of Hypertension in Childhood

| Author, Year | Age Range (Yr) | Total No. Screened | Position in Which Pressure Was Taken | Definition of Hypertension (mm Hg) | Incidence of Hypertension (%) |
|---|---|---|---|---|---|
| Londe, 1966 | 4–15 | 894 male<br>911 female | Supine | *Labile:* Systolic and/or diastolic pressure 90th percentile at one reading.<br>*Persistent:* Systolic and/or diastolic pressure repeatedly >95th percentile | Male 12.4<br>Female 11.6<br>1.9 |
| Kilcoyne et al., 1974 | 14–19 | First screen: 3537<br>Rescreen of hypertensives: 215 of 277 from 1st screen | Sitting | SBP ≥140<br>DBP ≥ 90 | 1st SBP 5.4<br>DBP 7.8<br>2nd SBP 1.2<br>DBP 2.4 |
| Lauer et al., 1975 | 6–13<br>14–18 | 3.528<br>1.301 | Sitting<br>Sitting | SBP ≥140<br>DBP ≥ 90 | SBP 4.9<br>DBP 8.2<br>SBP 8.9<br>DBP 12.2<br>Both 4.4 |
| Reichman et al., 1975 | 12–20 | 1.863 | Sitting | SBP ≥ 140<br>DBP ≥ 90 | SBP 5.9<br>DBP 2.5 |
| Kimura et al., 1965 | 0–19 | 2.728 | ? | SBP ≥ 160<br>and/or<br>DBP ≥ 95<br>(If BP less than 140/90 considered normotensive) | 0.6<br>(Borderline) 9.2 |
| Masland et al., 1956 | 12–21 | 1.795 | ? | BP > 140/90 | 1.4 |

dividual genetic influence although environmental factors cannot be excluded totally.

The relationship between *obesity and hypertension* has long been recognized for adults and was recently confirmed for the pediatric age group also.[49,60,68,74] All investigators found the prevalence of obesity to be significantly higher in the hypertensive children than in control groups.

The markedly higher incidence of hypertension in adult blacks than in adult whites has been well known for the last decade, but only recently has evidence accumulated showing that through childhood there is no significant racial difference[60,74] except in the Bogalusa study.[118] The data on prevalence of hypertension in black adolescents, however, are controversial. Londe et al.[74] again could not demonstrate a significant difference in the incidence of hypertension in black (6.7%) and white students (8%) aged 14 to 18 years. Kilcoyne,[48] on the other hand, found a sharp rise in the prevalence rate of systolic and diastolic hypertension in black males at 17 years.

The concept of many clinicians that a high blood pressure is a normal physiologic phenomenon during *puberty* could not be substantiated by the investigations of Londe et al.[75] who were unable to prove any significant correlation between blood pressure levels and any physical or biochemical criteria of sexual maturation. Thus high blood pressure during puberty should be followed with suspicion.

Another causative factor in essential hypertension probably is dietary *salt intake*.[83,84,121] It is more than likely one of the main contributing factors in those children who may be genetically predisposed to hypertension. Thus the Committee on Nutrition of the American Academy of Pediatrics[20] recommends re-

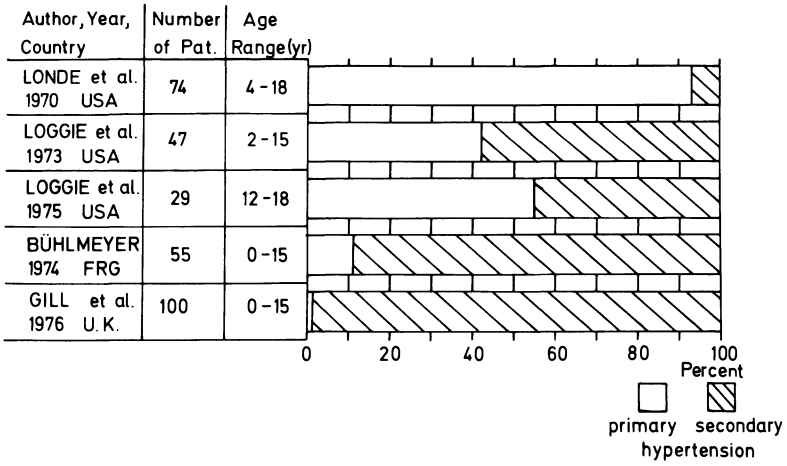


**Figure 4.** Relative incidence of primary and secondary hypertension in children and adolescents in five different studies.

ducing or avoiding increase in the present level of salt intake by children in the population at large. It is further stated that children with a family history of hypertension may benefit from a low-salt diet and that there is a reasonable possibility that a low-salt intake early in life may protect, to some extent, persons at risk from developing hypertension.

Our knowledge about the real incidence of secondary hypertension through childhood is poor. A few studies have been performed regarding the relative incidence. The data from Figure 4 clearly demonstrate the wide range (7% to 99%) of the relative incidence of secondary hypertension found in five different series. This obviously reflects the fact that the patient groups from Londe and Loggie are derived from screening a large number of normal individuals, whereas the hypertensive patients of Bühlmeyer[16] and Gill et al. [29] were highly selected and referred to a specialized center for further evaluation. Thus no valid conclusion can be drawn. However, there is some evidence that throughout childhood there is an approximate incidence of 50% for secondary hypertension.

## Causes of Secondary Hypertension in Childhood

Over and above the known causes of hypertension in adults, there are certain age-specific illnesses which, in infants and children, can lead to arterial hypertension (Table 5). In Table 6, the more important of the many possible causes (almost 100) have been summarized and arranged according to frequent and less common occurrence. A certain differential diagnostic clarification appears in Table 7, in which the more common causes of the disease are presented according to the different age groups.

As the other chapters of the book generally cover all the pathophysiologic, diagnostic, therapeutic, and prognostic aspects of secondary high blood pressure, the following section is limited to hypertension caused by cardiovascular and renal factors with special reference to childhood.

**Table 5.** Causes of Arterial Hypertension Specific to Childhood

| Organ System | Cause |
|---|---|
| Renal parenchyma | Infantile polycystic kidneys |
| | Congenital segmental hypoplasia—Ask-Upmark |
| | Wilms' tumor |
| | Obstructive uropathy |
| | Nephrocalcinosis due to idiopathic hypercalcemia |
| Heart and circulation | Syndrome of multiple peripheral arterial stenoses (Williams-Beuren) |
| | Multiple arterial stenoses from embryo—fetal rubella syndrome |
| | Congenital large A-V fistula (e.g., middle cerebral artery to Galen's vein) (only systolic) |
| Endocrine glands | Neuroblastoma |
| Nervous system | Intracranial bleeding due to birth trauma |

**Table 6.** Causes of Secondary Hypertension in Childhood

| Organ System | Common | Rare |
|---|---|---|
| Heart and circulation | Coarctation of the aorta<br>Persistent ductus arteriosus (only systolic) | Coarctation of the abdominal aorta<br>Syndrome of multiple peripheral arterial stenoses<br>Complete A-V block<br>Aortic incompetence<br>Large A-V fistula<br>Hyperkinetic circulatory state |
| Renal parenchyma | Chronic pyelonephritis<br>Chronic glomerulonephritis<br>Following kidney transplantation | Cystic kidneys<br>Congenital segmental hypoplasia—Ask-Upmark<br>Hydronephrosis<br>Tumor (especially Wilms' tumor)<br>Obstructive uropathy<br>Radiation nephritis<br>Schönlein-Henoch nephritis<br>Lupus erythematosus<br>Hemolytic-uremic syndrome<br>Renal trauma including puncture |
| Renal vessels | Stenosis of renal arteries | Renal vein thrombosis<br>Aneurysm of the renal arteries<br>Multiple neurofibromas |
| Endocrine glands | Steroid therapy | Cushing's syndrome<br>Adrenogenital syndrome<br>Primary hyperaldosteronism |
| | Neuroblastoma | Pheochromocytoma<br>Hyperthyroidism<br>Hyperparathyroidism |
| Central nervous system | | Increased intracranial pressure (edema, space-occupying process)<br>Encephalitis<br>Heavy metal poisoning (mercury, lead)<br>Guillain-Barré syndrome<br>Familial dysautonomia (Riley-Day) |
| Metabolic disorders | | Porphyria<br>Hypercalcemia |
| Others | | Congenital rubella syndrome<br>Pseudoxanthoma elasticum<br>Stevens-Johnson syndrome<br>Burns<br>After sympathomimetic drugs (nose and eye drops)<br>Reserpine and methyldopa overdose<br>Progeria |

## Hypertension Caused by the Cardiovascular System

### Coarctation of the Aorta

Coarctation of the aorta (CAA) is considered, to some extent, the classic cause of high blood pressure in infants. It was known that stenosis of the aorta led to high blood pressure in the upper half of the body long before the pathophysiologic relationship between renal and endocrine causes and hypertension was recognized. On the other hand, coarctation of the aorta was the first illness inducing hypertension which could be treated causally, i.e., by surgery.[22]

Many questions still remain unanswered today

**Table 7.** Frequent Causes of Sustained Secondary Hypertension In Various Age Groups

| | |
|---|---|
| Newborn | Coarctation of the aorta<br>Stenosis of renal arteries<br>Polycystic kidneys |
| Infants and small children | Coarctation of the aorta<br>Renovascular processes<br>Obstructive uropathy<br>Wilms' tumor<br>Polycystic kidneys<br>Neuroblastoma |
| Preschool children | Renovascular processes<br>Polycystic kidneys<br>Pyelonephritis<br>Hydronephrosis |
| School children and youths | Renovascular processes<br>Renal parenchymal disease |

despite decades of intensive pathological, clinical, and experimental work by numerous teams. Theories about the etiology of CAA are, as yet, in dispute, and the explanations of the pathogenesis of the associated hypertension are controversial. Finally, there are differences of opinion as to indication, timing, and type of surgical intervention.

### Pathological anatomy of coarctation of the aorta

A narrowing in the distal segment of the aortic arch is observed in 5% to 8% of all congenital heart or vessel malformations as either an isolated or associated defect. The most common form is the typical juxta- or preductal, or else ligamentary located, coarctation, which can occasionally develop into an atresia. This is not the same as an interruption of the aortic arch, which can be localized between the brachiocephalic artery and the left carotid artery, or between the former and the left subclavian artery. Anatomically two forms of CAA can be distinguished: (1) a mostly elongated diffuse stenosis of the aortic tube proximal to either the ductus junction or the insertion of the ligamentum arteriosum, also described as a tubular hypoplasia or a diffuse narrowing of the aortic isthmus, and (2) a short hourglass-shaped stenosis on the level of the ductus or ligament. The left subclavian artery can be involved in the stenosis in either form. The earlier subdivision into an infantile (1) and adult form (2) has been abandoned since it has been shown that, in the case of tubular hypoplasia, there are almost always serious associated defects, which naturally present pronounced symptoms, even in young infants, thus leading to the discovery of the malformation very early in life. On the other hand, a short stenosis without additional defects can also cause severe congestive heart failure as early as in the newborn.

Table 8 provides information about the type and frequency of associated malformations; to some extent these are subclassified according to the age at which the symptoms appear. Among the infants, 70% to 85% present with a combination of one or more defects, the most common of these being persistent ductus arteriosus, large ventricular septal defect, and malformation of the aortic valve. The numerical proportions become even less favorable in postmortem statistics,[7] according to which more than 90% of the infants suffered from serious additional defects, so that the coarctation can often be regarded only as a complicating associated malformation. If only the patients diagnosed beyond the age of infancy are taken into consideration, the fre-

**Table 8.** Malformations Associated with Coarctation of the Aorta

| | Hartmann et al., 1967 | | Sinha et al., 1969 | Simon and Zloto, 1974 | Wimmer, 1975 | Liberthson et al., 1979 | |
|---|---|---|---|---|---|---|---|
| Age of patients in years | <1 | 1–15 | <1/2 | 2–60 | 0–15 | 1 | 1–72 |
| Total no. of patients | 60 | 76 | 71 | 190 | 112 | 43 | 191 |
| Simple CAA | 9 | 24 | 16 | 69 | 43 | 14 | 140 |
| CAA + PDA | 30 | 3 | 46 | 35 | 38 | 26 | 14 |
| + VSD | 26 | 9 | 38 | 11 | 20 | 13 | 5 |
| + ASD | 26 | 1 | 6 | 2 | | | |
| + AS | ? | 4 | 5 | 15 | 11 | 1 | 27 |
| + AI | ? | 2 | | 38 | | | 9 |
| + aortic valve deformity | ? | 35 | | 22 | | | |
| + mitral lesion | | | 2 | 19 | | 1 | 4 |
| + EFE | 7 | | | | | | |
| + others | | | 8 | 11 | 20 | | |

PDA = persistent ductus arteriosus; VSD = ventricular septal defect; ASD = atrial septal defect; AS = aortic stenosis; AI = aortic insufficiency; EFE = endocardial fibroelastosis.

quency of associated defects is reduced to 60% to 70%, and these consist mainly of aortic and mitral lesions and smaller persistent ductus arteriosus.

While only a few small collateral arteries exist in the newborn, with time an extensive bypass circulation develops, especially from the lateral neck and scapular region to the upper intercostal arteries and over the internal mammary arteries to the lower intercostal and epigastric arteries. The widened, thin-walled intercostal arteries may show aneurysmatic changes in the upper parts of the thorax. These lead to erosions on the dorsal costal segments, which can be ascertained as rib notchings on X-rays from about 10 years of age on.

### Etiology of the coarctation

Although research on the causal origin or coarctation of the aorta has been undertaken since the middle of the last century, a uniform concept has not been developed. Craigie,[23] Skoda, and, more recently, Brom,[14] too, advocate the theory, which is supported by histologic findings, that muscular or fibrous tissue typical of the structure of the ductus arteriosus in the process of closure in the newborn, or else of the ligamentum arteriosum, encroaches upon the aorta wall in a ring- or pincerlike fashion and here, by contraction or stricture, causes a stenosis.

On the basis of pathological examinations Hutchins[45] formulates the hypothesis that the stenosis develops early on in the fetus. He could regularly prove a foldlike spur in the dorsal aortic wall opposite the entrance of the ductus, the structure of which was like that of a normal branching of the aorta. These findings led him to the assumption that the ductus, unlike the ascending aorta, is preferentially provided with blood during the fetal period and that the bloodstream undergoes a division at the ductus entrance, cranially (left subclavian artery and carotid artery) and caudally. This theory is supported by the known fact that more than 80% of those having a coarctation of the aorta have associated defects which provoke a relatively larger blood flow through the ductus before birth. On the other hand, CAA never appears in combination with other heart defects such as Fallot's tetralogy or pulmonary atresia.

Rudolph et al.,[102] on the strength of clinical observations and angiocardiographic findings in young infants as well as the results of animal experiments, put forward hypotheses which could explain the anatomic differences between the long diffuse hypoplasia of the distal aortic arch and the short, jux taducial, hourglass-shaped stenosis. Serious associated defects (especially large ventricular septal defects) could be proved in all patients with tubular hypoplasia of the aortic arch (see Fig. 7); these defects could lead to a relatively increased blood flow through the ductus and a comparatively smaller flow to the ascending aorta, so that the isthmus segment has only to cope with a smaller volume of blood than under normal conditions of blood flow. Conversely the short, localized coarctation is only rarely combined with associated defects which affect the hemodynamics.

The etiology of simple CAA is explained as follows: The existence of even a small fold on the dorsal wall of the aorta opposite the entrance of the ductus, which could be easily derived from the prenatal flow pattern in this area and which at birth has no significant hemodynamic effects yet, leads to a stenosis when the physiologic closure of the ductus occurs (see Fig. 6). The blood passes this section freely until the duct is constricted, as the entrance of the ductus here guarantees a somewhat wider diameter of the aorta. This theory may explain the relatively frequent clinical observation that the initially normal condition of the blood pressure in the newborn develops into one symptomatic of a serious CAA within days or weeks.[102,114] The manifestation of a CAA after ligation of the ductus is supposedly based on the same mechanism.[26] None of the aforementioned theories is able to explain all anatomic conditions satisfactorily. Nevertheless, it can be taken as certain that in by far the largest percentage of patients prenatal anomalies of blood flow dynamics play the main role in the etiology of CAA.

### Pathophysiology of coarctation of the aorta

In most cases the associated cardiovascular defects have a significant effect on the hemodynamic situation of a CAA; indeed, hemodynamics are frequently changed to such an extent that, from a pathophysiologic point of view, the aortic narrowing is of minor importance. Thus heart failure with virtually no hypertension is often the major clinical finding.

If, at the beginning, there is only a minor isolated stenosis or if the segment of the ductus arteriosus at the aorta is still patent, then the obstruction develops only slowly, over weeks or months. In these cases there is time for the necessary adaptation of the heart and circulation, with the result that these patients can reach school age or adolescence with few symptoms. Hence, the hemodynamic and clinical situation is significantly affected by the degree of severity of the coarctation and the rate of its development. At first the left ventricle tries to adjust to the increased afterload by corresponding hypertrophy. Especially in the infant and toddler, the left ventricular myocardial structure will develop more rapidly than it should according to its chronological age. The blood supply to the lower half of the body is ensured by the opening of sufficient collateral ar-

teries. In this way an abrupt rise in blood pressure and the consequent induction of heart failure are also counteracted. Anyhow, this development is exceptional and affects only about 10% to 15% of all those with a CAA.

On the other hand, if, after birth, the obstruction increases quickly and no adequate collateral arteries exist, then cardiac failure occurs. This, however, is often manifested only through a febrile respiratory tract infection in the young child. Certainly, the rapid growth of the young child and the thereby necessarily fast-increasing cardiac output also play a role in this context; because of this, a fixed stenosis becomes hemodynamically relatively more effective. If cardiac failure occurs, and therewith a reduction in cardiac output, the blood pressure in both the ascending and descending aorta will drop likewise. In this situation "normal" blood pressure will result so that, in the case of inadequate physical examination, the connection will not be correctly judged and the CAA will remain undiagnosed.

If sufficient collateral arteries have developed quickly enough, which is rather the exception in young infants, lower pressures result in the prestenotic arterial bed and the pressure difference between the ascending and descending aorta is diminished. Therefore, nothing about the actual severity of the CAA can be concluded from the finding of a slight blood pressure difference between the arms and legs. The hemodynamics in the case of a localized, short CAA with sufficient collateral circulation are schematically presented in Figure 5.[101]

If, postnatally, the severity of the CAA increases rapidly, very unfavorable changes with regard to blood flow, blood pressure, and resistance occur, which may be detrimental to the heart and circulation. Where, prenatally, there was no reason for the development of a bypass circulation, a sharp rise in the resistance to the blood flow suddenly occurs in the circulatory system and thereby creates an increase in the afterload for the nonadapted left ventricle. To begin, the systolic and diastolic pressures in the ascending aorta rise and the end-diastolic pressure in the left ventricle (LV) increases. However, as the reserves of this ventricle in the young infant are limited, the left atrial and the end-diastolic pressure in the LV mount further, whereas the stroke volume decreases. Finally, increasing left ventricular failure leads to pulmonary edema. The foramen ovale is opened as a result of hyperextension of the left atrium, especially of the septum, so that in addition a varyingly large left-to-right shunt develops on the atrium level. As a result of the extra volume load and, in some cases, also additional left-to-right shunt from the aortic arch over the still partly patent ductus into the pulmonary artery, the

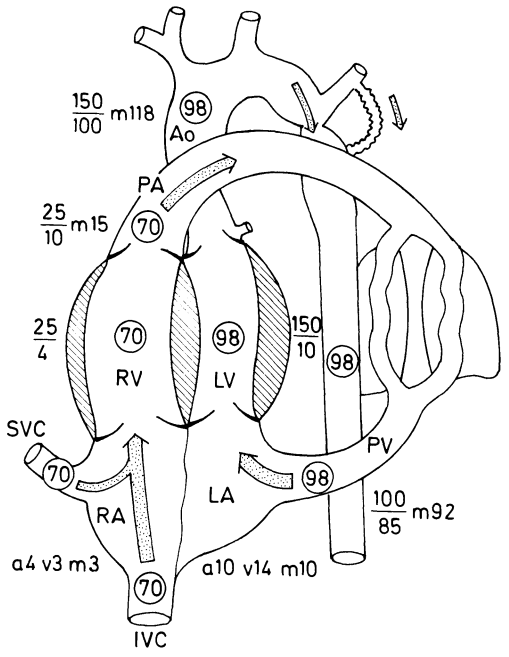


**Figure 5.** Schematic presentation of the hemodynamics—intracardial and intravascular pressures in mm Hg and oxygen saturation in % (*circled*)—in a child with a short, localized coarctation and sufficiently developed collateral circulation.

pressure in the latter can rise to a systolic value of 50 to 80 mm Hg. In this situation failure of the right ventricle is added to failure of the left because both ventricles are exposed to considerably increased pressure and output loads. Ostensibly, normal blood pressures are measured in the arms under these circumstances, too, and so the diagnosis is obscured.

Graham et al.[34] could show in an impressive manner that the younger the patient when cardiac failure became evident, the greater the damage to the function of the myocardium; they demonstrated this feature by analysis of the systolic and diastolic volumes and the ejection fraction of the right and left ventricle. Figure 6 shows the hemodynamics in an infant with localized, juxtaductal coarctation of the aorta and still partly open but mostly closed ductus as well as a left-to-right shunt over a patent foramen ovale.[101]

By far the most unfavorable hemodynamic situation is that of the frequent combination of a CAA with a large ventricular septal defect: the systemic resistance is particularly high owing to the obstruction; on the other hand, the pulmonary resistance, as a rule, decreases after birth, and usually a constriction of the ductus arteriosus occurs (Fig. 7). This results in an enlarging left-to-right shunt through the ventricular septal defect and a critical

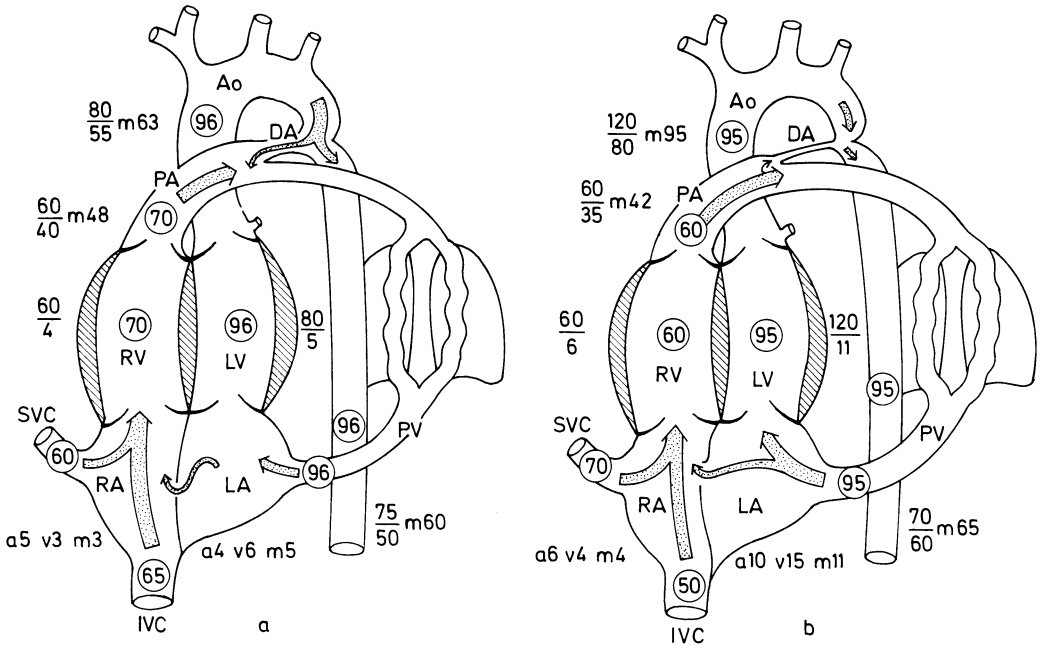


**Figure 6.** Schematic presentation of the hemodynamics—intracardial and intravascular pressures in mm Hg and oxygen saturation in % (*circled*)—in a newborn (**a**) and an older infant (**b**) with localized juxtaductal coarctation. In the newborn, because of the still patent ductus, there is only slight obstruction at the level of the stenosis, left-to-right shunt through the ductus, and a patent foramen ovale. Later (**b**) the stenosis has considerably increased as a result of the obliteration of the ductus and disappearance of the left-to-right shunt at the ductus level.

impairment of the perfusion of the lower part of the body, which again may lead to renal failure. The pulmonary venous backflow and therewith the end-diastolic pressure in the left atrium and ventricle increase, which soon leads to a global heart failure with dyspnea and tachypnea as well as hepatomegaly. As a result of the large left-to-right shunt, the oxygen saturations in the aorta and the pulmonary artery are initially at about the same level, yet the reduced perfusion of the lower half of the body leads to local hypoxia and thus to the development of a metabolic acidosis. The spontaneous survival of a carrier of such a combination of defects is only possible if either the coarctation is not very pronounced or the pulmonary resistance postnatally remains high and the ductus arteriosus stays sufficiently patent that an adequate perfusion to the lower half of the body can be maintained by these means. Indeed, this constellation, hemodynamically fortunate at the beginning, is to be found in only a few exceptional cases, which then, nevertheless, develop a progressive pulmonary sclerosis in the course of time and thus can no longer be operated upon.

### Pathogenesis of the hypertension

Essentially two theories exist which explain the prestenotic hypertension of CAA; they concern either mechanical or humoral-renal factors.

Gupta and Wiggers[35] were the first to refer to the significance of the diminished compliance and capacity of the short aortic segment, which in CAA is available as the arterial compression chamber. More recent animal experiments and clinical-hemodynamic examinations of patients with a CAA show unequivocally that, in addition to an increase in the total peripheral resistance as a result of the stenosis, a change in the pulse wave reflexion also takes place which, in turn, leads to a change in the aortic pressure curve. These anomalies can be estimated as evidence of the inadequate function of the arterial compression chamber, whereby the cushioning effect on the pulsatile flow is largely lost. At the same time, one must obviously bear in mind that the severity of the stenosis and the extent of the collateral circulation also essentially determine the level of the blood pressure.

Since the discovery of the renin-angiotensin system, numerous studies with patients and in animal experiments have been undertaken in order to clarify its role in the pathogenesis of hypertension. The results remain contradictory until now. In children as well as in adults the measured plasma-renin activities were within the standard range under both basal conditions and orthostasis.[3,78,112,124]

These findings are in agreement with the results of very thorough examinations of the renal hemo-

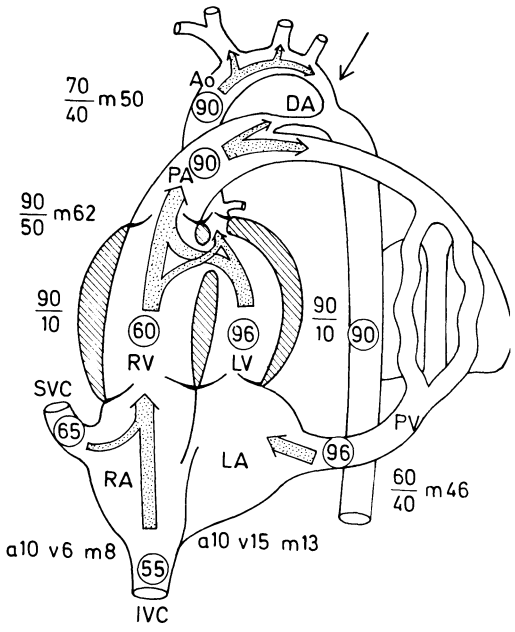


**Figure 7.** Schematic presentation of the hemodynamics—intracardial and intravascular blood pressure values in mm Hg and oxygen saturation in % (*circled*)—in an infant with preductal coarctation of the aorta and tubular hypoplasia of the distal aortic arch with a large ventricular septal defect as well as left ventricular outflow tract obstruction. Cross-shunt over the ventricular septal defect with predominant left-to-right shunt, shunt through the narrowed but still open ductus arteriosus from the pulmonary artery into the descending aorta. "Normal" blood pressure in the ascending aorta clearly increased pressures in both atria.

dynamics in CAA.[54] The renal blood flow, the glomerular filtration, and the mean arterial blood pressure were not significantly different from the corresponding normal values.

On the other hand, as long ago as 1951 Scott and Bahnson were able to show by animal experiments that renal factors must play a role in the genesis of hypertension in CAA.[105] Surgically induced coarctation of the aorta in dogs always led to hypertension in the upper half of the body in the course of 5 to 7 weeks. However, the high pressure dissipated when unilateral nephrectomy was performed and the other kidney was transplanted to the neck region and consequently received blood from the prestenotic aortic segment.

More recent studies[2] of CAA patients have shown that, under normal conditions and with lower salt intake, the plasma renin activity in these individuals was within normal limits similar to healthy controls and patients with essential idiopathic hypertension. Following administration of furosemide, however, the plasma renin activity in CAA patients increased significantly, whereas it remained within the normal range in the other two groups. Aldosterone, plasma volume, and extracellular fluid were already, beforehand, significantly higher in CAA. One can deduce from these findings that hypertension associated with CAA corresponds to the model of the unilateral Goldblatt kidney. The authors sum up the results in the hypothesis that CAA first reduces the renal blood flow whereby the juxtaglomerular apparatus is stimulated to secrete renin which, in turn, initiates the production of aldosterone and angiotensin. These hormones bring about water and salt retention from which an expansion of the blood volume and of the extracellular space follows, with a subsequent rise in blood pressure. As, thereby, the renal blood flow increases again, a restriction, i.e., normalization of the renin secretion, occurs as the result of a feedback.

In light of the above-mentioned results, there is strong indication for believing that hydromechanical as well as humoral-renal factors are responsible for the hypertension associated with CAA.

### Clinical features and diagnosis of coarctation of the aorta

A clearly distinguishable pattern, in terms of history, clinical findings, and course, is evident in the group of infants on the one hand and older children and adults on the other.

Patients beyond infancy till adolescence generally present an unremarkable or at least uncharacteristic previous history. Complaints of occasional headaches, epistaxis, impairment of physical strength, cool legs, or nocturnal leg pains are reported in only about a quarter of the cases.

If the children are asymptomatic and thus have probably no significant associated malformations, one usually finds a good, sometimes almost athletic physical development. Physical examination then reveals certainly a few findings which are typical of CAA: strong brachial pulses, missing or clearly weakened femoral pulses and, accordingly, a blood pressure increase of varying degree in the upper half of the body (Fig. 8) in association with low or unmeasurable pressures in the legs.

If one of the subclavian arteries originates below or directly from the stenotic area (about 10% of patients), the corresponding arm pulse (left in the case of normal origin, right in the case of an aberrant subclavian artery: arteria lusoria) is only weakly palpable and the blood pressure here is accordingly lower. Normal blood pressure in the arms at rest, at least in childhood, does occur occasionally if either the stenosis is not very pronounced or a good collateral circulation has developed (Fig. 8). Physical exertion then, of course, leads to an inadequate pressure rise in the upper part of the body with constant

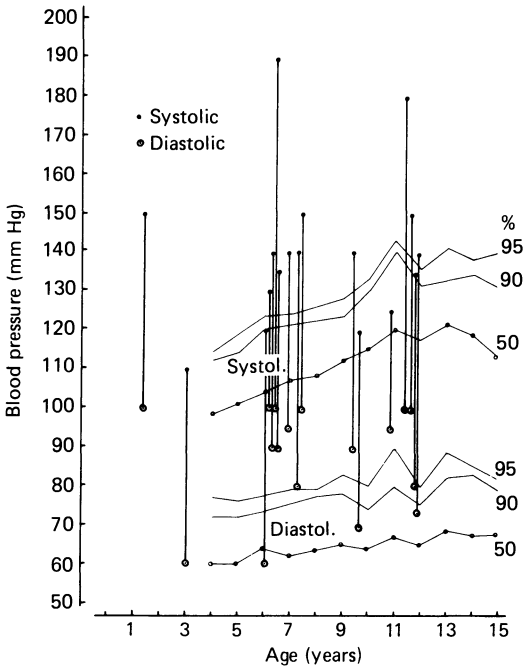


**Figure 8.** Blood pressure, according to Riva-Rocci, in the right arm in 20 children with a coarctation of the aorta without hemodynamically significant associated defects. The systolic and diastolic values in four patients lie below the 95th percentile, according to Londe. From Londe S, ref 70

or only slightly increasing pressure distal from the stenosis. Figure 9 shows the extent to which the level of the blood pressure can vary in individual patients in the course of a day; therefore, one can draw only inadequate conclusions as to the severity of the hypertension from a single measurement. The intraindividual variation is primarily dependent on the different states of vigility, i.e., finally, on cardiac

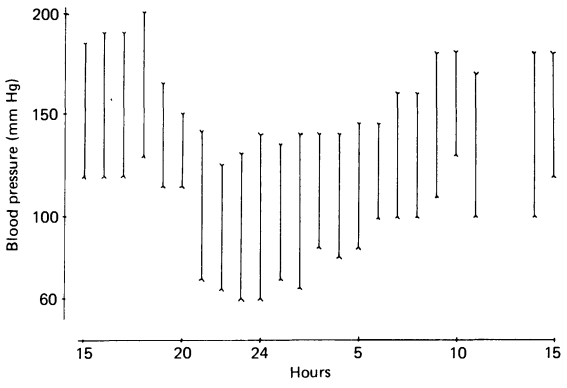


**Figure 9.** Blood pressure during the course of a day in an 18-month-old child with coarctation of the aorta.

output and peripheral resistance. Nevertheless this 24-h profile shows that even the lowest systolic pressure in deep sleep does not fall below the 90th percentile. If, in addition, one hears a precordial systolic murmur at the base of the heart or in the interscapular region in the back, then the diagnosis of coarctation of the aorta is almost certain.

In teenagers and young adults with a stenosis of severe degree and a well-developed collateral circulation, one can occasionally hear a continuous fistulalike murmur over the shoulder and upper back and feel a thrill. Heart failure is only seldom observed before the age of 40.[63]

*Electrocardiography* shows normal findings or mild to moderate left ventricular hypertrophy. Left ventricular strain pattern is seldom seen in isolated CAA and, if so, then almost exclusively in older patients.

If no additional defect is present, the *roentgenologic* findings are in most cases unremarkable until adolescence. The heart is not enlarged and the shape of the heart appears normal. The older the patient, the more likely the presence of dilatation of the ascending aorta and the typical, although not pathognomonic, rib notches, especially in the dorsal area of the fourth to eighth ribs as a result of the collateral circulation through the intercostal arteries. A noteworthy cardiomegaly becomes evident only with the development of cardiac failure. The figure of 3 on the left upper edge of the mediastinum, which is often quoted as due to the aortic constriction in the area of the stenosis, can be shown in only a small percentage of the patients.

An entirely different clinical picture[38,101,106,109] is present in *infants*, especially in the first months of life. More than 80% of the children whose CAA is diagnosed before the age of 1 year develop symptoms of cardiac failure, which is more strongly pronounced the earlier the signs appear. Cyanosis frequently supervenes. As a result of thorough investigation one can usually establish a difference in the quality of the arm and leg pulses and a difference in the blood pressures. Figure 10 illustrates to what extent the blood pressure measurements can vary from case to case, also in infancy. All patients younger than 3 weeks of age had severe cardiac failure. The diagnosis based on clinical features only is often unreliable because, in severe cardiac failure, especially in young infants, only faint pulses are palpable generally. Moreover, the lower half of the body can still be sufficiently perfused through a patent ductus where there is a preductal coarctation. The findings on auscultation are, likewise, usually not characteristic of CAA, as either the output is greatly reduced owing to cardiac failure and therefore the typical systolic murmur is fainter, or other

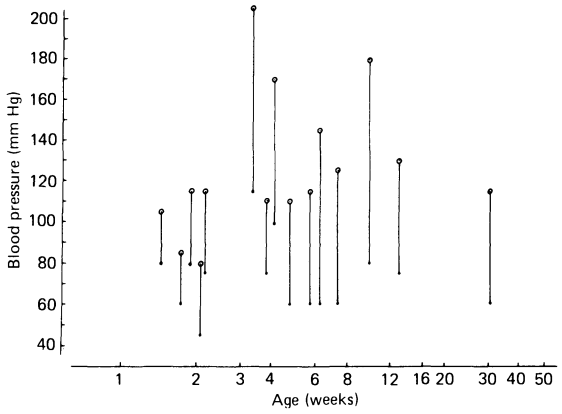


**Figure 10.** Blood pressure in 15 symptomatic infants with an isolated or preductal coarctation of the aorta without further hemodynamically significant associated defects. In two patients in the first 2 weeks of life the systolic and diastolic pressures lie within normal limits; in a further five, in the second to eighth months of life, only the diastolic pressure.

murmurs are present because of associated anomalies such as a ventricular septal defect or aortic valve stenosis. The murmur becomes more characteristic following successful anticongestive treatment; the expected systolic murmur becomes louder, and it can now also be heard dorsally between the shoulder blades.

The younger the infant when the aforementioned symptoms appear, the more likely one is to find in the *electrocardiogram:* a right ventricular hypertrophy with incomplete right bundle branch block and right axis deviation, particularly when there is also an associated atrial septal defect and patent ductus arteriosus. Diffuse ST-T changes are frequent. If the child survives with medical therapy, the ECG pattern changes only slowly and a left hypertrophy pattern may appear additionally. On the other hand, isolated left ventricular hypertrophy in the ECG at this age is very rare.

The chest X-ray of a symptomatic infant shows an unspecific cardiomegaly, often with marked prominence of the pulmonary segment; the pulmonary vascular markings in most cases seem definitely increased. Pathognomonic changes do not show up.

Early heart catheterization is always necessary because the diagnosis of CAA in young infants on the basis of clinical findings can only be suspected in most cases—seldom confirmed—and, in a high percentage of cases, it is associated with severe defects. With a view to surgical intervention, which is often necessary within the first weeks of life, the type, extent, and severity of the coarctation as well as possible associated defects ought to be determined as exactly as possible by catheterization and angiocardiography.

### Natural history of coarctation of the aorta

From personal observations over decades Campbell[17] was able to establish that 20% of the patients with an isolated CAA who had survived the first year of life without surgical treatment died before the age of 20. A further 60% of these did not survive the age of 50. The main causes of death besides cardiac failure and bacterial endocarditis were cerebral hemorrhage following atherosclerosis or cerebral aneurysms and rupture of the aorta. However, the latter complication may occur even in childhood.[91a] Hartmann et al.[38] arrived at even more unfavorable results regarding prognosis on the basis of an extensive study (710 cases) of infants with CAA in whom cardiac failure developed in the first 6 months of life. Without therapy, 36% of those with only an isolated CAA succumbed during the observation period. Only 21% of those with additional defects survived spontaneously. With exclusively medical therapy, 88% of the children with an isolated CAA stayed alive in contrast to only 22% of those with associated malformations. Obviously the prognosis can be improved only by means of surgical intervention: 288 (60%) of the 481 operated infants survived. Newborn infants who develop congestive heart failure in the first weeks of life have the least favorable chances of survival as, even with appropriate surgical treatment, hardly more than a third of the children can be saved.[38,115] The large number of severe associated defects is especially evident in this fraction. These associated defects add to the CAA in terms of hemodynamic effect and thereby enhance the development of cardiac failure. Generally, it is confirmed that the earlier the symptoms appear, the less favorable is the prognosis in the individual case.

### Treatment of coarctation of the aorta

Surgery is generally agreed to be the only sensible therapy for CAA. However, opinions vary considerably as to the most advantageous time and the best technique of operation.

In view of the unfavorable results of purely medical treatment among infants, early surgical intervention has long been given preference in cases where cardiac failure shows no signs of improving within 2 or 3 days of intensive anticongestive therapy.[109,115] Others regard each delay of a corrective operation as an additional danger for the young infant, and surgery is recommended as an urgent measure following clarification of the diagnosis and introduction of anticongestive treatment.[32,106] At the same time, the risk of a residual or recoarctation (20% to

30%) as a result of an incomplete elimination of the stenosis (hypoplastic segment) or insufficient growth of the vessel anastomosis is taken into account as the lesser evil—for it is a question of a life-saving operation for nearly every young infant and a second operation is, in general, unproblematic and of low risk.[123]

Early operation is equally striven for in infants with an isolated CAA for several reasons: even after cardiac failure has been overcome by means of medical measures, the hypertension in the upper half of the body remains unchanged, very often reaching considerable proportions and, moreover, the patients nearly always fail to thrive. In conclusion, it seems certain that the later the stenosis is eliminated, the less favorable the later morbidity will be, especially in terms of a persistent hypertension, and also, in association with this, the long-term prognosis.

While, as a rule, the clinical course compels early operation in patients under one year old, the most advantageous age for operating on asymptomatic toddlers and school-age children is still a matter for debate. Recommendations range from the first to the twentieth year. Many consider that a resection should not be performed earlier than school age because, if it is done in early childhood, they fear that the anastomosis will not grow sufficiently with the child so that there is danger of a restenosis. These ideas are based on the observation that a noticeable pressure difference is produced only by a stenosis of which the diameter amounts to less than 50% of the prestenotic aortic diameter. According to various measurements, the aortic cross section in healthy children between the ages of 3 and 8 years reaches about 50% of the adult aorta. Therefore no significant narrowing—also no more hypertension—should appear as a result of an operation at this age or later. However, as not only mechanical factors play a role in the production and persistence of hypertension, this idea is valid only in theory. The hypothesis is especially inconsistent with the frequent observation that the later the operation was carried out and the higher the presurgical pressures were, the higher is the percentage of patients with persistent hypertension following CAA resection.

Taking into consideration long experience and the results of extensive follow-up investigations as well as better surgical techniques, it is recommended nowadays that operation of the coarctation be carried out as early as the diagnosis is established, at least before the patient starts school, if feasible.[32,63] Definite hypertension—pressures constantly well above the 95th percentile for age—and additional cardiomegaly are criteria for early surgery. Thus, in these cases, coarctectomy should be performed as early as during the first year of life, even in the absence of frank congestive heart failure.

The classic operative procedure for CAA is the resection of the coarcted segment and anastomosis of the two ends of the aorta.[22] Although the original technique of continuous suture was abandoned in favor of interrupted sutures for about half of the circumference because of the high number of recoarctations, early and long-term results were not always satisfactory. The procedure proved to be unsuitable, especially with the presence of a considerable hypoplasia of the prestenotic segment. Various modifications were developed, all of which are based on a plastic widening by a gusset or a bypass of the narrow segment.

Today, a conventional end-to-end anastomosis should be limited to those patients who, because of later diagnosis, undergo surgery only when they are teenagers or adults and whose pre- and poststenotic aortic diameters are about the same size. The method of choice for infants and small children seems to be an excision of the stenosing membrane and a plastic widening of the segment using autologous material (pericardium, subclavian artery) or a synthetic prosthesis (Dacron, Gore-tex).

Operative mortality is essentially dependent on the age of the patient and the associated defects. Consequently, the results of surgery on the young infants who have serious associated cardiovascular malformations and develop cardiac failure early are the least favorable. According to larger statistics only 20% to 40% of this age group survive operation.[32,109,115] The results in our unit have been considerably improved with the better postoperative care and control: 30 of 38 patients survived. Older infants and young and school-age children have a definitely more favorable prognosis, as they seldom show hemodynamically significant associated defects, and one can perform surgery on an elective basis. The surgical mortality in these groups is below 3% nowadays. The same applies to young adults, whereas the risk obviously increases again for patients older than 30 years as atherosclerotic vessel changes can lead to life-threatening complications during and after the operation.[14]

### Course and prognosis following surgical correction

Soon after the introduction of the corrective operation for CAA, one had to recognize that though it led to a blood pressure drop in many patients, in a certain percentage, despite optimal technique, unexpected early or late complications occurred.

Postoperatively, in numerous patients, an exces-

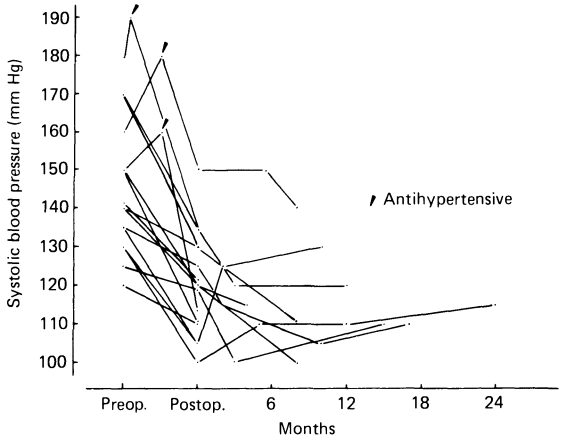


**Figure 11.** Pre- and postoperative systolic pressures (right arm) in 16 children over 5 years of age with coarctation of the aorta. A paradoxical hypertension occurred in three patients, which necessitated *antihypertensive* drugs.

sive increase in blood pressure occurs which is often well above the preoperative initial value[33,99] (Fig. 11). This phenomenon can be separated into two distinct phases. The first phase of this paradoxical hypertension begins soon after the end of the operation. The systolic blood pressure increases by 35 to 50 mm Hg; the diastolic pressure, on the other hand, hardly changes at first. In the second phase, which starts 24 to 48 h after the operation, the systolic pressure falls slightly—however, not below preoperative values—and the diastolic pressure increases by about 25 mm Hg. In the course of a week, the blood pressure often reaches its initial preoperative level again. In terms of pathogenesis, the first phase is based upon increased sympathetic activity with considerably increased norepinephrine production, whereas the second phase is explained by increased plasma renin activity. After 1 week the plasma renin values have actually already returned to normal.[78,99] The so-called postoperative mesenteric arteritis is also considered to be associated with this paradoxical rise in blood pressure. This condition manifests itself in severe abdominal pains and, in isolated cases, leads to rupture of the intestine. Early application of antihypertensive agents is recommended as a prophylaxis for this serious complication.

False or real dissecting aneurysms in the area of the anastomosis present a rare early complication of CAA resection.[63,79] If discovered in good time (neck and interscapular back pains are typical), they can be successfully operated on. Occasional paraplegia[107] as well as cerebral and subarachnoid hemorrhage have been described as extracardiovascular complications. Myocardial infarction and bacterial endocarditis are also considered as unusual early sequelae.[63]

Persistent or postoperatively reappearing hypertension, known as a complication for a long time, poses a large unresolved problem in terms of pathogenesis and etiology.[27,63,79,90,106,107] Residual stenosis, recoarctation, and as yet unknown factors are responsible for sustained hypertension or recurrence of hypertension. The causative associations are unequivocal only for residual stenosis or restenosis, which can be discovered after surgery in infancy in 15% to 20% and in about 10% of those operated on after the age of 1 year.

On the other hand, persistent hypertension without discernible causes is considerably more common (25% to 50%).[63,79,90] All postoperative checkups have shown that the later the correction was undertaken and the higher the preoperative pressure, the more frequently the increased blood pressure persisted. If one leaves the residual stenoses out of consideration, which occur in young infants owing to an aortic arch hyoplasia, this age-dependent tendency is recognized as early as in the first 5 years of life.[106] Changes in the elastic quality of the aortic wall, persistence of maladjustment of baroreceptors, and a promotion of the development of an essential hypertension are discussed here as possible factors. Attention has only recently been drawn to the phenomenon that a disproportionately large pressure rise occurs with physical work stress in patients with normal blood pressure at rest; this increase can, in part, be explained by a mild residual stenosis which is hardly noticeable at rest, but in part also remains unclear from an etiologic point of view[21,28,46] (Fig. 12).

The most comprehensive catamnestic study[79] involving 248 patients 11 to 25 years after a CAA operation (age at operation 2 to 50 years) found that in spite of good resection of the stenosis in most cases, cardiovascular diseases were present in a high percentage of the patients. During the period of observation, 12 percent of the patients had died; in 40% of those surviving, the postoperative blood pressure had not decreased or had even increased, and in a further 40% clinically comprehensible pathologic changes in the heart and vessels were present. In the light of these results, there is a high probability of a relationship between the level and duration of the hypertension before the operation and the unexpectedly high morbidity and early death rate following apparently successful surgery. The findings emphatically underline the importance of the earliest possible diagnosis and treatment of CAA. Careful follow-up care and control after a successful operation are of paramount importance, es-

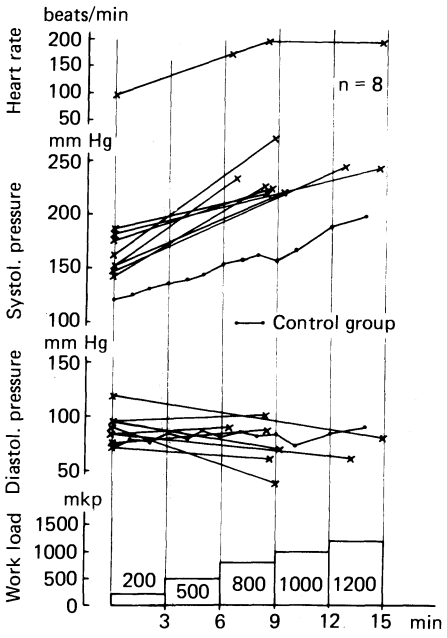


**Figure 12.** Response of blood pressure and heart rate to submaximal ergometer stress in eight teenage patients after resection of a CAA in comparison with healthy controls. From James FW, ref 46

pecially for the early identification and treatment of complications.

## Coarctation of the Abdominal Aorta

### Frequency and types

Coarctation of the abdominal aorta, which is also described as an atypical stenosis of the aorta, is very rare in comparison to coarctation of the aorta: only about 0.5% to 1% of all aortic stenoses are of this type. One differentiates morphologically between a short hourglass segmental and a diffuse hypoplastic type, which again can be localized suprarenally, interrenally, or infrarenally (Fig. 13). Of the four big visceral arteries (celiac trunk, superior mesenteric artery, right and left renal arteries) the renal arteries are by far the most frequently involved in the narrowing. In this case a branching stenosis is present on either one or both sides, or there is a suprarenal circumscribed narrowing or a diffuse hypoplasia for a distance of up to several centimeters.[56,116]

### Etiology

A coarctation of the abdominal aorta may have different causes of origin. Similar to the coarctation of the aorta, excessive obliteration processes leading to a circumscribed narrowing could possibly take place at the origin of the branchial arch arteries situated farther caudally. The coarctation may also be explained as a fusion error in the development of the paired dorsal aortas. The absence of histologically domonstrable inflammatory changes supports a prenatal genesis, as does the frequent combination with other malformations, such as congenital heart defects, multiple renal arteries and ureters, gonadal dysgenesis, and familial occurrence and symptoms from early childhood on. On the other hand, those stenoses which develop in panarteritis and are observed with exceptional frequency in East Asia, in particular Japan (Takayasu disease), are supposedly acquired.[39] Finally, about 50 patients with von Recklinghausen's disease (neurofibromatosis) have been described with coarctation of the abdominal aorta.[104] Arterial stenoses which have developed following fetal rubella are mostly not confined to the abdominal artery.[38] These are considered as of prenatal origin. However, they are not assessed as malformations in the strict sense.

### Pathophysiology

In principle there are no differences to the situation with coarctation of the aorta. The collateral circulation occurs essentially via the mammary and epi-

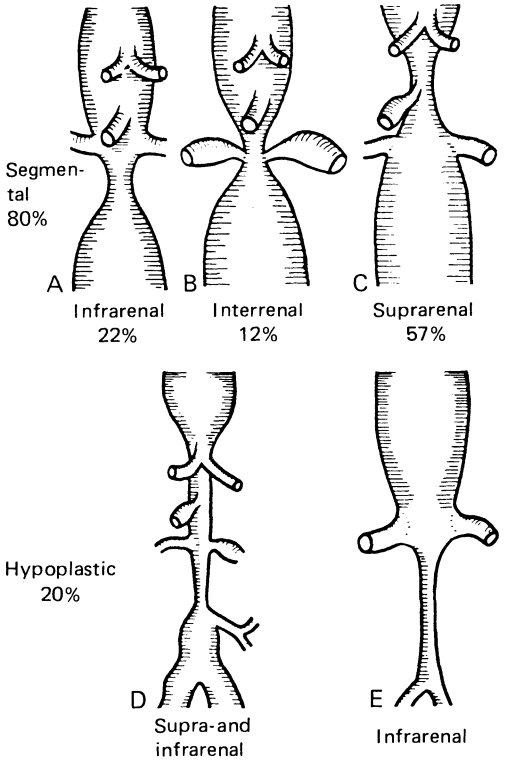


**Figure 13.** Morphologic distribution and localization as well as relative frequency of the different types of abdominal coarctation of the aorta. From Vollmar J, ref 116

gastric arteries as well as the lower intercostal arteries to the external iliac arteries so that, in general, a sufficient blood supply is maintained to the parts of the body distal to the stenosis. The observation that in the case of infrarenal stenoses in general no or only slight hypertension is demonstrable is both interesting and important for the explanation of the pathogenesis of high blood pressure in stenosis of the aorta. Evidently the size of the remaining aortic pressure chamber and the blood circulation over the collaterals is therefore sufficient in these patients to avoid hypertension due to a high vascular resistance. In contrast to this, a considerable hypertension is always present in the cases of an inter- or suprarenal stenosis regardless of whether this is segmentary or fusiform. The significance of the renin-angiotensin system is thereby underlined, although so far no appropriate biochemical data have been communicated, probably because of the rarity of these cases.

### Diagnosis

Symptoms of coarctation of the abdominal aorta seldom appear before puberty. Headaches, vertigo, and epistaxis are interpreted as results of hypertension. These symptoms, indeed, are reported by only the minority of patients. Beyond adolescence, dyspnea on exertion, limited working capacity, and palpitations can appear in patients with severe hypertension. Insufficient blood flow to the infrastenotic body parts is just as rare as in the case of a typical CAA. Symptoms of claudication are therefore the exception. If the superior mesenteric artery is involved in the case of an extreme hypoplasia of considerable length, the mesenteric blood flow may be impaired, which is manifested by relapsing epigastric pains that appear above all after mealtimes.[116] It is far more difficult to arrive at a correct diagnosis on the basis of clinical data than in classic CAA. Hypertension in the upper part of the body and missing or weakened femoral pulses are present in both types. The interscapular systolic murmur, which is typical for CAA, is, of course, missing. This finding can, however, also be established with isthmus atresia; therefore it has no great value in differential diagnosis. On abdominal auscultation blood flow murmurs are heard in most cases of circumscribed stenosis, but seldom in cases of fusiform narrowing. Relatively frequent continuous blood flow murmurs which originate in large collateral vessels can be heard in both types. An unequivocal diagnosis in terms of morphology and localization can be made only with the help of aortography.

### Therapy and prognosis

The spontaneous prognosis of coarctation of the abdominal aorta is almost as unfavorable as that of CAA. If no treatment is carried out, 27% of the patients die before the age of 20, 52.5% before the age of 30, and 75% before the age of 40 and, in fact, mostly from complications dependent on hypertension.[39,56] As no significant change in the spontaneous course is achieved by medical therapy using antihypertensive agents, the coarctation should be operated on, if possible immediately after the clarification of the diagnosis. From several possible operative procedures only the aorto-aortic bypass using a synthetic prosthesis has proved reliable. If the renal arteries or the superior mesenteric artery are involved in the stenosis, a plastic reconstruction should be carried out simultaneously if necessary, or revascularization by means of a direct anastomosis between the prosthesis and involved vessel should be undertaken.

According to a larger review[56] the operative mortality is 11%. A return to normal blood pressure is achieved in about 70% of the patients. If the hypertension persists postoperatively, an angiographic assessment of the surgical result is necessary. If there are still stenotic segments present in the renal arteries, a further reconstructive operation is indicated and, in individual cases, even a nephrectomy.

## Renal Hypertension in Childhood

A renal disease is the underlying cause in the great majority of children with secondary hypertension.[57,68,71] It is not unusual for a clinically quiescent renal disease to be first noticed as a result of hypertension being accidentally identified. Frequently, a renal cause can be ascertained on the basis of a thorough history-taking and clinical examination that is is unnecessary to extend the diagnostic procedures to rare endocrine, neurologic, or metabolic illnesses.

As the pathology and pathophysiology of diseases of the renal parenchyma and renal vessels which lead to hypertension have already been described in the foregoing chapters, only the age-specific particularities of childhood will be closely looked at here.

The parenchymatous and renovascular causes of hypertension found only, or also, in childhood are presented in Table 6, in which extremely rare diseases have not been included.

### Renal-Parenchymal Causes of Hypertension

Besides the known acquired renal-parenchymal diseases also found in adults, a large number of different congenital malformations may be responsible for

renal hypertension in childhood.[71] Whereas renovascular processes and obstructive uropathy, i.e., congenital malformation, present the main cause for hypertension in infancy, after the first year of life renal parenchymal diseases constitute in more and more cases the reason for an elevated blood pressure. Basically the pathogenetic relationships are the same as in adults: inflammatory or ischemic changes in the renal cortex activate the renin-angiotensin-aldosterone system and lead, as a result of dysfunction of the sodium-water balance, to high blood pressure. At the outset of hypertension vasoconstriction is the main hemodynamic deviation. However, with growing renal failure, hypervolemia plays an increasingly important role in sustaining the high blood pressure.

## Congenital diseases

***Polycystic Kidneys.*** In this term all those inhibitory malformations are included which lead to open or closed cysts in the course of the renal tubuli. Large solitary renal cysts, which occasionally lead to hypertension in adults but never in children, are pathologically and anatomically distinguished from polycystic kidneys, which become apparent especially in infants and children. The latter form is the result of an autosomal recessive inherited trait and often appears in combination with hepatic cysts. As a rule the infantile type of polycystic renal degeneration leads to death in the first months of life, whereas the juvenile form has a more prolonged course with survival up to the second or third decade of life.[65] Typical clinical findings in the infantile type, which are often already evident in the newborn, are very enlarged and firm kidneys leading to abdominal distension, hypertension, uremia, and anemia as well as excessive salt loss with forced polyuria as a result of insufficient tubular concentration. In the juvenile type, as a rule, findings such as albuminuria, uremia, and hypertension first appear in children between the ages of 5 and 10 years.

***Segmental Hypoplasia Ask-Upmark.*** This congenital malformation has to be classified as a form of renal dysplasia. Usually segmental hypoplasia Ask-Upmark leads to marked hypertension as early as during the first 2 years of life. A varyingly large segment of the kidney is affected. Histology characteristically shows dilated tubuli, hyalinosis and sclerosis of the arterioles, and absence of the glomeruli. Girls are affected twice as frequently as boys by this disease, which is not inherited. In terms of pathophysiology this form of hypertension is, at the beginning, exclusively induced by high vascular resistance, i.e., caused by increased renin activity. The kidneys can still be functioning normally, depending on the extent of the hypoplasia. Unequivocal diagnosis of this congenital anomaly is often very difficult because of the small size of the affected segment and doubtful angiographic and scintigraphic findings. If the hypoplastic segment can be removed, the prognosis for the patient is favorable.

## Acquired diseases

Acquired renoparenchymatous diseases form—infancy excepted—by far the most common cause for renal hypertension in childhood.[29,93]

***Acute Glomerulonephritis.*** From 1 to 3 weeks after a pharyngeal infection by $\beta$-hemolytic streptococci, an antigen-antibody complex is deposited at the basal membrane of the glomeruli. With this phenomenon complement consumption occurs. The clinical picture is characterized by edema, oliguria, hematuria, and hypertension. The most commonly affected age group is between 2 and 12 years with both sexes being equally affected. Ninety percent of the cases of acute glomerulonephritis recover spontaneously and, in general, blood pressure returns to normal, too. In cases of extremely high blood pressure with additional hypertensive crises, a hypertensive encephalopathy can develop which may sometimes lead to an incorrect diagnosis of encephalitis.[66,98]

***Chronic Glomerulonephritis.*** Chronic glomerulonephritis constitutes about half the renal parenchymal diseases which lead to high blood pressure. The various forms can be differentiated only histologically by means of a renal biopsy. The dominant features are clinical growth retardation, anemia, albuminuria, and hematuria. Urea and creatinine are increased according to the degree of renal failure. The clinical course of the disease can be as variable in a child as in adults; as a result the prognosis is poor and nearly always leads to terminal renal failure within a few years.

***Chronic Pyelonephritis.*** Whether chronic pyelonephritis is a primary cause for hypertension in children is even more controversial than whether it is in adults. Possibly, in the case of an unremarkable clinical course of the disease, it will be identified only at the stage of kidney atrophy with renal failure and, in a child, then falsely diagnosed as renal dysplasia. Retrospectively unexplained bouts of fever, nausea, and abdominal pains can point to a previous chronic urinary tract infection.[4,58]

***Obstructive Uropathy.*** Organic obstructions in the urinary tract, such as urethral valves or ureter stenoses, as well as functional disorders in voiding

urine, e.g., with neurogenic bladder, lead to a varyingly severe urinary stasis. Thus pressure builds up in the urinary tract, especially in the renal pelvis and calyces, and the renin-angiotensin-aldosterone system is thereby activated. Urethral valves can produce such an extreme obstruction that an excessive dilation of the urinary tract with formation of hydronephroses on both sides is already present at birth. Clinically, then, the patient presents with a distended abdomen with tumorlike, enlarged kidneys and a dilated bladder. Therefore, an extreme renal failure can already be present at birth. As a rule, however, the course of the disease is more protracted so that the above-mentioned findings and hypertension resulting from renal failure become noticeable only during the first 6 months of life.[126] In young infants an obstructive uropathy is often diagnosed only after urosepsis has developed.

If only a one-sided urinary tract obstruction is present, the course of the disease is prolonged and it is possibly first discovered only at toddler or school age. If formation of urinary calculi is the cause of the obstructive uropathy, metabolic disorders such as oxalosis and hyperparathyroidism should be excluded by performing the appropriate investigations in childhood. It is often possible to surmise the diagnosis on the strength of clinical findings; usually, however, it can be verified only by roentgenologic and endoscopic investigations. With almost all forms of obstructive uropathy considerable improvement and often, in fact, a cure can be effected by surgery. This is not the case, however, with patients suffering from a neurogenic bladder, which is found very frequently in children with myelomeningocele.

***Tumors.*** The pathogenesis of hypertension due to intra- and perirenal tumors is most probably nonhomogenous. Three mechanisms are discussed as possible causes for increased activity of the renin-angiotensin system. One or more intrarenal arteries, depending on the position and size of the tumor, can be compressed resulting in reduced blood supply to the pertinent renal area. A diminished blood supply of this kind, however, can also be the consequence of intrarenal arteriovenous shunts typical of malignant renal tumors. The production of vasoactive agents in the tumor itself can also be considered as a third cause of renal hypertension due to tumors.[18,86,128]

The Wilms' tumor, the most common renal tumor in children, is discovered most frequently between the ages of 1 and 4 years. The diagnosis is often suspected as a result of careful clinical examination and is confirmed by urogram and, if necessary, arteriogram. The prognosis is favorable if extirpation is carried out at stage I. As a rule the hypertension disappears completely following removal of the tumor, although it can reappear if metastases develop.

***Schönlein-Henoch Disease, Lupus Erythematosus.*** Generalized lesions of the arterial vessels are main features of these two diseases. As a result of the involvement of the glomerular arterioles, the kidneys, becoming the focal point of the disease, produce hypertension.

Schönlein-Henoch nephritis, a typical affection of childhood, is most common between the ages of 5 and 7 and affects boys especially.[100] Streptococcal infections, medications, vaccinations, primary tuberculous infection, and even insect stings are given as causative factors. Clinically, the diagnosis can often be made because of the typical position of the petechial hemorrhage on the lower extremities and in the area of the buttocks. Swelling of the joints, hematuria, proteinuria, and severe abdominal pains, sometimes with bloody stools, are associated with this condition. Histologically, a focal nephritis is almost always identifiable from renal needle biopsies. Furthermore, mesangial deposits of immune globulin and complement in individual glomeruli are typical. The serum complement can be lowered. If there is a noteworthy arterial hypertension, an unfavorable course of the disease has to be assumed, usually ending in terminal renal failure. Lupus erythematosus seldom appears before the age of 9 and rarely takes a peracute course during childhood or adolescence.

***Hemolytic-Uremic Syndome.*** This syndrome, which has not yet become quite clear in terms of etiology, constitutes the most common cause for acute renal failure in infants and small children. Older children seldom suffer from this condition. However, if they do, the disease is generally more severe. Virus infections are considered to be causative noxae. Anamnestically, a gastrointestinal infection almost always precedes the onset of the disease. Clinically, the hemolytic-uremic syndrome is characterized by marked hemolysis and the simultaneous appearance of renal failure. Histologically, endothelial lesions in the arterioles are manifest, which evidently can lead to microthromboses in the glomeruli and finally to necrosis of the renal cortex. Hypertension can appear when renal function is reduced by as little as 25%. Renal function in infants and toddlers is usually reestablished within 2 days to 6 weeks. On the other hand, however, older children often suffer from irreversible functional loss.

Fibrinolysis was recommended as treatment; however, this has been discarded, as it had little success. Better results seem to have been obtained by reduc-

ing the adhesiveness of the thrombocytes using dipyridamole or acetylsalicylic acid. It is not unusual for these patients to need temporary hemodialysis. However, hypertension persists during this treatment and often remains even after successful kidney transplantation, with the result that a bilateral nephrectomy can be indicated in some cases.

### Renovascular Hypertension

Renovascular hypertension is due to either a primary malformation of the renal vessels or a secondary disease involving the vessels. Table 6 shows the main causes of renovascular hypertension in childhood. Vascular processes constitute the most common cause for renal hypertension in young infants.[1] After the first year renovascular processes, especially stenoses of the renal arteries, are the cause in about 15% of the cases of high blood pressure in children.

#### Fibromuscular dysplasia

By far the majority of stenoses of the renal arteries are caused by fibromuscular dysplasia of the vascular wall. Histologically, there is hypertrophy of the medial and adventitial muscle fibers. The changes are either spread diffusely over the whole vessel or isolated, affecting only a short segment. Surgical correction is possible with the latter type, especially if it is unilaterally located.

#### Aneurysms of the renal arteries

Aneurysms of the renal arteries or their branches are congenital malformations which appear either as isolated lesions or as part of a generalized disease of the arteries. As a result of compression of the neighboring arteries, they cause a reduced supply of blood to the corresponding renal areas.

#### Thromboses and embolisms of the renal arteries

Nowadays thromboses of the renal arteries are the most common cause of hypertension in the newborn. In particular, they appear as a complication of the umbilical artery catheters which are inserted for better control of blood gases and pressure. Complication rates of from 4% to 95% must be considered, depending on the position of the catheter tip and the length of time it is in place.[31] Embolisms of the renal arteries have occasionally been observed in the course of spontaneous closure or surgical ligature of a persistent ductus arteriosus.

Clinical findings are nonspecific. Cardiorespiratory and neurologic symptoms such as tachypnea, cyanosis, hepatomegaly, and opisthotonos as well as convulsions are dominant. The prognosis for renovascular hypertension with this genesis is very unfavorable, having a mortality rate of up to 30%.

#### Thrombosis of the renal veins

Thromboses of the renal veins, on one or both sides, can already be present in the newborn, e.g., associated with polycythemia in infants of diabetic mothers. More common causes are severe dehydration and hypovolemia due to nephrotic syndrome. Predominant signs are oliguria, hematuria, and proteinuria. Frequently the affected kidney can be palpated as large and sensitive to pressure. Hypertension does not occur in every case.

### Kidney Transplantation

For the past several years more and more kidney transplantations have been carried out successfully in children suffering from terminal renal failure. At present in Europe there are about 500 to 550 children living with functioning transplants. In Hannover, Federal Republic of Germany, alone there are 71 children between the ages of 3 and 16 years being cared for following kidney transplantation.[92] All the patients in this age group have developed, or retained, hypertension postoperatively. According to Rance et al.[96] about 10% of children with hypertension have renal transplants. Pathogenetically, the high blood pressure is due to either a renal artery stenosis at the site of the anastomosis or a renoparenchymatous cause due to acute or chronic organ rejection.[24,77,125] However, hyperaldosteronism as a result of the steroid therapy or the primary disease can also be a causative factor. As yet, the hypothesis of Bachy et al.,[5] that an essential hypertension is transferred from the donor to the recipient, has gained no further support.

## Antihypertensive Therapy

Drug therapy should be initiated in cases of arterial hypertension which cannot be influenced or cured by surgical means, e.g., aortic stenoses, renal artery stenoses, or urinary tract obstruction. This is especially the case with bilateral renoparenchymal disease. In principle, a decrease in blood pressure should be striven for even when, as a result, an already present renal failure decompensates more quickly because nowadays dialysis and transplantation offer a considerably better prognosis for terminal renal failure in children as well as in adults.

Table 9 presents the most commonly used antihypertensive drugs with appropriate doses for children.[6,84a,96,108]

**Table 9.** Antihypertensive Drugs in Childhood—Dosage Regimen

| | Daily Starting and Maximum Doses (mg/kg) | | | |
|---|---|---|---|---|
| | | | Maximum | |
| Drug | Oral | Intravenous | Oral | IV |
| Diuretic agents | | | | |
| Furosemide | 2–3 | 1–2 | 10 | 6 |
| Spironolactone | 2–3 | 1–2 | 5 | 4 |
| Chlorothiazide | 10 | | 20 | |
| Hydrochlorothiazide | 1 | | 2 | |
| Chlorthalidone | 1 | | 1 | |
| Vasodilator agents | | | | |
| Hydralazine | 0.5–1 | 0.5–1 | 5 | 1.5 |
| Minoxidil | 0.1–0.5 | | 2 | |
| Adrenergic blocking agents | | | | |
| Propranolol | 0.5–1 | | 8 | |
| Methyldopa | 10 | | 40 | |
| Reserpine | 0.02 | 0.03 | 0.07 | 0.07 |
| Clonidine | 0.003 | 0.003 | 0.006 | ? |
| Guanethidine | 0.2–0.5 | | 1–2 | |

Drugs for Treating Hypertensive Crises

| Drug | Dosage |
|---|---|
| Diazoxide | 5 mg/kg iv (can be repeated after 30 min) |
| Sodium nitroprusside | 5–8 mg/kg/min continuous iv drip |

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# Diagnosis of Hypertension

# Measurement of Blood Pressure

# 22

S. D. Moulopoulos

The diagnosis of arterial hypertension starts with the procedure of measuring arterial blood pressure. The methodology has been developing for almost two and a half centuries (Table I). However, it still leaves much to be desired, if one can judge from the multiplicity of techniques and methods, as well as from a simple enumeration of the common pitfalls.

In this chapter the principle upon which blood pressure measurements are based, the methods applied, and the sources of error are followed by a brief description of direct, long-term, and telemetric measurements.

## Technique

The arterial pressure, as it is usually measured *(manometric pressure)*, is the difference between the intra-arterial and atmospheric pressures. There are rare instances where the *absolute pressure* (manometric plus atmospheric) should be considered.

Determining the arterial pressure, therefore, amounts to measuring the difference between intra-arterial and atmospheric pressures. This can be achieved by invasive and noninvasive techniques.

### Invasive Techniques

Access to the intra-arterial space by traumatic methods is used in this procedure. A needle or catheter is introduced into an artery, and the intra-arterial space is connected to the measuring device by means of a fluid column. This technique has the disadvantage of pressure damping introduced by the transfer of pressure through a long, narrow tube. Blood coagulation in the tubing and the usually necessary heparinization complicate the procedure. The technique is widely used, however, when accuracy requirements are such that the distortion of the pressure wave obtained is of no particular importance.

Miniaturized pressure transducers placed at the tip of the catheter are used to measure the pressure on the spot and avoid the interference of the fluid column. This technique provides the most accurate pressure wave contour and is used clinically mainly in contractility studies and experimentally in pressure wave analysis.

### Noninvasive Techniques

Current noninvasive techniques most commonly aim at measuring the pressure required to interrupt blood flow through an artery and compare the flow interruption pressure to the atmospheric pressure. Variations of the basic technique consist in the way the interruption of flow is recognized.

*Palpation* of the arterial pulse peripheral to the point of flow interruption or *auscultation* of the Korotkoff sounds at the distal part of the artery are the most commonly used techniques. *Microphones* are used to pick up the Korotkoff sounds when automated pressure recorders are employed. *Ultrasonic* transmitters can also monitor flow changes through an artery. *Infrasonic* vibrations have also been detected and signals heard as sounds over a loudspeaker. The changing magnitude of *oscillations* caused by pressure fluctuations has also been used

**Table 1.** Historical Development of Blood Pressure Measurement

| | |
|---|---|
| 1733 | Hales: Blood column in glass tube |
| 1828 | Poiseuille: Artery connected to mercury tube |
| 1861 | Marey-Chaveau: Direct recording with membrane and drum recorder |
| 1890 | Basch-Potain-Marey: Direct measuring devices |
| 1903 | Frank: Optical manometer |
| 1904 | Erlanger: Diastolic pressure from oscillation muffling |
| 1905 | Korotkoff: Description of sounds |
| 1909 | Pachon: Oscillometer |
| 1945 | Grundfest-Hay-Feitelberg: Strain gauge manometer |
| 1947 | Tybjaerg-Hanse-Warburg: Capacitance manometer |
| 1959 | Laurence: Catheter-tip manometer |
| 1965 | Ware: Ultrasonic recording |

for some time to detect the moment at which the flow is interrupted. *Visual* changes in the extremital skin, especially flushing distal to the point of interruption, have also been used as an indicator.

Clinically, the palpation-auscultation technique is most commonly used. Of the 27 automated pressure-measuring devices available, 21 operate on the auscultatory principle, 3 on infrasound, 2 on ultrasound, and 1 on the oscillometric technique.[8,9] Two other techniques are still in the testing stage.

The *phase-shift* technique relies on the principle of measuring the time difference of the flow wave arrival at two points. This difference is smallest when a pressure equal to diastolic is applied over the artery.

*Tonometry* is based on the external application of piezoelectric elements over an artery.

## Methods

The most common method of measuring arterial blood pressure in man is by use of a simple instrument, the *sphygmomanometer.* The compression bag of the instrument, completely enclosed in an inelastic cuff, is 30 cm long and 12–14 cm wide. The bag should be 20% wider than the circumference of the limb and longer than half the diameter of the limb. Cuffs used in children are therefore smaller in width and length.[6]

The cuff is placed around the arm approximately 2.5 cm above the antecubital space, with the bag positioned over the inner surface of the arm. It is held in place by a long (80 cm) cloth bandage, fasteners, or Velcro tabs. An integral inflatable cuff was recently suggested.[3] The bag is inflated by a bulb with an adjustable air valve to 30 mm Hg above the point at which the radial pulse disappears. It is subsequently deflated at a rate of 3 mm Hg/s.

The reappearance pressure of the radial pulse is designated as the systolic pressure. By applying the stethoscope over the brachial artery, one can determine the pressure at which a tapping sound appears for at least two consecutive beats as well as the point at which the sound is abruptly muffled. This muffling is caused by the disappearance of sounds with a frequency higher than 60 Hz. The muffling pressure is designated as the *diastolic pressure* (Korotkoff phase IV) but is in fact 7–10 mm Hg higher than the pressure measured intra-arterially. The disappearance of the sounds is closer to the intra-arterial diastolic pressure (Korotkoff phase V) but may vary considerably during exercise and therefore is not recommended as an indicator. The appearance of the first tapping sound is designated as the *systolic pressure,* unless the radial pulse is felt at a higher pressure, which is then designated as systolic.

Mercury or anaeroid manometers are used. The latter should be zeroed before starting the measurement. The *random-zero manometer*[15] is designed so that a random-zero setting is used for each measurement, thereby minimizing examiner bias.

Devices which operate by the microphone or ultrasound sensing of flow reappearance and conversion of the signals to either sound or light do not offer any particular advantage. They facilitate blood pressure measurement by inexperienced persons, such as patients, and are mostly used by them.

In the *oscillometer* two compression bags are used. One interrupts the flow and the other is connected to the oscillation indicator.

The *phase shift* method utilizes three cuffs, side by side. The cuffs are inflated, and during subsequent deflation their volume is recorded with pressure transducers. The time delay between proximal and distal cuffs is less than 1 m/s at the pressure which is designated as diastolic. Compared to the auscultatory method, the phase-shift diastolic pressure is slightly below the muffling level.

The *direct methods* make use of several types of devices.[4,12] Mechanical devices include simple anaeroid or mercury manometers. Mechanical recorders utilize rubber or beryllium-copper membranes coupled to recording instruments. Mirrors attached to the membranes transmit light beams, magnify their trajectory, and record them on photographic paper (optical manometers). Electrical transducers are most frequently used now. They operate on three principles. Resistive transducers use stress-sensitive wires which change their electrical resistance when subjected to varying pressures. Inductance trans-

ducers utilize current changes produced by an iron slug moved by a membrane within a magnetic coil. They are the most commonly used in hemodynamic measurements. Capacitance transducers offer some advantages. Pressure exerted on a metallic membrane alters the capacitance of a system operating as a capacitor. The sensitivity of these instruments should be at least $\pm 1$ mm Hg, and their frequency response must reach the 10th harmonic of the basic frequency (for pressure measurements in the arteries, 10–30 Hz). Piezoelectric, photoelectric, thermoelectric, electronic, and radioactive transducers and "pressure-sensitive" paint are seldom used for pressure recording in the laboratory.

## Sources of Error

The validity of the pressure measurement can be affected by flaws in the instrumentation and technique, by the momentary condition of the patient, and by observer variables.

### Instrumentation

If the width of the compression bag is too narrow for the patient's arm, the pressure will be falsely elevated because the full pressure is not applied to the artery. Inadequate covering of the bag by the inelastic cuff or the use of fastening hooks can also lead to higher pressure readings.

Mercury tubes should not be dirty or oxidized, and the air vent on the top must be patent. The mercury column should always be in a vertical position. Air bubbles may lead to erroneous readings and are usually present when the mercury reservoir is inadequately filled. In this case the zero reading is also inexact. If the mercury reservoir is less than 10 times larger in diameter than the mercury column, an adjustment should be made to correct for the difference in the reservoir level for several column readings. Anaeroid manometers should be frequently (at least yearly) calibrated against mercury manometers.

### The Patient

Positioning the arm at a level lower than the fourth intercostal space in the sitting or standing patient may give higher readings. In obese patients, or when measuring the pressure at the thigh, a wider and longer compression bag and cuff must be used. Otherwise the pressure readings will be erroneously high.

The reading is also strongly influenced by the momentary condition of the patient. The mere presence of a physician or even the thought of an impending examination can alter the reading in many individuals.

Taking the "basal blood pressure" involves several days of rest in a private hospital room, numerous pressure measurements for acclimation purposes, administration of a sedative the night before the measurement, and performance of the measurement early in the morning by a familiar individual who does not engage in conversation and measures the pressure repeatedly for 15 min.[11,13] The mean of the two lowest readings is the basal pressure.

The "casual" blood pressure is usually higher than the basal, and the relationship between the basal and the supplemental (casual minus basal), if there is any, tends to be inverse.

Common precautions to reduce patient-related errors of measurement include the avoidance of meals, exercise, changes in temperature, smoking, and excitement before the examination. Postural changes should also be avoided for at least 5 min before the measurement.

Measurement by the patient or by a family member may reduce patient sources of error in some instances. It may also increase examiner errors, however.

### The Examiner

Examiner errors are most important in patient follow-up, drug evaluation, and epidemiologic surveys. This has been documented by comparing examiner readings with automatic recordings. Examiner readings tend to be higher than recorder readings.[14] The most significant variations occur in determining the sound-muffling point of the diastolic pressure and the level of the systolic pressure. Rapid deflation erroneously increases the systolic pressure reading and probably lowers the diastolic one.

The so-called auscultatory gap is another source of error. In this rare case sounds disappear for an interval up to 40 mm Hg and then reappear. Pulse palpation findings are unaffected.

Psychological factors can apparently also influence examiner findings. The findings vary in accordance with examiner bias and digit preference. The random-zero manometer was designed to avoid these errors, which are significant in a large number of measurements.

Arrhythmias may be a source of examiner error if one does not ignore an occasional premature con-

traction or does not average several readings in more complex or "absolute" arrhythmias. Increased vascular resistance in shock can reduce arterial flow. Thus, the Korotkoff sounds may become faint or inaudible and pressure readings grossly inaccurate. Direct pressure determinations are recommended in such cases.

## Direct and Indirect Measurements

Direct measurements are more accurate than indirect ones. They avoid most of the errors attributed in this chapter to indirect measurements. They indicate the systolic, diastolic, and mean pressure and provide a graphic record of the pressure pulse wave for observation of specific features such as the dicrotic notch position, the slope of the upstroke, the presence of a second peak, etc.

Direct measurements may be made in any large artery and are not restricted to the extremities. On the other hand, direct measurements can be performed only by the invasive technique. These carry some risk of artery wall lesions or thromboembolic complications. Hence, direct measurements are done only in hemodynamic studies or for in-hospital continuous monitoring of blood pressure for periods of several days.

## Long-Term and Telemetric Measurements

The continuous recording and measurement of blood pressure are most accurately achieved by direct techniques. If a small polyethylene catheter is used, such measurements can be performed not only in immobilized patients but also in ambulatory cases for short periods. Portable tape recording systems can be used to record the amplified transducer signal.[7]

Noninvasive long-term measurements offer many advantages. A microphone picks up the signal and relays it via a transducer to a portable magnetic recorder.[14] The patient then measures the pressure in the usual way every 30 min.

In a modified technique, compression and decompression of the cuff can take place every 5 min[5] or every 30 s with a 15-s interval between determinations.[10]

The constant cuff pressure technique is also a phonoarteriographic one, in which the pressure in the cuff is maintained at the systolic or diastolic level for 50 consecutive strokes and then deflated.

In the technique of tonometry,[2] a force-sensitive transducer is placed over a superficial artery. A continuous recording of beat-to-beat pressures can be obtained in this way. This technique is most promising, despite difficulties involved in securing the transducer over the artery.

The correlation between long-term measurements and the "casual" blood pressure is poor and indicates the need for improved long-term recordings. Irving et al. found that the automatically recorded pressures tended to be lower than casual by as much as 20%.[5]

Automatic, portable recording devices as well as direct measurements can also be used for telemetric determinations. The signal from the amplifier can be transmitted to a receiver in the laboratory, where it can be continuously recorded over a distance up to 250 km.[1] However, technical difficulties have restricted the use of these devices to a very few (mostly aerospace) laboratories.

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# Arterial Blood Pressure—the Variable Parameter

# 23

P.W. de Leeuw, W.H. Birkenhäger

## Introduction

It has long been recognized that blood pressure is an unstable parameter. It varies with the time of day and in accordance with the mental and physical activity of the individual. This spontaneous variability of blood pressure raises several problems with respect to the interpretation of epidemiologic or clinical studies of hypertension. Blood pressure readings can also be influenced by factors external to the individual, such as observer bias and environmental conditions.

Blood pressure can be measured either directly, i.e., by an indwelling catheter, or indirectly by sphygmomanometry or by automatic devices. The direct method requires arterial puncture, which in itself may elicit an emotional response with a rise in pressure. It is evident that such factors as accuracy and calibration of the sphygmomanometer, cuff size, and arm size will affect the reading. Other factors include the position of the patient, the position of the arm, the speed with which the cuff is inflated or deflated, respiration, the presence of arrhythmias, an auscultatory gap, and spontaneous vascular bruits. Moreover, many variables on the part of the observer, such as concentration, auditory and visual acuity, digit preference, and wishful thinking represent potential sources of error.

The mere presence of an observer can in itself raise the arterial pressure; moreover, blood pressure tends to be higher when measured by a physician than when measured by a nurse. Observer bias and observer errors can be avoided by the use of automatic devices. In the last 20 years several devices have been developed which have made it possible to obtain continuous recordings of blood pressure throughout the day. Much progress has been made with these instruments, and there is even experience with portable recorders which measure intra-arterial pressure directly in free-ranging patients.

## Casual and Basal Blood Pressure

The terms *casual* and *basal* blood pressure were introduced by Addis in 1922.[1] This investigator measured arterial pressure in the morning soon after the subject had awakened but before rising. This was called the basal blood pressure. Any other pressure taken during the day was called the casual pressure.

This concept was adopted and expanded by Alam and Smirk.[2] While Addis had recommended that for a basal pressure the patient should be prepared as for a basal metabolic rate, these authors modified the determination by rest and emotional desensitization: continued repetition of a stimulus (in this case the blood pressure measurement) and the avoidance of new stimuli. The entire procedure was explained to all patients; they were seated in a warm, quiet room, and no conversation was allowed, since even quiet conversation can raise the blood pressure.[50] Frequent measurements were carried out for about half an hour. Basal blood pressure was defined as the lowest pressure obtained in three consecutive readings during the half-hour rest period and acclimation of the subject to the presence of the observer and to the procedure itself. In 25 normotensive subjects the average basal pressure was 106/67 compared to 151/95 in 27 patients with essential

hypertension. Casual blood pressures taken soon after the patient had entered the room were 121/71 and 195/116, respectively. The difference between casual and basal blood pressure was called the *supplemental pressure.*

Whereas it was first thought that the basal blood pressure was relatively stable, it was soon learned that this was not invariably so.[25] The criteria for obtaining a true basal blood pressure were later modified by Smirk.[46] Measurements were taken in passive patients after a night's rest, and the average of the two lowest pressures was taken as the basal value. Usually a mild sedative was taken on the previous evening. Doyle and Smirk found that the basal blood pressure obtained in this way was at least partially neurogenically maintained, since ganglion-blocking drugs reduced the blood pressure even further.[15]

It should be emphasized at this point that basal blood pressure as defined by Smirk is by no means synonymous with lowest pressure. In later years it was demonstrated by the use of automatic devices that minimum levels of blood pressure usually occur during sleep.[5,7,8,12,24,34,41,45]

In view of the differences between casual, basal, and lowest blood pressures, considerable uncertainty exists as to the real significance of casual blood pressure readings. Besides the 24-h variations of blood pressure, which will be discussed below, the blood pressure tends also to vary with time. This must be taken into account in the evaluation of epidemiologic studies. In several of these it has been shown that blood pressure tends to increase with age.[13,16,22,26,35,53] It has even been shown that subjects with initially high pressures may show a fall in pressure when examined several years later.[3,4,20,37] This phenomenon, often referred to as regression toward the mean, makes it impossible to compare casual blood pressure in cross-sectional studies unless a standardized protocol is followed with measurements conducted over an adequate period of time. Since it is impossible to obtain basal or even lowest blood pressure readings in large epidemiologic studies, little is known about the behavior of these variables with time.

Kilpatrick showed that daily fluctuations of basal blood pressure were less than those of casual pressure. In patients with essential hypertension, these basal fluctuations were more pronounced than in normotensives. In a cross-sectional study of 55 subjects with essential hypertension, de Leeuw found that both the basal and lowest blood pressure increased significantly with age.[29] It seems to be important, therefore, to define the daily blood pressure variations and the mechanisms involved.

## Diurnal Variability of Blood Pressure

Despite numerous physiologic mechanisms which act to keep the blood pressure within normal limits, there is hardly a variable that changes more during the day than blood pressure. For most subjects, however, the pattern of 24-h blood pressure variations is quite similar. As early as 1898, Hill reported a fall in blood pressure during sleep,[17] a finding which has been frequently confirmed by others. Unfortunately, initial studies on this subject were fraught with errors, since there was still interaction with the observer. It was not until the advent of automatic devices that more reliable studies could be undertaken.

Shaw and co-workers[45] were the first to study 24-h variations in blood pressure with an automatic instrument which was set to measure the blood pressure indirectly at 30-min intervals. Of the 28 patients studied, 16 had benign essential hypertension and 12 had malignant hypertension. The patients were hospitalized for the study. It was found that absolute variations (i.e., difference between highest and lowest readings) were similar in both groups: 71 and 62 mm Hg for systolic and 41 and 40 mg Hg for diastolic, respectively. Obviously, absolute variations are greater for systolic than for diastolic pressure. Surprisingly, the authors found that during sleep the average pressure was 15/9 mm Hg lower than during the daytime in patients with benign hypertension, but that no fall of blood pressure occurred in the patients with malignant hypertension. This could not be explained by the severity of the hypertension as determined from casual readings, and the findings were attributed to a relatively "fixed" vascular resistance in malignant hypertension. This cannot be the sole explanation, however, since the absolute variations in pressure were similar. A difference in sleeping behavior, unstated by the authors, could equally well be responsible for these features.

A convincing study was conducted by Richardson et al.[41] With an oscillograph, blood pressure recordings were obtained from 8 normal and 30 hypertensive subjects over at least a 12-h period, including at least 4 h of sleep. In five subjects the accuracy of the measurements was assessed by comparison with simultaneous intra-arterial recordings. In 87% of these paired observations, indirect values differed from the intra-arterial pressure by 10% or less. Also, the effect of the procedure itself was tested. Whereas intra-arterial pressure rose slightly during inflation of the cuff, it usually returned to control values while cuff pressure was still above systolic pressure, and thus before the measurement was re-

corded. In this way reliable results were obtained with the automatic device.

Marked variations were found with respect to systolic and diastolic blood pressures. Both were significantly higher in the late afternoon and evening than in the morning. The lowest values were found during the early hours of sleep; in the hour of awakening pressure rose again. Despite differences in the magnitude of the variations, the same general pattern was found in both normotensives and hypertensives, regardless of etiology. Eight subjects took a nap during daytime of less than 1-h duration. In half of them no change in blood pressure occurred, while it fell in the others. In subjects who awoke in the night, blood pressure rose markedly and then fell again when the subjects went back to sleep. Variability was apparently unaffected by meals. The difference between highest and lowest readings averaged 31/23 mm Hg for normotensives, 53/34 mm Hg for patients with uncomplicated essential hypertension, and 46/29 mm Hg for patients in whom hypertension was complicated by myocardial infarction, heart failure, or cerebral vascular disease. In patients with secondary hypertension, variability was 35/19, which was significantly less than in patients with essential hypertension.

Although no significant correlation was found between the level of pressure and its variability, patients with the highest pressures tended to show the least variation. In contrast, older subjects tended to exhibit little more variability than young ones. Nevertheless, these results do not permit the division of patients into those with a more labile and those with a more sustained form of hypertension, with the possible exception of secondary forms of hypertension, which may be more sustained. In this study the basal blood pressure was also recorded by the method of Alam and Smirk.[2] Basal blood pressures were never so low as those measured during sleep and were often close to the highest pressures measured during the daytime. Occasionally, basal pressure was higher than the lowest casual pressure.

A comparable study was performed by Bock and Kreuzenbeck.[11] The results of these authors are comparable to those of Richardson et al.,[41] but in their patients the nocturnal fall of blood pressure was absent. Maximum blood pressure variations were 24/14 mm Hg for normotensives, 37/16 mm Hg for patients with essential hypertension, and 43/13 mm Hg for those with secondary hypertension. None of the differences were significant. However, the patients with benign essential hypertension exhibited significantly larger variations in systolic pressure (39 mm Hg) than normotensives. In malignant hypertension, blood pressure varied by 31/10 mm Hg.

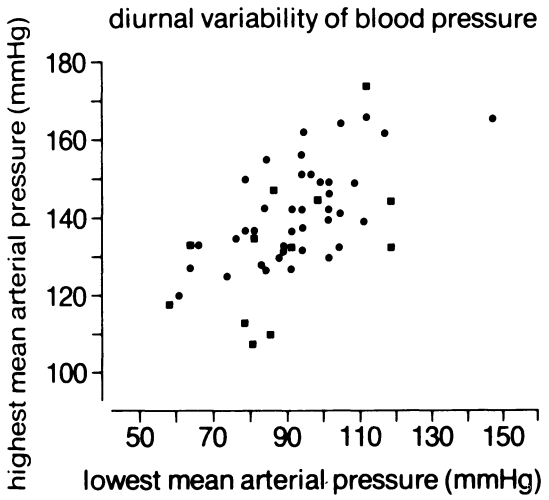


**Figure 1.** Relationship between lowest and highest blood pressures during a 24-h observation period. From Birkenhäger WH, Schalekamp MADH, ref 10

Birkenhäger and co-workers were the first to try to quantify the lability of blood pressure.[8,10,43] By use of a phase-shift oscillograph, the blood pressure was recorded at 5-min intervals for several 1-h periods during the day. Overnight blood pressure was determined at 20-min intervals from 8 P.M. to 8 A.M. Variability of blood pressure was expressed as follows: The difference between the highest and the lowest readings was expressed as a percentage of the highest. This was done for both systolic and diastolic pressure. The mean of these two percentages was termed the *blood pressure variability*. In these studies blood pressure variations ranged from 12% to 50% of the highest value. With one exception they were always greater than 20%. Only patients with uncomplicated essential hypertension were studied, and all showed peak values of blood pressure during the daytime (usually during visiting hours) and lowest values at night. A direct relationship was observed between lowest and highest mean arterial pressure (Fig. 1).

Variability as such was not related to the level of casual blood pressure (measured at noon). These results suggest that there are only gradual differences in variability between subjects with uncomplicated hypertension. No justification is found for dividing this population into subgroups with labile or fixed hypertension.

Athanassiadis et al. did a similar study in 10 normotensives, but they made recordings over 3 consecutive days and again for 24 h after 1 and 2 weeks.[5] They observed no acclimatization to the apparatus: that is, there was no trend in the direction of lower pressures or decreased range of blood pressure vari-

ation with time. The only cause of significant alterations in blood pressure was sleep. The average waking blood pressures were directly related to average sleeping pressures, which is in accordance with the findings of Birkenhäger and Schalekamp.[10] Short naps taken during the day had a much smaller effect on blood pressure than nocturnal sleep.

Schneider and Costiloe reported on five patients in whom 24-h measurements of blood pressure and heart rate were made with an automatic portable instrument.[44] This allowed study of the patients while they were home. The information given in this paper largely confirms the results of the studies cited above. Of interest is the fact that in all subjects both blood pressure and heart rate were higher during the first 3 to 5 h after waking in the morning than during the rest of the day.

Thus far we have focused on studies in which blood pressure was measured indirectly. However, during the last 15 years several reports have been published with respect to intra-arterial measurements. In particular, this has become fruitful since the development of a portable automatic apparatus capable of recording intra-arterial pressure continuously in unrestrained subjects.[6] Initially 22 subjects were studied.[7] Eight of them were normotensive, eight had uncomplicated essential hypertension, and six had essential hypertension in the malignant phase. All but four of the control subjects were hospitalized during the measurements. Systolic pressure fell significantly more during sleep in the subjects who slept at home than in the others. For diastolic pressure this was less apparent. Small fluctuations were detected for both systolic and diastolic pressure, but were more pronounced for the former. During waking hours there was somewhat more fluctuation than during sleep.

The variability of arterial pressure appeared to be larger than was suspected from indirect data. When variability was expressed in terms of percentage, similar to that described by Birkenhäger et al.,[8] systolic pressure varied by 44% to 58%. Variability of diastolic pressure ranged from 45 to 70%, those subjects with malignant hypertension showing the least variation and those with normal pressures showing the most. In absolute terms, however, changes were larger for the hypertensives than for the controls. Even in the patients with malignant hypertension, blood pressure fell during sleep.

In subsequent years the Oxford group collected extensive material from the continuous direct recording of blood pressure.[30–34] Blood pressure was studied at work, while driving, during episodes of pain, exercise, coitus, and sleep. All these studies showed intermittent rises during the day, depending on mental and physical activity, and a fall during the night. Sleep at home tended to lower pressure more noticeably than sleep in the laboratory or in the hospital.

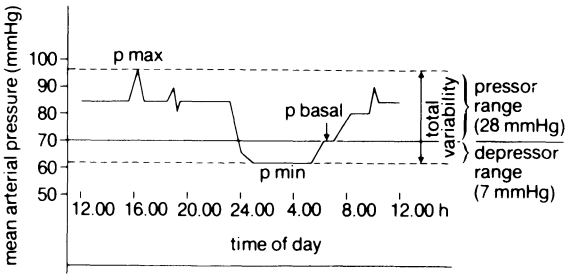


**Figure 2.** Schematic representation of the diurnal fluctuations of blood pressure. From Birkenhäger WH, Schalekamp MADH, ref. 10

Recently Birkenhäger and Schalekamp proposed a simple scheme for the computation of mean blood pressure values in an attempt to standardize blood pressure variability (Fig. 2).[10] The basal blood pressure taken immediately after waking is used as a reference. Peak blood pressures measured during the day represent pressor responses to stimuli. The maximum excursion in daytime blood pressure is noted, and the difference from the basal pressure is called the *pressor range*. Similarly, the lowest blood pressure during sleep is subtracted from the basal pressure to give the *depressor range*. The sum of both ranges is considered the total variability of mean blood pressure.

This concept was applied to 80 subjects with uncomplicated essential hypertension in whom indirect recordings were obtained over a 3-day period with an Arteriosonde.[29] Average values were as follows: 139 mm Hg for the maximum and 101 mm Hg for the minimum level of mean arterial pressure. Basal pressure was 116 mm Hg on the average. This resulted in a mean pressor range of 24 mm Hg (or 23% of basal pressure) and a mean depressor range of 18 mm Hg (or 15% of basal pressure).

## Determinants of Blood Pressure Variability

Despite a long list of publications dealing with variations in blood pressure, little attention has been paid to the mechanisms underlying the instability of pressure. As mentioned above, the most conspicuous feature of the variability is the fall of blood pressure during sleep. But there may also be considerable variations during the day, usually in response to environmental stimuli. Peak values occur in the morn-

ing and evening. No data are available relating these changes in pressure during the day to hemodynamic parameters or the activity of pressor hormones. Apparently, it is taken for granted that the episodic rises in blood pressure associated with fear, exercise, and so on are mediated by the sympathetic nervous system. Below we shall discuss several factors which might influence the pattern of 24-h variability of blood pressure, especially in relation to sleep.

## Age and Sex

There is no evidence that blood pressure is more variable in men than in women. However, age seems to alter the pattern of variability. Richardson et al. found the daily range of blood pressure variation to be slightly greater in older patients than in younger ones, though the difference was not statistically significant.[41]

In the study of Bevan et al.[7] blood pressure fell more clearly in four younger patients, but the design of that study does not permit us to conclude that this was due to age alone. No effect of age was found by Athanassiadis, but only 10 subjects aged 18 to 42 were studied.[5]

Birkenhäger et al. found variability to decrease slightly with age.[9] The components of blood pressure variability shown in Figure 2 were studied by de Leeuw[29] as a function of age. In 80 subjects with uncomplicated essential hypertension, highly significant direct relationships were found for both maximum and minimum levels of the systolic, diastolic, and mean blood pressures. In 55 of the patients basal blood pressure could be accurately measured. This variable was also directly related to age. In absolute terms the range of variation in systolic, diastolic, and mean blood pressures was not related to age, but when the ranges were expressed as a percentage of the highest reading, an inverse relationship between age and systolic and diastolic variability was found. The average of the two, called the *total variability*, also decreases with age (Fig. 3). The pressor range appeared to be inversely related to age both in absolute and in percentile terms. The depressor range increases with age, but only when this is expressed in absolute terms. Figure 4 gives the averages and standard deviations for basal, maximum, and minimum mean arterial pressures as a function of age (i.e., the mean age for each decade). The figure shows that, at least after age 40, basal blood pressure tends to increase faster with age than maximum pressure, with the result that the pressor range falls.

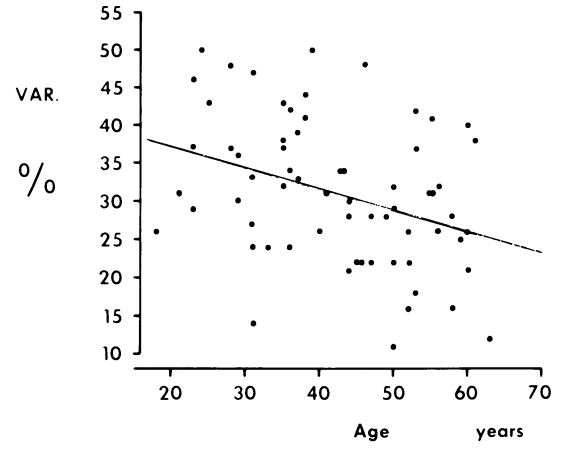


**Figure 3.** Relationship between total variability of blood pressure (i.e., average of systolic and diastolic variability) and age. From de Leeuw PW, et al., ref. 28

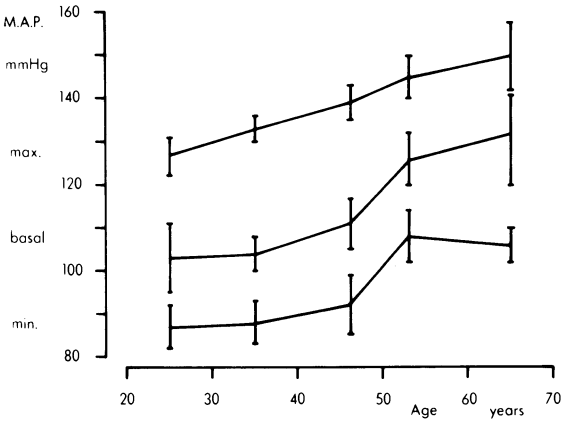


**Figure 4.** Average and standard deviation of basal, minimum, and maximum blood pressure for each decade in 55 patients with essential hypertension. From de Leeuw PW, ref. 29

A situation which has also been described for malignant hypertension is frequently seen in older subjects. While the total range of blood pressure variation does not appear to be diminished, there is less tendency for blood pressure to fall during sleep. In contrast, lowest values are often found during the day. The results indicate that in older age groups blood pressure tends to be less labile, with a diminution of pressor activity; this might be accompanied by a reversal of the normal diurnal cycle, which thus far has been demonstrated only in some hypertensive pregnancies.[40,52] It is not certain, however, that these trends are due to age per se. From a theoretical standpoint it is also possible that cardiovascular complications occur in those patients who exhibit the largest variations in pressure. Indeed, Schneider and Costiloe found marked fluctuations

in one patient with angina pectoris and a previous myocardial infarction.[44]

### Level of Blood Pressure

There is no conclusive evidence that the degree of blood pressure variability is related to the severity of hypertension or even to the presence of hypertension iteself. Although Richardson et al. noted the least variation in those hypertensives with the highest median systolic and diastolic pressures,[41] no significant correlation could be demonstrated. Ibrahim et al. found significant lability of blood pressure even in severe hypertension.[18] Most authors, however, agree that the nocturnal fall in pressure is less pronounced in more severe hypertension. De Leeuw took blood pressure measured at 10 A.M. as a reference for casual pressure.[29] Total variability (average of systolic and diastolic variability) appeared to be unrelated to 10 A.M. blood pressure when the effect of age was excluded. In contrast, a highly significant inverse relationship was observed between total variability and basal blood pressure. Sokolow et al. investigated diurnal blood pressure variations in 124 patients with mild to moderate hypertension.[49] No relationship was found with the severity of the disease.

In all, there is no sound basis for the concept that hypertension starts with a labile phase and then becomes progressively sustained.

To define the stage of hypertension somewhat differently, Birkenhäger et al. measured resting cardiac output in a number of hypertensive patients in whom 24-h variability was also determined.[8,9] Variability was directly related to cardiac output and inversely related to peripheral vascular resistance. When the observations were extended, these relations remained.[29] In the latter study no relationships were found between systemic hemodynamics and pressor or depressor range. These observations suggest that, irrespective of the level of blood pressure, an increase in vascular resistance sets limits on the lability of blood pressure.

## Mechanisms of Blood Pressure Variability

Variations in blood pressure could depend on alterations in cardiac output, peripheral vascular resistance, or both. No systematic studies have been carried out with respect to the hemodynamic basis of blood pressure variability during the day. However, when one compares average levels during the day and at night, it seems that, despite the fact that cardiac output may slightly decrease during sleep, alterations in vascular wall tone are of prime importance for the fluctuations of blood pressure.[12,24,38] When cardiac output is lowered by beta blockade, the pressor range, being a quantitative expression of the diurnal lability of blood pressure, may either decrease or increase.[27] This also indicates that vascular tone rather than myocardial function is responsible for the phenomenon of variability.

The mechanisms involved in vasoconstriction and vasodilatation are still unknown. Contrary to expectations, the pressor range bears an inverse relation to norepinephrine levels, and the same is true for variability of mean arterial pressure. Although these reactions are quite weak under basal conditions, the shift of these parameters during treatment with propranolol (Fig. 5) suggests that we are dealing with a real mechanism. This may mean that norepinephrine secretion is stimulated or inhibited (by feedback) to compensate for alterations in vascular tone induced by an as yet unidentified mechanism. Whether this is related to presynaptic stimulation of alpha receptors or to interference with reuptake cannot yet be determined. Modulation of sympathetic outflow from the central nervous system is still another possibility. In this respect the role of

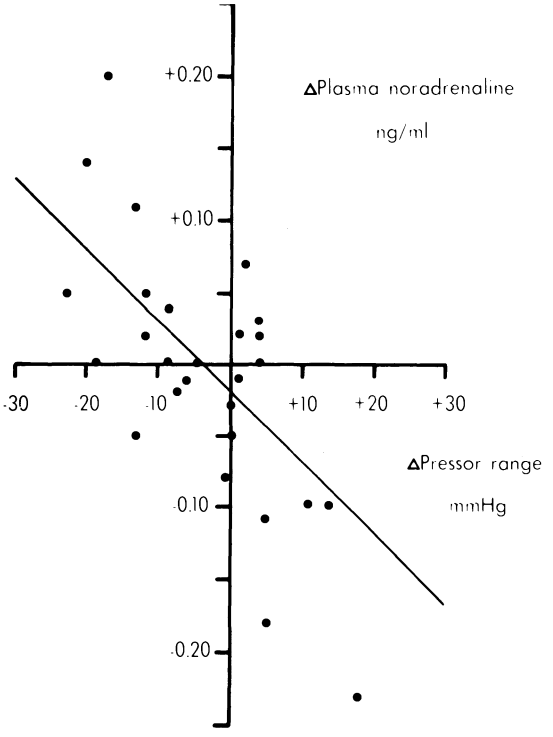


**Figure 5.** Relationship between changes in pressor range and changes in norepinephrine levels during treatment with propranolol. From de Leeuw PW, ref. 29

the baroreceptors should be considered more closely. Resetting and an increase in the sensitivity of the baroreceptors occurs rapidly and reversibly during sleep.[12] Changes in sensitivity, however, appear to be variable and seem to be most pronounced during periods of dreaming or, more accurately, during rapid eye movement (REM) sleep. This sleep phase is associated with transient increases of blood pressure, and some correlation exists between the number of rapid eye movements and the level of mean arterial pressure during the night.[48] During the REM phase blood pressure is much more variable than at other times during sleep. Sometimes both the highest and the lowest pressure levels are found in this period.

No nocturnal fall in pressure occurs in the absence of sleep, yet the degree of fall bears no relation to the depth of sleep. Rather uniformly, pressure begins to fall with the disappearance of alpha rhythm in the electroencephalogram.[39] However, the recording of the EEG itself restricts the patient, and thus the fall of blood pressure is less than in subjects without EEG monitoring.[42]

In all, little information is available at present on the exact relations between cerebral activity, sympathetic function, and blood pressure regulation during sleep.

## Significance of Blood Pressure Variability

To date, none of the studies dealing with blood pressure variability has provided any insight into the true significance of this phenomenon. While Smirk et al.[47] found that life expectancy correlated better with basal than with casual blood pressure, even the latter carries prognostic significance.[23] In addition, Sokolow et al.[49] found no correlation between blood pressure variability and the severity of hypertension or the severity of complications. Though attempts have been made to relate complications such as cardiac asthma, myocardial infarction, and stroke to specific times of the day and blood pressure changes, this matter is still far from settled.

Another problem associated with the variability of blood pressure is the transition from normotension to hypertension. Since it is impossible to draw a clear dividing line between the two ranges,[38] a number of subjects cannot be classified precisely as being normotensive or hypertensive. This has led to the concept of borderline hypertension, a condition defined differently by various authors. Many studies have been devoted to the demonstration of hemodynamic abnormalities in this group of patients. (For review, see Birkenhäger and Schalekamp.[10]) Labile hypertension was usually found in young subjects with a high cardiac output, but regardless of hemodynamics, this condition in itself is a fairly good predictor of future sustained hypertension.[21] In most instances, however, a diagnosis of borderline hypertension is based on three casual blood pressure readings. Since in most laboratories hypertensive patients are examined during the day, it is not surprising that marked lability of blood pressure (cf. pressor range) has been associated with young patients with early hypertension. Finally, blood pressure variability is something which is frequently overlooked in the assessment of antihypertensive drug therapy. Several reports indicate that treatment with a variety of drugs does not greatly alter total variability.[11,14,19,27,30,51] which makes evaluation of therapy from casual readings extremely risky.

## Summary

Despite a number of physiologic mechanisms which act to keep the blood pressure within normal limits, there is hardly a variable which changes more during the day than blood pressure. This phenomenon has been observed in both normotensives and hypertensives alike. During sleep there is a pronounced fall in pressure, which may be related to changes in brain activity. In patients with malignant hypertension this nocturnal fall is less apparent, but total variability is not much different from that in other patient groups. There is as yet no uniform quantitation of the diurnal variations in blood pressure. Such a quantitation would be desirable, however, in order to grasp the physiologic significance of this phenomenon. It could also provide an important clue for the evaluation of antihypertensive therapy.

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# Significance of Fundus Diagnosis in Arterial Hypertension

# 24

P.-D. Steinbach

Funduscopy is an important step in the comprehensive examination of a hypertensive patient. The value of this method of examination is that it allows, as nothing else, a direct, unbiased, in vivo observation of a circumscribed vascular region.

With respect to the diagnostic and prognostic value of optic fundus changes, it must be kept in mind that only vessels of a certain size, i.e., arterioles and venules, can be observed in the fundus. Clinical experience has shown repeatedly that only under certain circumstances and only to a limited degree can inferences drawn from these vessels be applied to the state of other, especially larger, vessels.

For clinical and teaching purposes, many attempts have been made to organize these symptoms into a pattern. Two main classifications are in use at present: the classification of Keith et al.[1] and Thiel's classification,[2] used primarily in the German-speaking world. Both recognize four grades (Table 1).

## Fluorescein Angiography

Besides direct and indirect ophthalmoscopy, fluorescein angiography has been available to the ophthalmologist as an additional method of examination[3,4] for over a decade. It consists of the intravital staining of the fundus vessels with sodium fluorescein. The dye is injected intravenously, reaches the optical and retinal vessels by way of the internal carotid artery, ophthalmic artery, and central retinal artery, perfuses the retinal capillaries and the arteriovenous anastomoses in the periphery of the retina, and finally leaves the eye by way of the central retinal vein and ophthalmic vein (Fig. 1a and b).

## Description of Findings

In this section we shall describe the development of optic fundus changes in hypertension according to their degree of severity. Crucial for evaluation are the changes in the arterial vessels of the retina.[22]

***Grade I.*** At first a narrowing of the smaller retinal vessels and a straightening of their course may be observed without any apparent changes in their caliber. The large arteries of the retina are often engorged and perhaps passively distended; the vascular light reflexes are still normal at first. These signs indicate incipient atherosclerosis of the retinal vessels, such as can be found after age 45 in patients without hypertensive disease. But these sclerotic changes can be observed in younger patients about a year after the onset of hypertension. Initially the process is still functional, since the narrowing is reversible.

***Grade II.*** If the high blood pressure persists, the vascular wall shows a thickening, especially of the media, accompanied by hyperplasia of the tunica elastica, manifested by a strengthening and widening of the vascular light reflex. Constriction of the vascular lumen is clinically evident as irregularities in caliber (Fig. 2a and b). Furthermore, increased tortuosity as well as engorgement of the vessels can be observed. At the sites of arteriovenous crossings, the venous lumen appears to be narrowed and even

partially interrupted (Gunn's crossing sign) (Fig. 3). However, it can be demonstrated with fluorescein angiography that this narrowing is only apparent. Seitz showed in histologic experiments that these crossing signs are due to the proliferation of adventitia and surrounding tissue at the crossings, causing the veins to be obscured at these points.[6] In the further course of the disease, small diapedetic hemorrhages may occur, and sporadic fatty degeneration may be found as well. As a consequence of these vascular changes and the resulting impairment of blood flow, the pigment cell layer of the retina is loosened in the region of the macula. These changes are not necessarily associated with hypertension; they are also observed in older, nonhypertensive patients with arteriosclerosis. If hypertensive disease is present, however, these pigment layer changes are found even in younger patients. The influence of the severity and duration of hypertension is less pronounced in the young patient, however, for the juvenile vessel can withstand elevated blood pressures for a longer period of time without damage.[7]

***Grade III.*** The severe changes in the retinal vessels and retina itself that are associated with angiospastic or hypertensive retinopathy consist of marked constriction of the arteries ("silver wire" arteries, Fig. 4) and pronounced crossing signs. Histologically, these arteries have an extremely hyperplastic wall[6] and a narrowed blood column. The entire fundus appears pale, and ischemic infarctions ("cotton-wool" exudates) appear in the retinal capillary bed (Fig. 5a and b). Hemmorhages occur in the nerve fiber layer as a result of damage to capillaries and arterioles. Lipoids are deposited, particularly in the area of the posterior optic pole, and sometimes form a "machlar star" figure (Fig. 6). Hyperemia of the papilla is observed. Cotton-wool patches develop within 24 to 48 h, appearing at first fluffy white, later becoming light gray, and eventually disappearing. If the patient goes untreated for weeks and months, fresh and old cotton-wool patches can be observed side by side.

Ophthalmoscopically, white, shiny, atheromatous plaques are sometimes found in hypertensive patients. These changes have puzzled ophthalmologists ever since Hollenhorst reported finding with remarkable frequency light, shiny, orange-colored plaques at the bifurcations of the retinal arterioles in patients with an obstructive disease of the carotid artery or basilar vertebral artery system.[8] Only by means of fluorescein angiography has it been possible to demonstrate that these plaques lie outside the artery and do not penetrate the lumen; they represent degenerative products of the arterial wall.

## Color Plates (see pages 349–350)

**Figure 1.** **a** Right optic fundus (30-year-old woman) showing functional narrowing of arteries and an omega-shaped division of the arteries. **b** Fluorescein angiogram of the same eye. The pictures demonstrate more clearly that no luminal constrictions are present.

**Figure 2.** **a** Right optic fundus showing conspicuous caliber changes and constriction of arteries and arterioles. **b** Fluorescein angiogram of the same eye. The aforementioned changes are more distinct and are visible in their full extent.

**Figure 3.** Detail of Gunn's crossing sign (the vein appears interrupted in its course by the superimposed artery). Diapedetic hemorrhages are also present.

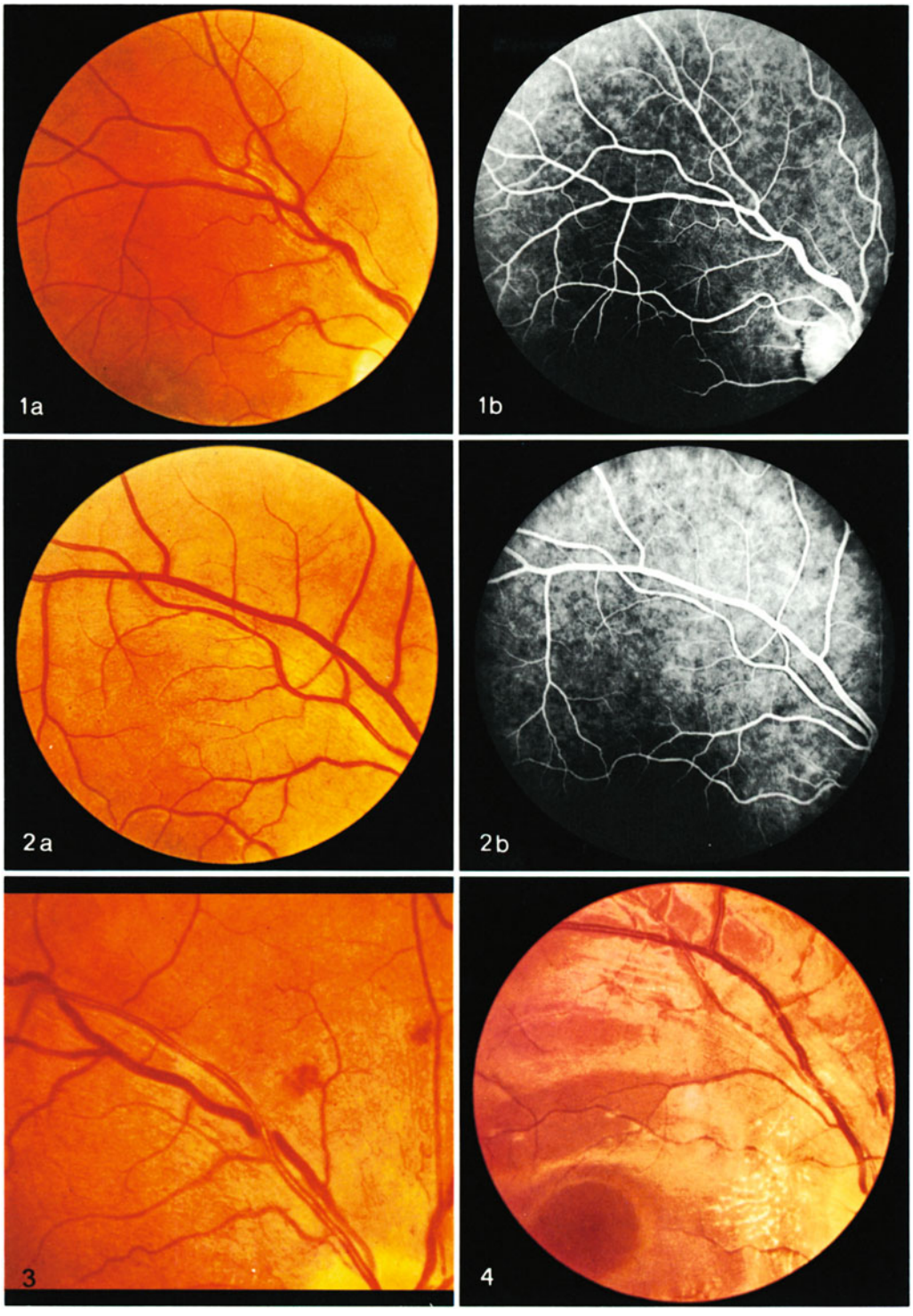
**Figure 4.** Incipient angiospastic retinopathy. Particularly conspicuous are the narrow, pale arteries and the beginning of fatty exudations between papilla and macula.

**Figure 5.** **a** Angiospastic retinopathy. Numerous white fluffy patches, the so-called cotton-wool exudates, are seen in the fundus. **b** Fluorescein angiogram of the same eye, showing the area of the cotton-wool patches. The capillary-free areas, at whose edges the dye leaks from the thickened capillaries (ischemic infarctions in the nerve fiber layer), are clearly visible.

**Figure 6.** Angiospastic retinopathy with cotton-wool patches and fatty exudation in the area of the macula.

**Figure 7.** Angiospastic retinopathy with pronounced papilledema and hemorrhages, very narrow arteries, and fatty exudations between papilla and macula.

**Figure 8.** **a** Left optic fundus with moderate arterial narrowing and widened arterial light reflex; a somewhat thickened, meandering vein, considered pathologic, is seen at the top of the picture. Ophthalmoscopically, this is a grade II fundus. **b** Fluorescein angiogram of the same eye. Besides arterial narrowing, note the pathologic changes in the capillaries, which are not restricted to the upper retinal region. On the basis of the fluorescein angiogram, this may be classified as a grade III fundus.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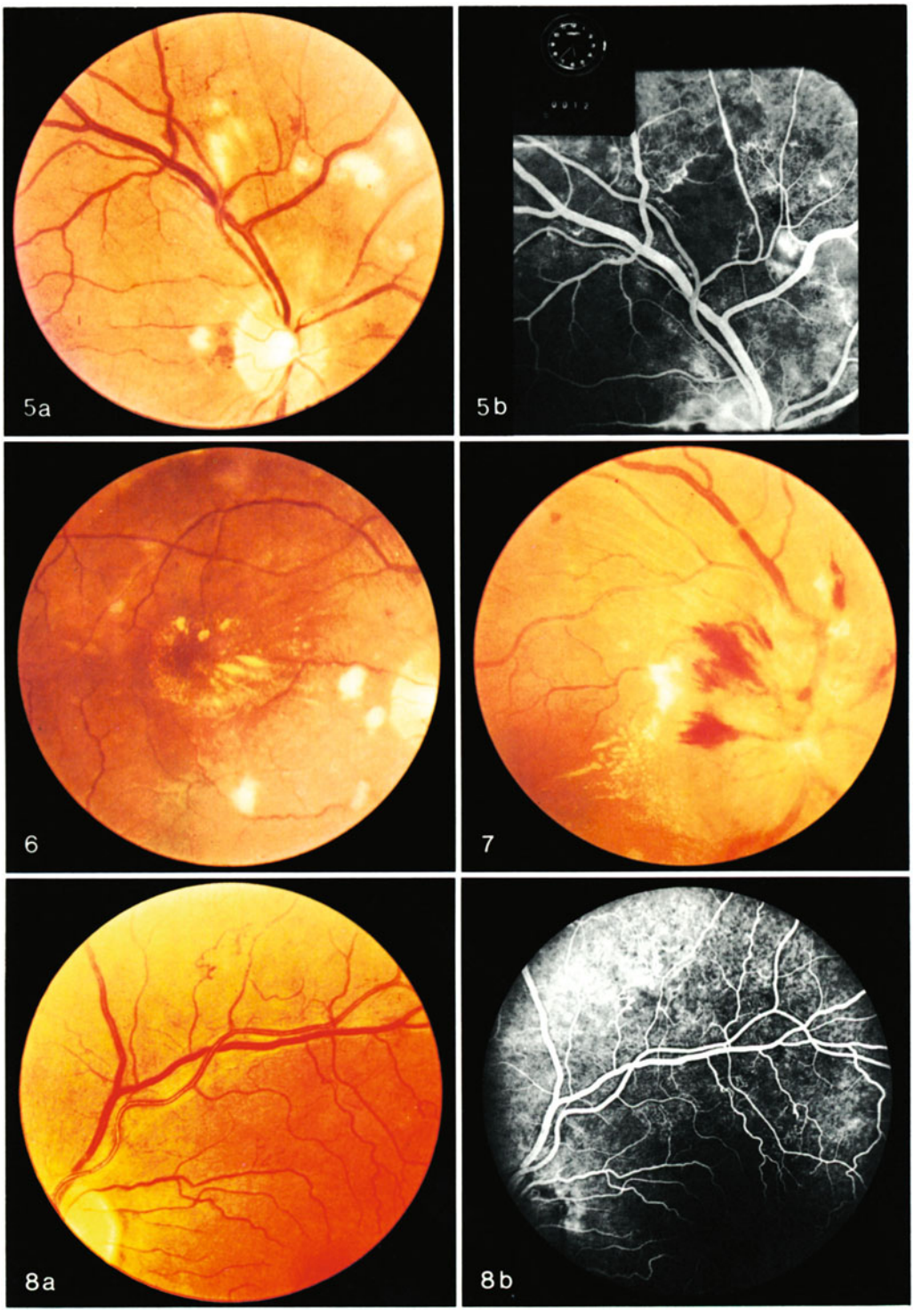
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**Table 1.** Classification of Fundus Changes in Hypertension

| Keith, Wagener, and Barker (Ref 1) | Thiel (Ref 2) |
|---|---|
| Grade I: Incipient sclerosis and narrowing of the retinal arterioles | Grade I: Deep-red coloration of the fundus. "Copper wire" arteries (engorged arteries with broad, golden-yellow reflex streaks), also engorged veins, crossing signs, corkscrewlike tortuosity of venules |
| Grade II: Moderate atherosclerosis, widened arterial light reflex; crossing signs; general or focal narrowing of the arterioles | Grade II: In addition to the changes of Grade I, varying width and opacity of the arteries, isolated small foci of fatty degeneration and clusters of retinal hemorrhages |
| Grade III: Angiospastic retinitis characterized by edema, exudates, and retinal hemorrhages; sclerotic and spastic changes of the arterioles | Grade III: Delicate papillary and peripapillary edema; constricted arteries with narrow, brightly shining reflex streaks; extreme narrowing of the arterioles. Crossing signs; veins appear "deflected and compressed." Cotton-wool exudates, very fine streaklike hemorrhages |
| Grade IV: "Measurable" papilledema present in addition to the features of grade III | Grade IV: Pale coloration of the fundus; papilledema and peripapillary edema; white degeneration patches; star configuration in the macula; silver-wire arteries; linear, punctate, and blotchy retinal hemorrhages |
| Only signs of sclerosis in the fundus are described in grades I and II. The only difference between grades III and IV is the presence of "measurable papilledema" in grade IV | |

***Grade IV.*** The development of papilledema, starting with a grayish discoloration at the temporal border of the papilla, is indicative of grade IV angiospastic retinopathy (Fig. 7). The veins appear congested and dark; the arteries are extremely narrow and often difficult to recognize owing to progressive retinal edema. There is a spastic-tonic constriction of the arteries.[9] The extent of capillary damage may be assessed by fluorescin angiography.[10] The microaneurysms may reach 100 $\mu$m in size,[11] with the largest number occurring at the edge of visible cotton-wool patches.[12]

## Prognostic Considerations

The hypertensive vascular changes develop more rapidly in women than in men (author's study of 1000 hypertensive patients). The aforementioned irregularities in caliber, the narrowing of the arterioles, and the occurrence of crossing signs and pigmentation changes in the macular area are significantly influenced by the patient's age. Moreover, the level of the blood pressure and duration of the hypertension have a major effect on the development of pathologic vascular changes. Patients under digitalis medication, and thus with a certain degree of congestive failure, were found to exhibit far more frequent and more severe changes in the retinal vessels, such as Gunn's crossing signs or even exudative retinal changes. Such patients also showed characteristic ECG abnormalities such as a depression of the ST segment and a change in the QRS vector, as well as inversion of the T wave.[23]

In determining which variables were important in the occurrence of pathologic fundus changes, it was found that sex and duration of hypertension are of less significance than the degree of blood pressure elevation, the rise in serum triglycerides, and T-wave inversion in the ECG.[13] The glucose tolerance test shows a significant negative correlation, i.e., the more severe the fundus changes, the more nearly normal the glucose tolerance. This reflects the presence of impaired renal function leading to a decrease in insulin excretion. Triglyceride determination, ECG, and the glucose tolerance test are useful tools in finding indications of changes in the retinal vessels. If these were pathologic, or if a previously pathologic glucose tolerance became normal during the course of the disease, then clear signs of sclerosis could be observed in the retinal vessels.

The accurate recognition of vascular changes, particularly those which are initially mild, has been improved by fluorescein angiography. This technique allows an accurate evaluation of the state of the vascular lumen and the presence of crossing signs. Furthermore, the morphologic state of the capillaries

may be determined, allowing early identification of areas in which complications in the retinal parenchyma, such as hemorrhages and ischemic infarctions, may occur (Fig. 5b). The dye cannot leak from a healthy vessel, so that the vessel is clearly visualized during the entire transit time (called the *retinal circulation time*). In pathologically altered vessels, however, the dye extravasates because of its low molecular weight and stains adjacent tissues. The clear visualization of even the smallest retinal capillaries in hypertensive patients also reveals microaneurysmal dilatations of the capillary network, which previously were deemed especially typical of diabetic retinopathy. While such lesions are more frequent and extensive in this form of retinopathy, hypertensives with only moderate caliber changes of the retinal arteries also show capillary dilatation, microaneurysms, and isolated capillary destruction in many cases (Fig. 8a and b). As a result, reactive changes leading to hemorrhages and vascularization are not infrequent. Thus, microaneurysms and capillary destruction are evidence of severe injury to the capillary network and indicate the sites of predilection for later hemorrhage and necrosis.

In younger patients these capillary changes occur only after a long history of hypertension with high blood pressure values, while in older patients they can be demonstrated as early as 1 year after the onset of hypertension, as is also the case for changes in the retinal pigment of the macula.[7] With remarkable frequency, an incipient macular degeneration can be demonstrated in juvenile hypertensives even in the presence of mild retinal vascular sclerosis; the incidence and extent of the macular changes increase sharply with the patient's age. It can thus be concluded that, besides sclerosis of the retinal vessels, there must also be marked sclerosis of the choroidal vessels in hypertension, whose deficient blood flow causes disruption of the choroid capillary layer and degeneration of the pigment layer and sensory epithelium of the retina, which are nourished by the choroid capillary layer. The choroid vessels may even show more severe sclerotic changes in hypertension than the retinal vessels, as Marquardt indicated in 1968 on the basis of histologic studies.[14]

With the appearance of cotton-wool patches and flame-shaped hemorrhages, a benign hypertension may progress to a malignant one. While formerly the prognosis was unfavorable with the onset of angiospastic retinopathy, Heydenreich reporting in 1967 a life expectancy of 5 years on the average,[5] Hany et al. reported that 50% of treated hypertensive patients were still alive after 5 years.[15] Progress in modern therapy has improved life expectancy to a significant degree.[16,17]

## Reversibility of Hypertensive Changes

While the spastic changes of the arterioles are reversible,[18] the organic vascular changes, such as Gunn's crossing signs, are not.[19]

According to the observations of Hill and Dollery, the narrowed arterioles may dilate again with adequate antihypertensive treatment.[20] The large, passively distended, sclerotic arteries become narrower after the arterial pressure is lowered.[21] Such regressions, however, are found almost exclusively in young patients with a short history of the disease.

Secondary changes, such as hemorrhages and fatty exudations, disappear after treatment. While ophthalmoscopic findings show a regression of microaneurysms and cotton-wool patches, the consequences of these changes may be demonstrated later by fluorescein angiography. Papilledema also regresses after a few months of treatment. If the changes are present for only a short time, as in toxicosis of pregnancy, the pathologic changes disappear soon after normalization of the blood pressure.

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# Basic Investigation of the Hypertensive Patient

25

A. Distler

## Cost-Effectiveness Considerations

A large number of methods have been developed to detect the cause of hypertension, some of which are costly or potentially hazardous. With the enormous number of hypertensives in the industrial countries, attempts have to be made in practice to attain a reasonable relation between expenditure of money (and of time) and effectiveness. All reflections on rationalization of the diagnostic procedure must take into account that secondary forms of hypertension amount to a maximum of only 10 to 15% of all cases of hypertension. Among a total of 4939 patients with hypertension examined in the Cleveland Clinic during 1966–1967, specific therapeutic interventions were potentially available for only 5.9% of hypertensives and were apparently applied in 2.8% or less.[6] The cost-effectiveness analysis of an extensive diagnostic program is thus inevitably unfavorable in view of the small propotion of specifically curable forms of hypertension. This is illustrated by an analysis by McNeil and Adelstein[10] according to which the cost for the diagnosis of a renal artery stenosis using intravenous pyelography as the screening method was $2000 and the costs for surgical correction of a renal artery stenosis ranged from $11,800 to $33,800 per patient, depending on age, sex, and diagnosis (fibromuscular hyperplasia or atherosclerotic stenosis). These cost-related considerations naturally do not apply to secondary forms of hypertension, such as coarctation of the aorta, Cushing's syndrome, or contraceptive-induced hypertension, which can be discovered by simple examinations.

The advantages of a specific therapy should not be overlooked. With successful specific therapy, the patient does not need to take drugs for the rest of his or her life. Side effects due to the drugs are not to be feared, and the reliability with which the drugs are taken is unimportant. However, the available alternative of drug therapy for hypertension, which can be used in almost all cases, makes it unnecessary to adopt screening programs that can detect all secondary forms of hypertension. The average costs of lifelong drug therapy are very much lower than the estimated costs for detection and successful surgery of renal arterial stenosis.[11]

The current widespread enthusiasm in searching for secondary types of hypertension in all hypertensives is no doubt supported by the insurance companies' practices, which (especially in the United States) often provide full coverage for hospitalization and surgical expenses while paying for none or only part of ambulatory services and costs for lifelong antihypertensive therapy.

Rethinking will doubtless become necessary here in the future in order to keep the financial expense in combating hypertension within justifiable limits.

## Aims of Basic Investigation

The aims of the basic diagnostic evaluation of hypertension are:

1. To detect secondary causes of hypertension, in particular those amenable to specific therapy
2. To assess the extent of organ damage secondary to the hypertensive process as well as to detect other cardiovascular risk factors
3. To establish the state before therapy by making a record of symptoms and of laboratory status to aid in the detection of side effects due to therapy

**Table 1.** Recommendations of the Joint National Committee on Dectection, Evaluation, and Treatment of High Blood Pressure

| |
|---|
| Medical history |
| Physical evaluation |
| Two or more blood pressure measurements (one standing) |
| Height and weight |
| Funduscopic examination (especially important in persons with diastolic blood pressure of 110 mm Hg or higher) |
| Examination of the neck for thyroid enlargement, bruits, and distended veins |
| Auscultation of the lungs |
| Examination of the heart for increased rate, size, precordial heave, murmurs, arrhythmias, and gallops |
| Examination of the abdomen for bruits, large kidneys, or dialtation of the aorta |
| Examination of the extremities for edema, peripheral pulses, and neurologic deficits associated with stroke |
| Basic laboratory tests |
| Hematocrit |
| Urinalysis for protein, blood, and glucose (dipstick) |
| Creatinine and/or blood urea nitrogen |
| Serum potassium |
| Electrocardiogram |
| Other tests which may be helpful include a chest X-ray, blood sugar, serum cholesterol, serum uric acid, microscopic urinalysis, and blood count. Clinical judgment or abnormal findings obtained during the routine evaluation may suggest other tests, such as an intravenous urogram and urinary catecholamines. |
| *Comment:* In view of the rarity of the specific recognizable causes of high blood pressure, coupled with both the cost in dollars and the small but real risk to the patients of certain diagnostic procedures, it is recommended that all routine pretreatment work-ups be limited to defining the severity of the blood pressure and to identifying its complications and associated cardiovascular risk factors. |
| More complex diagnostic procedures designed to discover specific causes of high blood pressure, such as primary aldosteronism, renovascular disease, or pheochromocytoma, can be reasonably reserved for those subjects (1) in whom routine history, physical examination, or the recommended laboratory findings suggest one of the specific recognizable causes; (2) who are under the age of 30, since they have the greatest prevalence of correctable secondary high blood pressure; or (3) in whom drug therapy proves inadequate or unsatisfactory. |

From Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, ref 12.

In recent years, expert committees in different countries have elaborated recommendations for the basic diagnostic evaluation of hypertensive patients. Table 1 shows an abridgment of the recommendations of the American Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[12] The diagnostic basic program proposed by the American Joint National Committee is less extensive than that suggested by the German League against High Blood Pressure,[2] which is shown in Table 2.

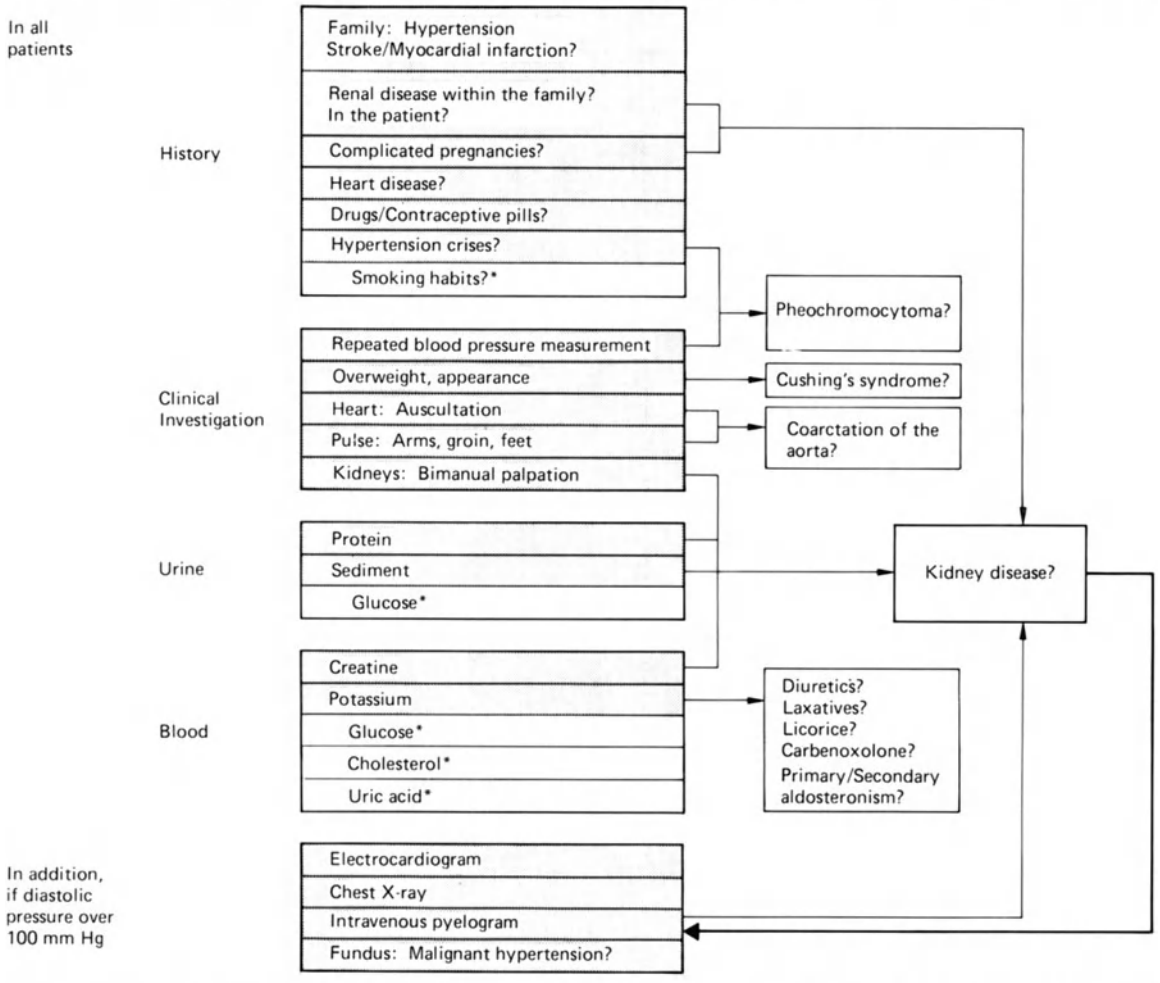
## Supplementary Comments on the Basic Diagnostic Program

### History

***Family History.*** High blood pressure or sequelae of hypertension such as stroke and myocardial infarction can frequently be demonstrated in the parents, grandparents, brothers and sisters, or children of patients with essential hypertension. However, even in patients with hypertension resulting from renal artery stenosis or chronic pyelonephritis, an increased incidence of hypertensive conditions in the family has been observed. Pheochromocytoma can likewise occur in familial forms. Survey of the family history in hypertensives accordingly provides important information on a possible hereditary predisposition. However, differential diagnostic conclusions with regard to the genesis of the hypertension cannot be drawn from the family history.

***Previous Diseases.*** It is important to establish how long elevated blood pressure values have been known, what the highest blood pressure value has been, what treatment had been previously given, whether the patient had gone through previous kidney diseases, the course of any pregnancies (indications of pyelonephritis or EPH toxemia of pregnancy?). It is also important to establish whether

**Table 2.** Recommendations for Basic Investigation of the Hypertensive Patient ofthe German League against High Blood Pressure (1980)




*Not required for diagnostic evaluation of hypertension; however, recommended for detection of additional cardiovascular risk factors.

complications of hypertension, such as stroke, cardiac insufficiency, angina pectoris, or myocardial infarction, have already occurred.

***Occupational and Social Situation.*** Since environmental factors can influence the blood pressure, knowledge of the occupational and private situation of the hypertensive patient (nature of the occupation, satisfaction, disappointment, or excessive demands at work, economic difficulties, living conditions, marriage and family conditions, sexual problems) is indispensable for the investigator.

***Medication.*** Since certain drugs can induce hypertension, a meticulous recording of the medication history is important. In particular, the patient must be asked about the use of contraceptive pills or other drugs or substances which may induce hypertension (e.g., carbenoxolone, licorice, steroids, indomethacin) or can induce potassium deficiency (e.g., saluretics, carbenoxolone, licorice, laxatives). In addition, inquiries should be made with regard to possible analgesic abuse (which might cause analgesic nephropathy). Since cigarette smoking is an additional cardiovascular risk factor, smoking habits should also be noted.

## Symptoms

The symptoms presented can provide important information on the nature and severity of a hypertensive condition. According to a study of Bechgaard,[1]

the following symptoms are found in patients with hypertension of more than 10 years' duration:

| | % |
|---|---|
| Exercise dyspnea | 42 |
| "Nervousness" | 35 |
| Palpitations | 32 |
| Dizziness | 30 |
| Precordial pain of general nature | 26 |
| Typical angina pectoris | 7 |
| Headache | 23 |
| Depression | 7 |
| Resting dyspnea | 4 |
| Epistaxis | 3 |

It is evident that none of the symptoms listed is specific for hypertension. All these symptoms can also be observed in normotensives. Conversely, a large number of hypertensives do not display any symptoms at all.

### Clinical picture in pheochromocytoma

Patients with pheochromocytoma frequently display a relatively typical clinical picture (Table 3) which is particularly suggestive when such symptoms occur episodically.

### Symptoms in primary aldosteronism

The typical symptoms of patients with primary aldosteronism (Table 4) are attributable to the potassium deficiency. Similar symptoms may develop in potassium deficiency of any etiology. Other forms of hypertension, especially essential and renal hypertension, do not lead to a specific clinical picture.

## Physical Examination

***Blood Pressure Measurement.*** Except for excessively raised values, the diagnosis "hypertension" should never be made on the basis of a single measurement of blood pressure. It is a well-known fact that blood pressure readings at the first visit to the physician are frequently higher than in later follow-up examinations. The presence of chronic hypertension is to be assumed only when the blood pressure displays unequivocally raised values in at least three measurements on two different occasions. At least two blood pressure measurements should be performed at each visit to the physician and the values obtained should be averaged. Initially, the blood pressure should be determined in both arms. In further measurements, measurement on the arm in which the higher blood pressure was identified is suf-

**Table 3.** Symptoms in 76 Patients with Pheochromocytoma

| | Approximate Percent | |
|---|---|---|
| | Paroxysmal Hypertension (37 Patients) | Persistent Hypertension (39 Patients) |
| Symptoms presumably due to excess catecholamines and/or hypertension | | |
| Headaches (severe) | 92 | 72 |
| Excess sweating (generalized) | 65 | 69 |
| Palpitations ± tachycardia | 73 | 51 |
| Anxiety or nervousness (± fear of impending death; panic) | 60 | 28 |
| Tremulousness | 51 | 26 |
| Pain in chest and/or abdomen (usually epigastric) and/or lumbar regions and/or lower abdomen and/or groin | 48 | 28 |
| Nausea ± vomiting | 43 | 26 |
| Weakness, fatigue, prostration | 38 | 15 |
| Weight loss (severe) | 14 | 15 |
| Dyspnea | 11 | 18 |
| Warmth ± heat intolerance | 13 | 15 |
| Visual disturbances | 3 | 21 |
| "Dizziness" or faintness | 11 | 3 |
| Constipation | 0 | 13 |
| Paresthesia or pain in arms | 11 | 0 |
| Bradycardia (noted by patient) | 8 | 3 |
| Grand mal | 5 | 3 |

From Manger WM and Gifford RW, ref 9.

**Table 4.** Symptoms in 103 Patients with Primary Aldosteronism.

| | % |
|---|---|
| Muscle weakness | 73 |
| Polyuria (nocturia) | 72 |
| Headache | 51 |
| Polydipsia | 46 |
| Paresthesias | 24 |
| Visual disturbance | 21 |
| Intermittent paralysis | 21 |
| Tetany | 21 |
| Fatigue | 19 |
| Muscle discomfort | 16 |
| No symptoms | 6 |

From Conn JW, Knopf RF, Nesbit RM, ref 4.

ficient. Differences in blood pressure between the right and the left arm can be evaluated diagnostically only when they constantly exceed 20 mm Hg systolic or 15 mm Hg diastolic. If the foot pulse appears to be weakened, blood pressure should also be taken in the leg. In the first investigation as well as in control check-ups under therapy, a measurement of blood pressure after standing for several minutes should be done in addition to the measurement in the sitting position in order to detect orthostatic reactions.

***Procedure in Borderline Hypertension.*** If in a patient occasionally slightly raised and sometimes normal blood pressure values are registered in multiple blood pressure readings on different days, the presence of a "borderline hypertension" can be assumed. A true chronic hypertension eventually develops only in some of these patients: data in the literature on the proportion vary substantially (see literature review in ref. 8). However, since a transition to chronic hypertension is not to be feared in the majority of patients with borderline hypertension, there is no general necessity for a detailed diagnostic clarification of the labile blood pressure elevation in this patient group.

If doubt as to whether a chronic or merely an intermittent raised blood pressure is present still remains even after multiple blood pressure readings on different days, an attempt can be made to obtain additional information by taking the blood pressure in the domestic environment of the patient performed by a member of the family or by the patient (e.g., blood pressure measurements in the morning and evening over a period of 2 weeks).[5]

When there is certainty that merely a borderline hypertension is present, patients under 35 years old should be summoned for control measurements of blood pressure at least once a year, and patients over 35 years old at least twice a year.[7]

***Nutritional State.*** Since obesity can unfavorably influence the blood pressure, the determination of height and weight has particular importance in adipose patients for documentation of the overweight.

***Clinical Examination.*** Special attention has to be paid to the investigation of the heart as well as auscultation and palpation of the large vessels and arteries of the limbs.

The following causes of hypertension can be at least suspected on the basis of the physical examination: Cushing's syndrome ("moon" facies, "buffalo" hump, striae rubrae); coarctation of the aorta (difference in blood pressure between the arms and legs, typical auscultatory finding over the heart); renal artery stenosis (a vascular murmur can be auscultated in about 50% of the cases in the epigastrium or in the region of the renal hili); and polycystic kidney disease (typical palpatory finding).

The physical examination, moreover, reveals sequelae of the hypertension or manifestations of arteriosclerosis (e.g., left ventricular hypertrophy, cardiac insufficiency, stenotic murmurs over certain vessel areas such as the carotids, lack of foot pulses) which may already have occurred.

## Urinalysis

The minimum program includes an analysis of fresh morning urine for protein and formed elements. If proteinuria is discovered, a quantitative determination of protein excretion in 24-h collected urine should be performed.

## Blood Tests

***Serum Creatinine.*** To detect impaired renal function determination of the serum creatinine level is appropriate because of its close correlation with the glomerular filtration rate and its independence of dietary protein intake. Determination of serum urea or urea nitrogen concentration is to be recommended only when the serum creatinine levels are markedly raised.

***Serum Potassium.*** Hypokalemia may be the first indication of the presence of primary aldosteronism or of another rare form of mineralocorticoid hypertension. However, the most frequent cause of hypokalemia in hypertension is a prior saluretic medication. Saluretics must therefore be discontinued at

least 14 days before determination of the serum potassium level. This also applies to potassium-sparing diuretics and aldosterone antagonists, since a raised or false normal serum potassium level can occur under administration of these drugs. Taking of laxatives, licorice, or carbenoxolone can likewise lead to hypokalemia.

***Additional Blood Work*** Parameters which are not necessary for diagnosis of hypertension, but which are to be recommended for detection of further cardiovascular risk factors or to establish the initial status before therapy, include the determination of blood glucose (fasting or 2 h postprandial), cholesterol, serum triglycerides, and uric acid.

## Urography

The question as to whether excretion urography should be applied routinely in the diagnostic evaluation of hypertension is controversial. Thus the German League against High Blood Pressure recommends a urogram in all patients with diastolic blood pressure values over 100 mm Hg, whereas, for example, the American Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure[12] does not consider this a routine measure (see above).

The intravenous pyelogram enables detection of unilateral or bilateral shrunken kidney, alterations of the renal cavity system, of cysts, tumors, urinary tract obstruction, etc. Furthermore it can provide indirect indications of the presence of a unilateral renal artery stenosis.[3] With regard to the rare occurrence of renal artery stenoses or a unilateral shrunken kidney, which can be potentially treated by surgery or by catheter dilatation, it must be borne in mind that the result of intravenous pyelography leads to direct therapeutic consequences only in very few cases. The relatively high costs, the substantial time expenditure for physician and patient as well as the radiation exposure of the patient are weighty objections to the routine use of the urogram.

If the decision to perform an intravenous pyelogram is deferred, *ultrasonography examination* can be considered as an orientative morphologic investigation of the kidneys. It may also provide important information on kidney size, shape, cavity system, stones, cysts, etc.

Urography is to be preferred to *isotope nephrography,* since the former has the same accuracy with regard to the detection of a unilateral renal artery stenosis. In addition, it provides abundant further information on kidney position, size, morphology of the renal cavity system, cysts, etc. *Renal scintigraphy* is also inferior to urography in the diagnostic information it provides. Isotope nephrogram and renal scintigraphy should therefore be used in the context of basic diagnostics of hypertension only in patients with contrast medium intolerance.

## Determination of the Catecholamine and Metanephrine Excretion

Routine determination of the catecholamine and/or metanephrine excretion was not included in the basic program for reasons of cost. However, if the presence of a pheochromocytoma is suspected (50% of the patients with pheochromocytoma exhibit a chronic hypertension!) on the basis of typical history (see Table 3) or an especially labile blood pressure, then it becomes necessary to determine the metanephrine or catecholamine excretion or the plasma catecholamines.

## Investigations to Detect Hypertensive Organ Damage

Apart from the physical examination and the determination of serum creatinine levels already mentioned, the *electrocardiogram,* the chest *X-ray examination,* and the *funduscopic investigation* are suitable methods to establish whether organ damage due to hypertension is already present.

***Electrocardiogram.*** The ECG investigation primarily serves to detect left ventricular hypertrophy. The accuracy of the electrocardiogram with regard to the detection of left ventricular hypertrophy is greater than that of a chest X-ray examination. Patients with "definite" electrocardiographic signs of left ventricular hypertrophy (high R waves in the left precordial and low S waves in the right precordial recordings associated with lowering of the ST segment and flattening or inversion of the T waves) display a three times higher risk of clinically manifest coronary heart disease than hypertensives without corresponding ECG changes.[8]

***Chest X-ray Examination.*** The chest X-ray provides information on the presence of left ventricular hypertrophy or dilatation. Pulmonary congestion due to left ventricular failure or (as an indication of an aortic isthmus stenosis) rib lesions can be discovered in addition.

***Funduscopic Examination.*** It is especially important to detect alterations of the fundus of the eye, such as hemorrhages, exudates, and papilledema. These alterations can easily be diagnosed by any physician with the speculum.

## Conclusions

Besides providing (although incomplete) diagnostic evaluation of hypertension, the basic program which has been sketched also enables at the same time the detection of the degree of severity and possible complications of the hypertension as well as the discovery of further cardiovascular risk factors. If the suspicion of a secondary and, in particular, potentially surgically curable form of hypertension is revealed by the basic program, further investigations which are reserved for appropriately equipped special outpatient departments and clinics are necessary provided that therapeutic consequences are to be expected on the basis of the age and the general condition of the patient.

The following can be regarded as indications for further special diagnostics:

1. *Forms of hypertension which potentially can be cured by surgery:*
   Suspicion of pheochromocytoma (typical symptoms; especially labile blood pressure behavior)
   Suspicion of Cushing's syndrome ("moon" facies, "buffalo" hump, striae rubrae)
   Suspicion of mineralocorticoid hypertension (key symptom: hypokalemia)
   Suspicion of unilateral renal artery stenosis (vascular murmur in the abdomen; indirect indications in the iv pyelogram)
   Unilateral shrunken kidney (corresponding finding in the urogram or ultrasonogram)
   Suspicion of coarctation of the aorta (blood pressure difference between the arms and legs; typical auscultatory finding over the heart)
2. Suspicion of renal parenchymatous hypertension (proteinuria, erythrocyturia, cylindruria, elevation of the serum creatinine level, pathologically altered urogram)

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# Laboratory Diagnosis in Hypertension

# 26

H. Wernze

## Introduction

Laboratory studies are indispensable for the differentiation of the various forms of hypertension. With the introduction of new methods, most notably radioimmunoassay, the diagnostic possibilities for the identification of endocrine forms of hypertension have been significantly expanded. The application of these procedures has been broadened greatly by kits offered by pharmaceutical companies and is therefore no longer restricted to specialized laboratories. Extensive and nonspecific analytical methods need not be employed in every form of hypertension, however. In the majority of hypertensive patients, particularly the elderly, it is not necessary to carry out an extensive program of analytical laboratory tests based on differential diagnostic and therapeutic considerations. The dilemma of laboratory diagnosis lies in the lack of reliable, simple methods for identification of the frequently occurring primary (essential) hypertension. As a result, the necessary differentiating laboratory tests are neglected or applied insufficiently in the rare secondary forms of hypertension which sometimes are amenable to causal therapy. Findings of blood chemistry and urinalysis may offer valuable indications not only for differentiation but also for evaluating the course of hypertension with manifest or imminent complications of the primary disease. But knowledge of the methodological assumptions relating to the patient, and especially of the sometimes complicated and sensitive techniques, should be thorough enough to enable the physician to avoid being misled by erroneous laboratory results. For practical purposes, it seems advisable to differentiate between (1) a *standard program of simple analytical laboratory tests,* and (2) *special endocrine studies for specific problems.*

## Standard Laboratory Tests

### Preliminary Note

Selected tests of urine and blood chemistry are carried out in hypertensive patients for the following purposes:

1. Identification or exclusion of renal function impairments to rule out secondary forms of hypertension in congenital anomalies and inflammatory and (rarely) malignant or postrenal (urologic) diseases of the kidneys
2. Recognition of metabolic diseases that are frequently associated with primary hypertension and may cause the hypertension to become complicated by diabetes, gout, hyperlipemia, etc.
3. Detection of hypermineralocorticoid hypertension by systematic screening of the electrolyte metabolism (potassium!) so that specific endocrine studies can be employed
4. Evaluation of the development of organ damage (kidney) in every case of longstanding hypertension
5. Control of possible side effects of antihypertensive therapy
   a. Salidiuretics: hypokalemia, hyperuricemia, hyperglycemia
   b. Antikaliuretics: hyperkalemia, elevation of serum creatinine and urea

At least in the initial examination of a hypertensive patient, the following standard laboratory tests should be available for total evaluation based upon a mosaic of case history, clinical work-up, and radiologic and radioisotope findings. The evaluation of largely nonspecific laboratory results must always take into account hypertension-independent coexisting diseases, a consideration that makes the diagnostic task even more difficult, especially in older patients.

## Blood

### Potassium and sodium

The flame-photometric analysis of *potassium* is methodologically simple (automatic evaluation) and reliable with the routine use of gauging standards. *Hypokalemia* may become a diagnostic milestone in untreated hypertensive patients, with the need to take into account all forms of endogenous hypermineralocorticoid syndrome or exogenous intake of mineralocorticoid-like substances (carbenoxolone, glycyrrhinicic acid). The following points are crucial for a correct evaluation of $K^+$ alterations:

1. Not only clearly hypokalemic values (<3.3 mEq/liter) but also low-normal values are of importance.
2. Owing to inconstancy of $K^+$ alterations, several (five to seven!) measurements should be carried out.
3. Hypokalemia may also be encountered in accelerated (malignant) hypertension with secondary hyperaldosteronism.
4. Drug-induced hypokalemia (salidiuretics and their combination products) represents the most frequent cause in hypertensive patients.
5. The hypokalemic tendency is aggravated in primary aldosteronism by the administration of NaCl (200–300 mEq $Na^+$ over 3 to 5 days) and may be utilized diagnostically.
6. Hypokalemic states of different origin may coincide with hypertension in terms of time but not of cause.

*Hypercalcemia* may be indicative of renal failure or may be attributable to an overdose of antikaliuretics (spironolactone, triamterene, amiloride).

The analysis of serum *sodium* (by flame photometry) is less conclusive in the differential diagnosis of hypertension. A tendency toward elevated $Na^+$ levels or *hypernatremia* (rarely observed) is indicative of primary hyperaldosteronism. *Hyponatremia* occurs in advanced (malignant) hypertension and is the result of increased renal sodium losses or a sign of universal cell damage (nonuniform distribution). High doses of spironolactone or salidiuretics (rarely) may lead to hyponatremia.

### Calcium

Blood screening for *hypercalcemia* should be carried out in every patient with established hypertension to detect or to exclude primary hyperparathyroidism (pHPT). According to newer findings[95] deterioration of calcium homeostasis may lead to hypertension directly and does not exclusively follow PHT-induced renal failure due to nephrolithiasis and nephrocalcinosis. Borderline values should be repeated under limited fluid intake to unmask hypercalcemia. Analysis (total calcium) can be performed either by flame photometry, titrimetry, or atomic absorption spectrophotometry.

### Creatinine

The determination of serum creatinine is the most important test for the detection of impaired glomerular function and for the follow-up of a manifest renal failure. Serum creatinine, as opposed to urea, is almost independent of the protein balance. There is a close correlation between serum creatinine and the creatinine clearance, but an elevation of creatinine occurs only when clearance falls below 40% to 50% of normal. Thus, normal values do not preclude discrete to mild disturbances of renal function, and so the endogenous creatinine clearance (Cl), expressed as

$$Cl_{creat} = \frac{urine_{creat} \times urine_{vol}}{plasma_{creat}} \text{ ml/min}$$

is more predicative.

The creatinine determination may be influenced by the presence of reducing substances; automatic colorimetry yields reliable results owing to the time-dependence of the Jaffé color reaction (picric acid). Increased serum bilirubin interferes with the analysis and cannot be corrected adequately.

### Urea

Elevated plasma urea levels may represent an increased residue from protein metabolism (catabolism), or may stem from a high-protein intake as well as a reduced renal excretion. Thus, extrarenal factors play such a major role that the urea assay can hardly be considered a reliable measure of renal function. Test sticks permit a qualitative or (with prolonged incubation) semiquantitative estimation of elevated urea concentrations. Accurate quantitative determinations are possible with the urease method using manual or automatic evaluation.

### Uric acid

Uric acid levels are of little importance as a measure of renal function. For evaluation of hyperuricemia due to gout, a 4-day purine-free diet must precede the study. It must be borne in mind that hyperuricemia not related to gout may be induced by abnormal cell destruction (leukemia, polycythemia, treatment with cytostatics plus radiation therapy) and even more frequently by drugs (saluretics) or fasting. An enzymatic color test is available for analysis.

### Glucose

The quantitative analysis of blood glucose concentrations is carried out by specific hexokinase reaction. Immediate qualitative determinations by test sticks are available. These sticks can also be used with the test stick photometer for quantitative results.

### Cholesterol and triglycerides

The quantitative determination of cholesterol by color reaction is a very delicate procedure (temperature, dampness affect it). The enzymatic and specific color tests yield values lower by an average of 30 mg per 100 ml. The spectrum of differential diagnosis must be considered in all states of hypercholesterolemia. No drug is known to interfere with the enzymatic color test. The determination of triglycerides requires the breakdown of glycerine esters, whereupon the glycerine can be reliably measured in an enzymatic reaction via NADH. Blood samples should be drawn after 12 h of fasting and alcohol abstinence.

### ESR electrophoresis and total protein

Determinations of erythrocyte sedimentation rate (ESR) and total protein, as well as the preparation of an electrophoresis diagram, are employed as exclusion tests in the diagnosis of hypertension. They should not be omitted, nevertheless, at least in the absence of earlier results.

### Quantitative and morphologic blood status

Each routine examination should include the determination of hemoglobin, red blood cell count, white blood cell count, and differential WBC in order to recognize typical signs of inflammatory processes or anemia of renal origin.

## Urine

### Urine concentration

Measurement of the specific gravity by aerometer is still an acceptable method, as long as reading errors (foam) are avoided. False readings caused by temperature and especially by sugar and protein excretions—and their correction—have to be kept in mind. A possible elevation of specific gravity by renally excreted X-ray contrast media (up to 1050!) must be considered, but cannot be corrected. Determination of urine osmolarity requires too great an investment of equipment and time for routine examinations.

### pH value

The urinary pH can be reliably measured with test sticks; electrometric measurement is unnecessary.

### Protein

The qualitative demonstration of proteins in the urine by sulfosalicylic acid covers concentrations of 15 mg/liter; a physiologic proteinuria (up to 50 mg/liter may cause opalescence. False-positive results caused by a number of drugs are well known. The reliable boiling test has been almost totally replaced by many highly specific test sticks (albumin), but the semiquantitative assessment remains inexact. The biuret method (photometric analysis) can be used for quantitative measurements of protein excretion. Electrophoretic studies of urinary proteins go beyond the basic program for the diagnosis of hypertension.

### Glucose

For specific enzymatic glucose identification (glucose oxidase, peroxidase), test sticks may generally be considered the method of choice. The semiquantitative assessment is quite reliable with some experience and correct handling.

### Electrolyte analyses

The quantitative (flame photometric) measurement of sodium and potassium in the 24-h urine is of no practical importance in the diagnosis of hypertension. Even when dietary intake is constant in electrolyte composition (as assessed by nutrition tables), large differences in the excretion of various electrolytes can be seen.[8] The precise collection of 24-h urine specimens from many patients is always difficult. Assessment of increased mineralocorticoid activity solely by measuring the Na/K ratio in random urine samples is completely unreliable.

### Cellular and other structural elements

A prerequisite for the qualitative assessment of the urinary sediment is a freshly voided urine (morning midstream urine) no more than 3 h old. While *epithelial cells,* some *leukocytes,* and even *erythrocytes* may also be found under physiologic conditions, a marked accumulation of leukocytes and erythrocytes is pathologic. For borderline results or

for course studies, it is advisable to count the number of cells in the counting chamber, referring to an exact period of urine collection, as recommended by Addis. Normal values: up to 3 million erythrocytes per 24 h up to 5 million leukocytes per 24 h. *Hyaline casts* are indicative of inflammatory renal disease but may also occur in physical exertion, infections with fever, and cardiac congestion. *Granular casts* formed from cellular debris indicate acute and chronic renal parenchymal diseases. *Leukocyte casts* caused by the aggregation of leukocytes in the tubule system are indicative of pyelonephritis. The occurrence of *erythrocyte casts* is possible in any hematuria of renal cause.

### Bacteriologic studies

The culture analysis of midstream urine for the demonstration of microorganisms should be mandatory in each leukocyturia originating in the urinary tract because of the frequency of bacterial processes (cystitis, pyelonephritis). The bacterial count should be performed with the aid of immersion culture media; counts over 100,000/ml are considered pathologic, although this number may be lower for some organisms (enterococci, *Pseudomonas*). For the qualitative demonstration of bacteriuria, test sticks to identify nitrite excretion (reduction of nitrate to nitrite by bacteria) have proved valuable. They have been found more than 90% accurate in first-morning urine samples.

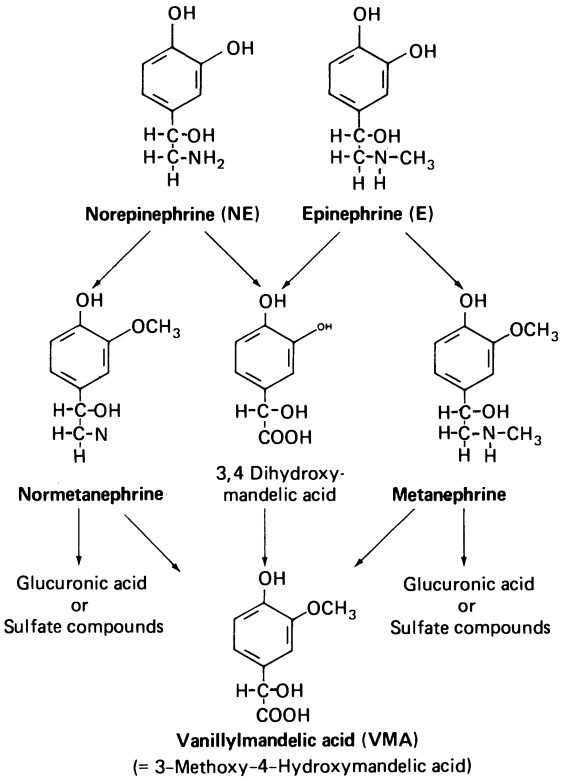



**Figure 1.** Structural formulas of norepinephrine (NE) and epinephrine (E) and their metabolites normetanephrine and metanephrine as well as vanillylmandelic acid (VMA).

## Endocrine Studies

### Catecholamines, Catecholamine Metabolism, and Catecholamine Metabolites

#### Preliminary remarks

The scientific study of catecholamine metabolism in the various forms of hypertension remains a matter of much current interest. In the diagnosis of hypertension, the demonstration of quantitative changes in the catecholamine balance is the key to therapeutic measures in all patients with *pheochromocytoma*. Positive as well as negative findings are of much diagnostic importance, therefore. The analysis of large numbers of pheochromocytoma patients has shown that in some instances the overproduction of a hormone can be demonstrated only by the *combined application of several analytical methods.*[47,75] Nevertheless, it remains extremely difficult to utilize all the quantities which characterize the catecholamine metabolism in establishing the diagnosis. Analyses are available for the following agents and metabolites (Fig. 1):

1. Epinephrine and norepinephrine
2. Metanephrine and normetanephrine
3. Vanillylmandelic acid

The tumor size and turnover rate of the secreted catecholamines determine the qualitative excretory pattern.[14] In the very rare cases of pheochromocytoma without sustained hypertension and an absence of catecholamine excess, *provocative measures* in the form of physical maneuvers (e.g., flank massage) or pharmacologic tests (glucagon, histamine) are still necessary as a means of precipitating an attack and measuring the catecholamines or their metabolites in the plasma and/or urine.[47] Despite the large number of negative analyses obtained—which is understandable in view of the low incidence of pheochromocytoma (0.7%)—the diagnosis of catecholamine-producing tumors nevertheless merits very close attention. The aforementioned techniques are employed not just on the appearance of the classic signs of a pheochromocytoma crisis but,

in view of the varied symptomatology of these tumors (approximately 50% sustained hypertension), must be applied in every patient with unexplained hypertension, often *repeatedly* and *at the start of the diagnostic program.* Research into new simple and reliable *screening methods* is welcome, indeed, in view of the high cost and complexity of traditional analytical techniques. The demonstration of plasma catecholamines (total) with the radioenzymatic (RE) technique, for which a kit (Upjohn Diagnostics) is now available, may also represent a highly accurate method of the future.*

## Epinephrine (E) and norepinephrine (NE)

***Urinalyses.*** The quantitative determination of the *free catecholamines*, and to some extent the *conjugated catecholamines*, epinephrine and norepinephrine in the urine has a satisfactory accuracy rate in the biochemical diagnosis of pheochromocytoma but is a laborious procedure. Still most frequently used are the fluorometric methods and their modifications,[46,86] in which E and NE can be assayed separately owing to the differences in their spectra and pH dependence. The NE/E ratio varies from one author to the next, ranging from 3:1 to 8:1. The catecholamine excretion (free portion) varies as a function of the body position and physical activity (NE during bed rest = 10 to 20 μg per 24 h, NE during moderate activity = 30 to 60 μg per 24 h.[22] Moreover, there are diurnal variations,[2] and NE tends to increase with age,[85] although this is of little importance for the interpretation of a heightened excretion in pheochromocytoma. In children, on the other hand, the total catechol excretion per kilogram of body weight considerably exceeds the upper-normal value for adults.[94] Values of about 45 μg per 24 h can be considered midnormal for free catecholamine excretion,[29,66,93] with 100 μg per 24 h being the upper limit of the normal range.[14,29,75] In pheochromocytoma, an extreme variation of values between 80 and 9000 μg per 24 h is known (Fig. 2). Thus, there is a distinct overlap with the normal range, which accounts for the varying reports of different authors as to the accuracy of the catecholamine assay (from 50% to 95%). This uncertainty makes it essential to perform multiple determinations as well as supplementary determinations of metanephrines or vanillylmandelic acid if pheochromocytoma is suspected. Diagnosis is further complicated by the fact that patients with "resting pheochromocytoma" (approximately 1% to 2%) display only periodic excretions of catecholamines, separated by intervals of normal excretion. In sustained hypertension, the measurement of E and NE in the 24-h or 12-h (overnight) urine is preferred to the analysis of urine collected on a short-term basis. In paroxysmal hypertension, the urine collected several hours (3 to 4) after the hypertensive crisis should be analyzed. The widespread practice of utilizing not the urinary volume but the 24-h excretion of creatinine as an index for accurate urine collection and calculation (micrograms of catecholamines per gram of creatinine) remains controversial but is favored by some authors. Apparently the day-to-day variation of creatinine excretion is far greater than previously assumed.[30] When analyzing NE and E in the short-term urine, such indexing is undoubtedly useful. Prior acidification of the urine, i.e., the preliminary addition of 10 ml of 10% HCl to the collection vessel, is essential to avoid E and NE losses in the neutral or alkaline milieu. Differentiation of the total catecholamines into the NE and E portions (E normally 5% to 10%) to characterize the pheochromocytoma as adrenal or extra-adrenal is seldom employed. Be-

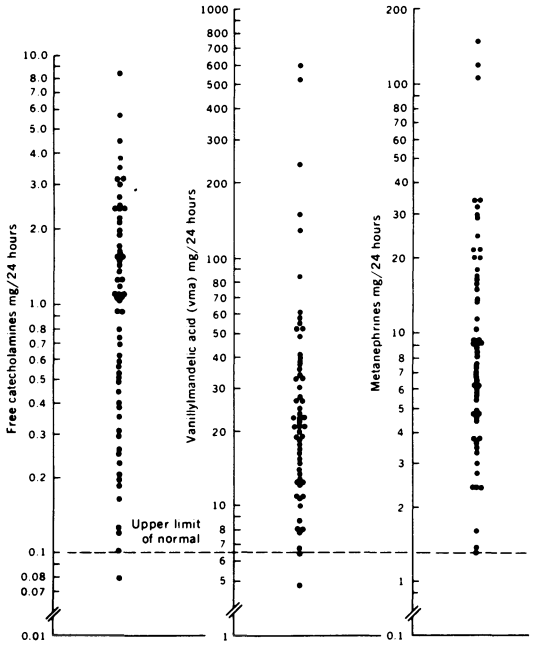



**Figure 2.** Comparison of the excretion of free catecholamines, metanephrines, and vanillylmandelic acid in 64 patients with histologically documented pheochromocytoma. From Sjoerdsma A et al., ref 75

*A recently developed, relatively uncomplicated urinary screening test (Catecult, Röhm Pharma GmbH), which demonstrates a general elevation in the excretion of NE, E, DP, and intermediate products of catecholamine metabolism with an unchanged catechol structure, has a reported accuracy rate of 90% (Cordes et al., 1979, DMW 104:1339). Comprehensive comparative investigations are lacking, however.

sides false-negative results, false-positive catecholamine excretion values must also be critically analyzed. The following clinical situations may be associated with an elevated excretion: cardiac failure, acute myocardial infarction, hypothyroidism, thallium intoxication, intermittent porphyria, depression and persistent stress situations, strenuous physical exertion (sports), hypoglycemia, acidosis, as well as excessive (malignant) hypertension with involvement of the central nervous system and states with increased cerebrospinal fluid pressure. False-positive catecholamine values have been noted in uremia, depending on the methodology employed (fluorometric ethylenediamine method!). In primary hypertension, mild elevations of catecholamine excretion and deviations in the NE/E ratio have been noted in isolated cases.[41] The fact that pheochromocytomas do not necessarily exhibit excessive values (see Fig. 2) merits particular attention.

Of critical importance for a correct interpretation is a knowledge of drug-induced changes in catecholamine excretion (Table 1), especially since numerous patients must be treated, or are being treated, with antihypertensive medications. If at all possible, it is desirable to precede drug therapy with a 1-week period without treatment in order to facilitate analysis. We have found that hospitalized patients with marked hypertension can be safely carried through this period with barbiturates alone (0.1 to 0.2 g of phenobarbital).

Among the antihypertensive drugs, α-methyldopa causes a particularly marked rise of catecholamine levels. Opinions vary as to the action of some agents (cf. ref. 47). Excessively high values, even if obtained under therapeutic influence, are usually indicative of pheochromocytoma. If suspected pheochromocytoma is confirmed (e.g., after a hypertensive crisis), a catecholamine determination may be prudent even under the influence of drug therapy.

The effect of alcohol, coffee, tea, and nicotine on catecholamine release should be taken into account, although these interfering factors are of minimal importance in the analysis of the 24-h urine specimen. The effect of bananas is also of minor significance with moderate consumption (<200 g/day).

***Plasma Analyses.*** Under normal circumstances the catecholamine concentration in the plasma is about 100 times lower than in the urine. So far, E and NE plasma analyses have been carried out less as screening tests than as supplementary studies in provocative tests or in cases of established catecholamine excess whose etiology is obscure. Catheterization of the adrenal veins or staged blood sampling in the various segments of the vena cava to localize adrenal, extra-adrenal, or even multiple tumors is not foolproof, however. A single determination with the less sensitive fluorometric methods requires at least 10 ml of plasma. With the introduction of radioenzymatic techniques,[21,58,62] a significant improvement has been achieved from an analytical standpoint in terms of precision and sensitivity. In addition, such techniques are capable of demonstrating epinephrine, norepinephrine, and dopamine in plasma volumes smaller than 0.1 ml. The concentration of total catecholamines in normal individuals varies considerably with the relatively nonspecific fluorometric methods and may exceed by a factor of 10 the values measured by radioenzymatic (RE) methods. The mean normal ranges measured by various groups with the RE method range from 141 to 230 pg/ml for NE and from 13 to 70 pg/ml for E. The total catecholamine concentration is about 200 ± 60 (±SEM) pg/ml.[36] Thus, standardized conditions for collection of the blood specimen (recumbent position, painless needle insertion; prior placement of a venous indwelling catheter is best) and ice-cooling of the specimen are of prime importance. The treatment cf the specimen itself varies from one author to the next[21,36,58,62] with respect to (1) collection of the plasma in heparin or in ethylene glycol-bis(α-aminoethyl ether)*N'N*-tetraacetic acid (EGTA), (2) the addition of antioxidants (reduced glutathione), and (3) protein precipitation by perch-

**Table 1.** Established (or Possible) Effects of Various Drugs on Plasma Catecholamine Levels or Urinary Metabolites

| |
|---|
| Elevation |
| Exogenous catecholamines or sympathicomimetics (especially those in nose drops, asthma medications, or "cold remedies") |
| α-Methyldopa* |
| Monamine oxidase (MAO) inhibitors |
| L-Dopa |
| Diuretics |
| Methylxanthine (caffeine, theophylline) |
| Chlorpromazine (effect depends on method of analysis) |
| Fluorescent substances† |
| Reduction |
| Clonidine |
| Reserpine alkaloids |
| Guanethidine |
| β-Receptor blocking drugs |

*α-Methyldopa and MAO inhibitors reduce the excretion of VMA.

†Quinidine, quinine, tetracycline, ampicillin, chloral hydrate, and vitamin C affect the fluorescence measurement of urinary and plasma catecholamines.

Modified from Strong CG, Northcutt RC, Sheps SG, ref 77a.

loric acid. The differentiated determination of NE and E to establish an adrenal or extra-adrenal pheochromocytoma by use of the RE method may well assume greater importance in the future.

Recently it was shown that plasma catecholamine determinations performed by the RE technique are superior to comparative measurements of catecholamine metabolites performed in the urine.[10a] It is noteworthy that it was possible in this study to identify six patients with operatively confirmed pheochromocytoma but normotensive blood pressures at the time of blood sampling based on elevated plasma concentrations of NE and E. Quite recently, an oral clonidine-suppression test was proposed[10b] to differentiate moderately elevated NE and E plasma levels induced either by pheochromocytoma or essential hypertension.

### Metanephrine (MN) and normetanephrine

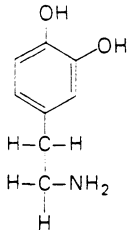
The determination of the urinary E and NE metabolites metanephrine and normetanephrine is less common in Europe than is the determination of VMA. The products called metanephrines (MN), which are excreted mainly in conjugated form (as sulfates or glucuronides ), are always determined as total metanephrines after acid hydrolysis.[60] Following this step the MN analysis includes: (1) column chromatography (adsorption on Amberlite CG 50), (2) elution, (3) conversion of MN to vanillin, and (4) spectrophotometry of the dye at 350 nm. Analogous to the findings for E, NE, and VMA, the excretion of MN is elevated in children and declines until about age 18; the mean normal value for ages 2 to 5 is 1.25 $\mu$g/mg of creatinine and for ages 15 to 18, 0.24 $\mu$g/mg of creatinine.[27] The upper-normal limit in adults varies from author to author, ranging from 1.25 to 1.90 mg per 24 h. The maximum excretion found in patients with pheochromocytoma may reach 160 mg per 24 h (Fig. 2); the average reported by most authors is 7 to 8 mg per 24 h. The accuracy of the MN determination in pheochromocytoma is between 87% and 100%. With large tumors ($>$ 50 g) and a catecholamine content greater than 100 mg, the MN excretion can exceed the catecholamine excretion by a relatively wide margin.[14]

Pharmacologic agents and substances that influence the catecholamine balance or interfere with analysis can of course distort the values (cf. Table 1). Owing to its relative resistance to drug interferences, its practicability, and the infrequency of false-negative and false-positive results, the metanephrine assay appears to represent a first-line diagnostic method. It is significant, moreover, that the metanephrines apparently more accurately reflect the entry of free amines into the bloodstream than does the analysis of VMA.

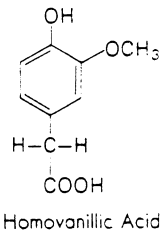
### Vanillylmandelic acid (VMA)

The analysis of urinary VMA in healthy persons encompasses 80% to 85% of the substances generated by catecholamine metabolism. Analyses which include suitable separation techniques (paper or thin-layer chromatography) to isolate the components of the phenol–carbonic-acid mixture with subsequent diazotation and photometry have a high specificity. Nevertheless, the spectrophotometric determination of VMA after its conversion to vanillin[61] is generally preferred owing to its better practicability. VMA excretion is elevated in childhood, varies considerably, and reaches the normal adult value at about age 15.[27] The daytime and nighttime excretions vary in a ratio of 3:1.[16] The mean total excretion in adults is about 4.0 mg per 24 h, with variations between 0.6 and 11.1 mg per 24 h (cf. ref 13). The majority of authors report a borderline range of 6 to 8 mg per 24 h, or 3.5 to 4 micrograms of VMA per milligram of creatinine.[28] With the high diagnostic accuracy of 80% to 97%, borderline values are always an indication for repeat determinations and additional catecholamine or metanephrine measurements. Occasional false-positive VMA tests must be accepted. Most investigators report average excretory values in pheochromocytoma of 20 mg per 24 h (cf ref. 66), sporadic values up to 600 mg per 24 h in isolated cases (Fig. 2). Pheochromocytomas with a relatively high VMA excretion (compared to NE and E) usually have a weight exceeding 50 g and display a low catecholamine turnover rate. High excretory values are found in ganglioneuroma and neuroblastoma in childhood, here combined with an elevation of homovanillic acid excretion.[26,29] A knowledge of drug interferences (Table 1), especially the negative influence of $\alpha$-methyldopa (VMA decrease!), is indispensable.

### Dopamine (DP) and homovanillic acid (HVA)



Dopamine



Homovanillic Acid

The diagnostic determination of dopamine and its main degradation product homovanillic acid is limited to tumors arising from the sympathetic tissue or sympathetic ganglia (neuroblastoma, ganglioneuroma, ganglioneuroblastoma). The quantitative relations of the individual catecholamines E, NE, and

DP in these tumors, which usually occur in childhood, differ from those in pheochromocytomas. A strong liberation of dopamine or its precursor, dopa, is a rare finding in pheochromocytoma and generally is indicative of malignancy. The measurement of DP or HVA is unnecessary if pheochromocytoma is suspected.

Formerly, HVA was demonstrated in the urine spectrophotometrically following extraction and paper (thin-layer) chromatography. Today this is done more simply and just as specifically by fluorometry.[9] The HVA excretion is elevated in childhood and declines until age 15.[27] At ages 10 to 15, the mean value is 5.1 mg per 24 h (cf ref. 66), or 2.42 μg/mg of creatinine.[27] This range also holds for adults.[26] In neuroblastoma, average values of around 32 mg per 24 h (up to 150 mg per 24 h in isolated cases) can be demonstrated (cf. ref. 66). The quantitative determination of dopamine in the urine is not a common technique but, like the catecholamine assay, can be done fluorometrically.[9] The excretion in adults is 200 μg per 24 h. The radioenzymatic and specific demonstration of DP may well acquire further importance in the future.

### Dopamine-β-hydroxylase (DPH)

This enzyme, which is essential in the conversion of dopamine to norepinephrine, has not yet become important in the differential diagnosis of hypertension, although a moderate elevation has been described in patients with pheochromocytoma.[5,24,35] A marked ninefold activity increase has been demonstrated in tumor homogenates from pheochromocytomas.[35] Due to the large interindividual variation of the serum DPH with a correspondingly extreme scatter of the normal range from zero to several hundred units, it is not yet possible to obtain reliable diagnostic information; indeed, it cannot even be determined whether an E- or NE-producing tumor is present.

## Renin-Angiotensin System (RAS)

### Preliminary remarks

Not all components of the RAS (Fig. 3) are of equal importance in the differential diagnosis of hypertension. *Plasma renin assays* are widely used both in the scientific research of hypertension and in the area of practical diagnosis. The broad potential of the plasma renin assay is further demonstrated by attempts to administer various antihypertensive agents according to the level of the plasma renin,[11] thus utilizing the renin level as a key to differential therapy. The accuracy of plasma renin activity (PRA) measurements is not inferior to that of the plasma renin concentration (PRC) determinations, which generally are favored on kinetic grounds. The end-product measurement of angiotensin I or II by radioimmunoassay (RIA), which evolved from the renin bioassay, has contributed worldwide to an understanding of the diagnostic value of PRA determinations. From the highly significant correlation between the angiotensin II plasma level and the PRA,[84] it can be concluded that the in vitro liberation of angiotensin I (as a measure of renin activity) reliably reflects the in vivo concentration of angiotensin II in the majority of clinical situations. From a practical diagnostic standpoint, as well as on methodological grounds (antibody specificity), *an-*

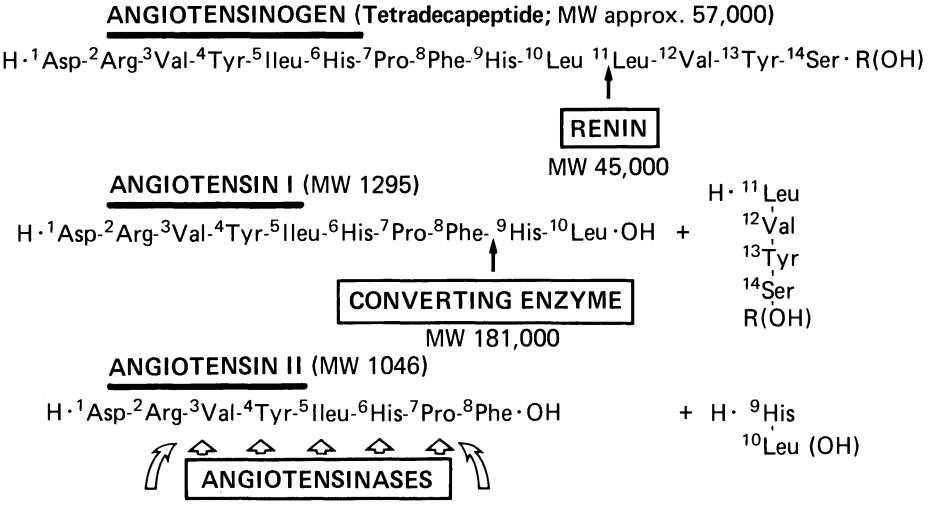



**Figure 3.** Simplified scheme of the substrate (*underscored*) and enzyme (*boxed*) components in angiotensin system.

*giotensin II determinations,* as well as measurements of other components of the RAS (angiotensinogen, angiotensin I–converting enzyme, angiotensinases), are at present of little or no importance in hypertension.

## Renin

The measurement of the plasma renin by bioassay in the hypertensive rat (or vascular strip preparation) compares favorably with the results of RIA measurements, despite quantitative discrepancies.[70]

In contrast to the more laborious PRC analysis, PRA determinations (see Table 2) are commonly performed worldwide in hypertensive patients. The results of ring tests in various reputable laboratories are disappointing for both methods.[6] To date no international agreement has been reached concerning the most favorable working procedure with regard to: (1) the optimum buffer medium and pH value during incubation of the plasma (pH 7.4, 5.9, or 5.5), (2) the concentration and composition of inhibitors added to inhibit angiotensinases and converting enzyme, (3) single-point or kinetic measurements, (4) the use of an angiotensin I reference standard or external calibration with an international renin standard, and (5) the optimum working procedure for the measurement of specimens with very high or low renin.

Since relatively high values are obtained on strong dilution of the incubated plasma,[71,87] we avoid dilution prior to the RIA reaction; for PRA determinations we incubate all plasmas uniformly for 15, 45, 90, or in some cases 180 min at pH 5.9 before carrying out the RIA measurement. The superiority of phenylmethylsulfonyl fluoride (PMSF) as a peptidase inhibitor, which is used by us and a few other laboratories, has been reconfirmed in a recent study.[20]

In view of the large number of methods and modifications proposed, as well as the various renin kits available commercially, the large variation in normal values is hardly surprising on methodological grounds alone (cf. ref. 6). For the establishment of normal values, which is best done individually by each laboratory in a large population, analysis-independent factors such as (1) diurnal variations, (2) body position and physical activity before the sample is drawn, (3) age-dependence, and (4) sodium intake are of fundamental importance.

The PRA range in our laboratory for normal control subjects of both sexes ranging in age from 14 to 81 ($n$ = 126) is between 0.4 and 3.4 ng/ml/h and was determined under the following conditions: > 2 h recumbency, no dietary restriction, blood drawn on empty stomach between 7:30 and 9:30 A.M, plasma incubation at pH 5.9, inhibitors (see below), international reference standard: Ileu-5-angiotensin I (Medical Research Council No. 71/328, London).

In many centers, especially outpatient clinics, the "orthostatic" renin obtained in the ambulatory patient is preferred to the "resting" renin for practical reasons. This stimulated renin, possibly increased by a combination of alimentary salt restriction and the administration of a saluretic (20 to 80 mg of furosemide iv or by mouth), has proved its worth not only in the hypermineralocorticoid syndromes but also, and especially, in the classification of "low-renin" hypertension.

For the combined measurement of the resting and orthostatic renin, it is necessary that the patient be recumbent for at least 1½ to 2 h (Fig. 4) to permit the orthostatically induced renin increase to subside fully. The blood sample should be drawn after 2 to 3 h at the time of maximum stimulation. Renin determinations in the arterial and peripheral venous blood yield equal results.

Allowance for the sodium balance measured on the basis of the preceding 24-h $Na^+$ excretion to con-

**Table 2.** Comparison of Conditions Under Which Plasma Renin Activity (PRA) Determinations and Various Plasma Renin Concentration (PRC) Determinations Are Carried Out

| Renin | Substrate | Product |
|---|---|---|
| PRA = renin (endogenous) | Renin substrate (RS) (endogenous) | AT I |
| PRC = renin | RS | AT I |
| a. After plasma extraction by column chromatography (DEA = cellulose) | a. Endogenous RS inactivated at pH 3.3 + addition (excess) of heterologous RS (swine, bovine, sheep) | |
| b. Renin (endogenous) | b. Endogenous RS + addition (excess) of heterologous RS | |

*In all procedures which involve acidification of the plasma (< pH 3.0), of the renin extracted from the plasma, or of the entire reaction material, it must be taken into account that *inactive,* acid-activated prorenin is determined along with the active renin, i.e., that the determination is a *total renin* assay.

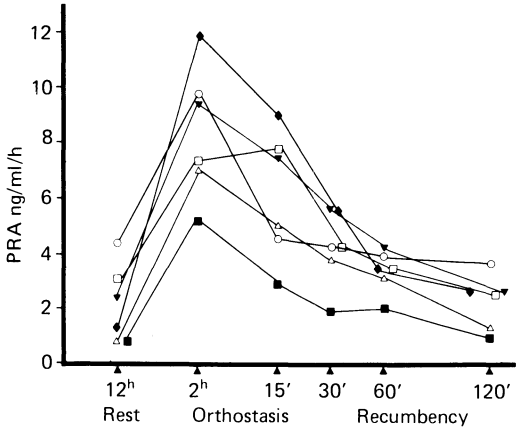



**Figure 4.** Changes in PRA (measured by radioimmunoassay) in six hypertensive patients after 2-h orthostasis and resumed recumbency after 15, 30, 60, and 120 min; resting blood sample drawn at 7 A.M.

struct renin/$Na^+$ nomograms[43,64] remains a difficult requirement due to the problems involved in quantitative urine collection. The single measurement of the 24-h sodium excretion, moreover, must be considered an unreliable index of $Na^+$ intake.[8] Since no inverse relationship has been found between the basal renin and $Na^+$ excretion with a normal $Na^+$ intake (more than 75 mmol/day) (cf. refs. 64,80), the additional trouble is hardly justified for either the patient or the laboratory. Only in alimentary sodium deficiency or sodium excess for about 4 to 5 days does one find a clear inverse relationship of both quantities.

The duration of the preservation of blood samples at −20°C is not without influence owing to the cold activation of prorenin.[72] On the other hand, it has been our experience that the preservation of blood samples in an ice bath is by no means essential, as is generally assumed. Storage of the plasma for 2 to 3 h at 20°C does not influence the PRA.[23,88] When resting PRA values are subject to repeat determinations on three consecutive days, considerable fluctuations can occur in some cases (Fig. 5). Some 30% of patients with essential hypertension cannot be assigned to the same renin category when repeat determinations are done.[13]

To confirm reduced renin values in hyporeninemic hypertensives, therefore, *three measurements* in the peripheral venous blood should be available if possible. In hyperreninemic hypertension, which is usually based on unilateral or bilateral renal lesions, additional renal vein renin determinations in the separate kidneys can be highly informative. Prior renin stimulation with furosemide and/or further sodium restriction (10 mmol for 3 to 5 days) for better lateralization of an elevated renin secretion (ratio of affected kidney to healthy kidney $> 1.5$) are helpful. Adherence to a standardized procedure[25] ensures comparable results. *Note:* Even normal peripheral venous renin values do not exclude a functionally significant lateral disparity of renin secretion in patients with unilateral renal lesions.

Drug effects on renin (Table 3) offer a variety of sources of error and uncertainty, in the case of both conventional drugs and those newly introduced. Uncertainties may relate to the impact of the drug dosage as well as the duration of prior drug therapy. The practically important question of when values

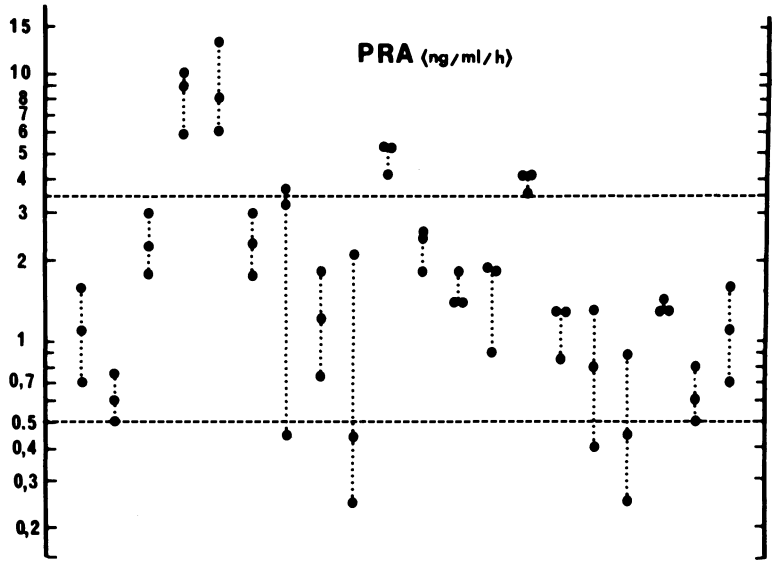



**Figure 5.** Repeat measurements of PRA on three consecutive days in 20 patients with pharmacologically untreated hypertension of varying etiology. All blood samples were drawn at the same time of day (8:15 to 8:30 A.M.) on an empty stomach after 8-h bed rest. Plasma treated for RIA work-up. The broken lines indicate the upper and lower limits of normal.

**Table 3.** Substances and Drugs Which Interfere with the Renin-Angiotensin-Aldosterone System

| Type of Substance | Effect on Renin (Increase ↑, Decrease ↓, No Change →) | Normalization After Withdrawal (Days) |
|---|---|---|
| Sympathicomimetics | | |
| Epinephrine, Norepinephrine, Isoproterenol, Dopamine | ↑ | Short-term effect |
| β-Receptor blocking drugs | | |
| Propranolol, Metoprolol, Oxprenolol | → ↑ | 1–3 |
| Antihypertensives, vasodilators | | |
| Clonidine | ↓ | 1–2 |
| Diazoxide | ↑ | |
| Reserpine | ↓ → | |
| Nepresol | ↑ | |
| α-Methyldopa | ↑ | |
| Guanethidine | ↓ | |
| Sodium nitroprusside | ↑ | |
| Phentolamine | ↓ | |
| Labetalol | → | |
| Saralasin | ↑ | |
| Converting enzyme inhibitor (SQ 14225) | ↑ | |
| Diuretics | | |
| Loop diuretics (furosemide, bumetanide, ethacrynic acid) | ↑ | 2–4 |
| Benzothiadiacine derivatives and substances with analogous actions (chlorothiazide, thiabutacide, clopamide, chlorthalidone) | ↑ → | 2–5 |
| Antikaliuretics [spironolactone, triamterene, amiloride (?)] | ↑ | 5–21 |
| Antacids | | |
| Carbenoxolone | ↓ | Up to 8 |
| Nonsteroidal anti-inflammatory and antirheumatic agents of the indomethacin type | ↓ | 1–2 |
| Antidepressants | | |
| Lithium | ↑ → | |
| Psychostimulants | | |
| Theophylline, caffeine | ↑ | Short-term effect |
| Hormones | | |
| Estrogens | ↓ ↑ | 2–14 |
| Desoxycorticosterone | ↓ | 3–5 |
| Aldosterone | ↓ | |
| Dexamethasone | ↓ | |
| ADH | ↓ | |
| ACTH | ↓ | |
| Angiotensin II | ↓ | |
| Glucagon | ↑ | |
| Insulin | ↑ | |
| Prostaglandin E | ↑ | |
| Chemotherapeutic agents | | |
| Gentamicin | ↑ | |
| Vinblastine | ↑ | |

Expanded from Werning C, ref 86a.

**Table 4.** Abnormal Findings, Clinical Situations, and Procedural Conditions Which Make Renin Assays Advisable *in Every Case* of Hypertension of *Useless* or *Misleading*

| Renin Analysis *Useful* in: | Renin Analysis *Useless* or *Misleading* in: |
|---|---|
| 1. All cases of hypokalemic hypertension (after exclusion of prior diuretic and laxative therapy) | 1. Acute renal parenchymal disease |
| 2. Angiographically proven renal artery stenosis | 2. Chronic renal disease (exception: therapy-resistant hypertension in renal failure and dialysis) |
| 3. Lateral disparity of renal size in X-ray (> 1.5 cm on long axis) | 3. Prior or current pharmacologic therapy (saluretics, antihypertensives, estrogens, contraceptives, spironolactone and other antikaliuretics, β-receptor blocking agents, glucocorticoids, mineralocorticoids) |
| 4. Abnormal pyelograms (unilateral: delayed visualization, deformation of calyces) | 4. Prolonged low-sodium diet |
| 5. Therapy-resistant hypertension in renal failure requiring dialysis | 5. Ignorance of patient's position prior to blood sampling |
| 6. All cases of childhood hypertension | 6. Absence of inhibitors added to drawn blood |
| | 7. Prolonged storage of the blood at room temperature |

can be expected to normalize following the discontinuance of a drug has been answered for only a few substances.

Since renin determinations generally contribute to the differential diagnosis of hypertension only in conjunction with other findings, the guidelines given in Table 4 should be taken into account in establishing a rational diagnostic program.

### Angiotensinogen (renin substrate, RS)

Angiotensinogen determinations in the plasma are of no diagnostic importance, despite the fact that some forms of hypertension (malignant hypertension, Cushing's syndrome, primary hyperaldosteronism, renoprival hypertension) may be associated with a rise of RS.[40,89] RS measurements can serve to help verify hypertension triggered by estrogens or contraceptives in cases where the blood pressure and plasma RS levels fall after therapy is terminated.

According to recent studies, plasma angiotensinogen can be separated into two main fractions and six subfractions.[45] The hepatic biosynthesis of the glycoprotein is stimulated by hormones (estrogens, glucocorticoids, angiotensin II) and, in renal insufficiency, by an as yet unidentified factor of protein character (cf. survey in ref. 89). An inverse relationship exists between the plasma renin and renin substrate only with a strongly elevated renin level. There is no diurnal variation.

In most studies angiotensinogen is measured indirectly by the "exhaustion" principle (human renin excess for the quantitative transformation of RS to AT I), with radioimmunoassay used to measure the AT I concentration (cf. ref. 89). A direct radioimmunoassay has also been developed.[19] In the more common indirect method, the plasma should be treated with inhibitors, as in the renin assay. According to one survey (cf. ref. 89) the normal values of various research groups vary over a wide range between 550 and 3315 ng/ml, apparently owing to differences in the angiotensin I standard, non-angiotensinase-free renin preparations, or excessive incubation times. Prolonged storage of the plasma at −20°C does not alter the RS concentration.[72]

### Angiotensin II (AT II)

Plasma angiotensin II determinations do not contribute to the clinical diagnosis of hypertension from the standpoint of supplementing the renin assay. As a single test for the demonstration of angiotensin-dependent forms of hypertension, the AT II analysis is inferior to the renin assay on methodological and theoretical grounds. Changes in the renin level (with a normal renin substrate content) by a factor of 6 raise the AT II concentration by only about a factor of 2.[84] Since, in radioimmunoassay, most antibodies do not react exclusively with AT II but also with its metabolites, variable peptide concentrations of AT II, its heptapeptide (AT III), and further bioinert fragments (hexapeptide and pentapeptide) are measured in the plasma. The separate determination of AT II and AT III is difficult and necessitates further separation techniques (paper or thin-layer chromatography). From 55% to 100% of the "angiotensins" in the plasma are represented by AT II.[73,76] No distinct differences are found between the AT II concentrations in the venous and arterial blood when considering averages for large study populations, although marked deviations in either direction may be noted in individual cases. While some groups determine AT II in the fresh plasma, extraction tech-

niques [adsorption on ion exchanger (Dowex, Amberlite)], ultrafiltration, or ethanol precipitation of the plasma are widely used and have their advantages. Simple ethanol precipitation is not inferior to the widely used Dowex method (with column chromatography or the batch technique), though working with a relatively impure, lipid-rich residue is necessary.[77] The results are critically influenced by rapid treatment of the blood in an ice bath with inhibitor solutions for peptidase suppression.

The following inhibitor combinations are utilized in our laboratory: 0.5 ml 0.25 *M* $Na_2EDTA$ + 0.05 *M* *O*-phenanthroline and 0.1 ml 0.378 *M* PMSF in ethanol.

The AT II concentration in normal subjects at rest and with unrestricted $Na^+$ intake ranges from 4 to 26 pg/ml.

### Angiotensin I–converting enzyme (CE)

The determination of AT I–converting enzyme (identical to kininase II) has not acquired importance in the laboratory diagnosis of hypertension. The CE fixed in the tissues, especially in the pulmonary vascular wall, probably plays the main role in the conversion of AT I to AT II. Changes in the plasma concentration in various forms of hypertension have not yet been demonstrated with certainty.

Reductions have been found in diseases of the pulmonary parenchyma (carcinoma, tuberculosis, cystic fibrosis), and elevations in patients with sarcoidosis, Gaucher's disease, and leprosy.[57] Recently a significant rise of CE has also been noted in cases of acute viral hepatitis and cirrhosis of the liver.[69]

It is likely that in the future CE analysis will gain importance in antihypertensive therapy with iv and orally active CE inhibitors. CE is relatively stable and is not affected by 8 days' storage of the serum at 4°C (or at −20°C for several months). The relatively simple enzyme determination with synthetic substrates can be done in the serum or plasma (heparin) using fluorometric, colorimetric, or radiometric means (survey of methods cf. ref. 10). The normal ranges vary with the method and substrate used.

### Angiotensinases

Measurement of the activity of angiotensin II–splitting enzymes in the plasma is of no diagnostic importance in hypertensive patients. AT II is degraded less in the plasma than in the vascular wall. For the demonstration of heterogeneous plasma and tissue enzymes, in vitro determinations are mainly used. In these methods the residual activity of AT II is either measured biologically (rat blood pressure preparation) after incubation with plasma, or the splitting of AT II (amino acid analysis) is determined by the demonstration of aspartic acid in the optical test.[38]

## Steroid Hormones and Their Metabolites

### Preliminary remarks

The elevated secretion of adrenal steroids in essential hypertension has been the subject of exhaustive research in recent years,[54] yet no diagnostic significance has yet been derived. Laboratory analysis is aimed chiefly at the *hypermineralocorticoid forms of hypertension,* for which an excess of aldosterone (primary and idiopathic aldosteronism) can be demonstrated. According to recent findings,[59] additional steroid analyses [11-desoxycorticosterone (DOC), corticosterone] following the administration of dexamethasone can also be helpful in further differentiating the *hyperaldosteronism* associated with adrenocortical adenoma or bilateral adrenocortical hyperplasia, which is important on therapeutic grounds. The demonstration of a secondary aldosteronism in renin-angiotensin–dependent hypertension is not essential and contributes only in exceptional cases to a differential diagnosis. In congenital disturbances of the biosynthesis of adrenal steroids as well, determinations of DOC and corticosterone are of major importance. Despite the rarity of these hypermineralocorticoid syndromes with hypertension (*11-β-hydroxylase deficiency, 17-α-hydroxylase deficiency*), the possibility of abnormal hormone formation must be considered in every case of hypokalemic hypertension, especially in children and adolescents. The additional analysis of further steroids (androgens, estrogens, progesterone, 17-α-hydroxyprogesterone, and their metabolites) serves only a supplementary diagnostic function.

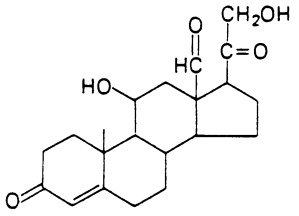
Although the hypertension in the various forms of *Cushing's syndrome* is not exclusively the product of a glucocorticoid excess, it is sufficient to demonstrate hypercortisolism that is resistant to inhibition by dexamethasone. Since hypertension represents only one portion of the symptom complex, important function tests such as the dexamethasone suppression test or metyrapone test should always be included in the overall diagnostic program. The measurement of 17-hydroxysteroids for the detection mainly, but not exclusively, of cortisol and cortisol metabolites in the urine is still justified, particularly in conjunction with the aforementioned function tests. The determination of $C_{17}$-ketosteroids, on the other hand, is overrated in the diagnosis of Cushing's syndrome.

The *analysis of steroid hormones in the plasma* has become the domain of radioimmunoassay techniques. The RIA *measurement of hormone metabolites in the urine* (e.g., the tetrahydro derivatives of cortisol, corticosterone, DOC, 18-OH-DOC, aldosterone), on the other hand, is less commonly practiced on methodological grounds. However, such de-

terminations are of much diagnostic value in that they convey a picture of the integral 24-h hormone secretion. The varying specificity of many steroid antibodies necessitates the *use of separation techniques* for both plasma and urine analysis. Methods for the simultaneous separation and subsequent RIA measurement of numerous steroids of adrenal and nonadrenal origin are becoming increasingly important.[67,74] At the same time, the technically complex *measurement of the secretion rates of individual steroids* following the in vivo administration of radiolabeled hormones is no longer a diagnostic necessity.

The large interindividual and sex-specific[68] *scatter of plasma steroids and their excretory products in the urine* must always be taken into account. The confirmation of a normal or abnormal finding by *repeat measurements* should be a routine part of all steroid analyses, therefore. Indeed, they are indispensable for the correct interpretation of plasma levels owing to the episodic character of hormone secretion.

## Plasma aldosterone analysis



Aldosterone

The cumbersome double-isotope derivative method,[56] which requires large amounts of plasma (20 to 30 ml), has been almost completely superseded by radioimmunoassay methods. Owing to the small aldosterone concentration in normal plasma (3 to 20 ng per 100 ml) and the relatively high concentration of other adrenocortical steroids, some of which are cross-reacting, the latter must be separated out by column chromatography,[55] paper chromatography,[82] or thin-layer chromatography (TLC)[33] following plasma extraction. So far only a few groups of researchers have succeeded in obtaining highly specific aldosterone antibodies that render separation techniques[83] or even plasma extraction[37] unnecessary. In a comparison of various techniques using commercial kits, the RIA aldosterone determination after preliminary TLC separation is found to be superior in high as well as low concentration ranges.[53a]

For optimum reproducibility, our laboratory employs TLC separation of the plasma (or urinary) extracts on silica gel; high blank values as a result of the pilot standard also run during the analysis (minimum concentration for identification in UV light = 0.5 μg!) are avoided by running inert substances such as caffeine and aminopyrine.

In accordance with the control of aldosterone secretion by changes in renin/angiotensin II, the dependence of aldosterone on (1) body position, (2) diurnal variation, (3) sodium and potassium intake, (4) menstrual cycle, and (5) drug actions that influence the renin-angiotensin-aldosterone system (see Table 3) must be taken into account.

A knowledge of the interfering effect of spironolactone is essential owing to its widespread use in antihypertensive therapy. Owing to the long half-life of the spironolactone metabolites, 2 to 3 weeks are required before the plasma aldosterone level can normalize. It should be noted, however, that in primary hyperaldosteronism spironolactone can lead to an initial fall of the elevated plasma aldosterone.[12]

Aldosterone analyses in the adrenal venous blood are sometimes of limited value for the localization of an aldosteronoma because of the difficulties involved in catheterizing the right suprarenal vein and because of possible intermixing of the adrenal venous blood with blood from the vena cava. As a rule, aldosterone determinations are performed in heparinized plasma, but we have found that determinations in serum or EDTA plasma are also satisfactory. It has been our experience that prolonged preservation at −20°C (up to 1 year) does not influence the results. The plasma can even be kept at +23°C for up to 3 days,[3] thus permitting it to be mailed.

### Urinalysis for aldosterone

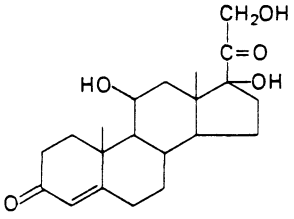
Although urinary aldosterone excretions include free aldosterone (0.1% to 0.3%), the renal metabolite aldosterone-18-glucuronide (5% to 12%), the hepatic metabolite tetrahydroaldosterone (20% to 40%), and aldosterone-1-monosulfate (0.5% to 1%), the renal metabolite aldosterone-18-glucuronide has traditionally served almost exclusively as the "urinary aldosterone" for the diagnosis of changes in the aldosterone balance. Indeed, there is a good correlation between the plasma aldosterone (8 A.M. values) and aldosterone-18-glucuronide excretion under various conditions.[80] The analyses are comparable to plasma aldosterone assays from the standpoint of the labor involved and the current RIA technique. The urinary aldosterone is of considerable value as an index of the 24-h secretion for orientative as well as outpatient studies. In fractional 12-h urine collections, the amount of aldosterone excreted during the night is only about one-third that excreted during the day.[16] The depen-

dence of the measured value on an accurate urine collection, as well as renal function, must always be borne in mind. With low urine volumes (< 600 ml), it is advisable to calculate the aldosterone excretion on the basis of the creatinine excretion (micrograms of aldosterone per gram of creatinine).

Since the development of specific antibodies for tetrahydro-aldosterone,[63] RIA measurements of the excretion of this metabolite will become increasingly important as a further index of aldosterone metabolism, especially in the area of research.

The measurement of free aldosterone in primary aldosteronism corresponds to the excretion of aldosterone-18-glucuronide,[15] but shows a closer correspondence to the tetrahydroaldosterone excretion in more recent studies[12a] in various forms of hypertension. The necessity of chromatography for the specific demonstration of urinary aldosterone metabolites has been confirmed by comparative determinations recently reported.[12a] The average 24-h excretion of aldosterone-18-glucuronide in persons with normal heart, liver, and kidneys is 11 μg with a wide scatter between 3 and 20 μg. For tetrahydroaldosterone the range is 10 to 70 μg, and for free aldosterone, 0.07 to 0.45 μg.[12a]

## Plasma cortisol assay



Cortisol

Indications for the diagnostic application of plasma cortisol assays in hypertensive patients are hypercortisolism in Cushing's syndrome as well as defects of cortisol biosynthesis (11-β-hydroxylase deficiency, 17-α-hydroxylase deficiency). In interpreting plasma cortisol findings, the following observations should be taken into account:

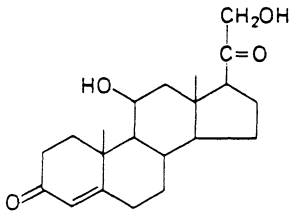
1. Single determinations are, as stressed earlier, of limited value owing to interindividual variations.
2. At least four determinations (8 A.M., 2 P.M., 6 P.M., 10 P.M.) are necessary to verify the diurnal variation.
3. Cortisol concentrations in the middle and upper borderline range, or intermittently elevated or normal values, do not exclude Cushing's syndrome.
4. The dexamethasone suppression test (2 mg overnight test, or 2 or 8 mg for several days) is helpful in differentiating the variants of Cushing's syndrome.
5. The cortisol values are generally influenced by an erect posture in the elderly (60 to 74 years), perhaps rising by 50%![85]
6. Substances which raise the transcortin level cause an elevation of the total cortisol; these include estrogens and contraceptives as well as states with an endogenous estrogen excess (pregnancy).

From a technical standpoint the fluorometric assay method[48] has numerous limitations due to its relative specificity (measurement of *all* 11-β-hydroxylated compounds) and proneness to interference by varying residual fluorescence (free cholesterol) and by the actions of detergents and drugs (spironolactone). The method has a lower limit of about 5 μg per 100 ml. Nevertheless, this analysis is suitable as long as interfering fluorescent substances are taken into account. Competitive binding analysis and RIA measurements are equivalent in their diagnostic value and can demonstrate concentrations below 5 μg per 100 ml. Higher progesterone levels (pregnancy) can distort the results measured for cortisol by both methods as a result of a cross reaction of poorly specific cortisol antibodies or binding to transcortin. The normal range (8 A.M.) varies between 5 and 25 μg per 100 ml. The most recent results of hormonal ring tests in Germany have shown that substantial (up to 100%) deviations can occur in RIA measurements from one laboratory to the next. Fluorometrically determined values may be more than twice the values measured by RIA.[31] Heparin is usually used as an anticoagulant, but we have found that equal values are obtained in the RIA test by the use of $Na_2$-EDTA.

## Urinalysis for cortisol

The relatively simple determination of free (unconjugated) cortisol in the 24-h urine is not widely practiced. With accurate urine collection, it can be considered a good measure of bioactive cortisol in the tissues and provides an integral measure of adrenocortical function. Again, RIA methods are more heavily relied upon than the fluorometric technique. Additional separation techniques (paper or thin-layer chromatography) are unnecessary in Cushing's syndrome but may be necessary in abnormal steroid patterns (biosynthesis defects) and in function tests (metyrapone). The average value is 65 μg per 24 h,[32] with a large scatter from 20 to 160 μg per 24 h. Normal values as high as 378 μg per 24 h are known from fluorometric measurements.[18]

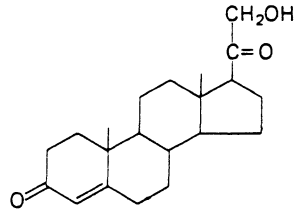
### Corticosterone



Corticosterone

The diagnostic importance of the plasma corticosterone is for the present still limited to hormone synthesis defects with hypertension. Owing to the adequate specificity of the majority of antibodies and relatively simple assay procedure (plasma extraction, recovery measurement, RIA reaction)[81] the plasma analysis is straightforward. The normal range is 0.5 to 2 $\mu$g per 100 ml. The values found in 11-$\beta$-hydroxylase deficiency are usually below 0.5 $\mu$g per 100 ml, and in 17-$\alpha$-hydroxylase deficiency, between 10.4 and 30 $\mu$g per 100 ml.[7] The administration of spironolactone can cause a considerable elevation of values, apparently by influencing the steroid balance on the adrenal level. With borderline findings, one should resort to the determination of tetrahydrocorticosterone in the 24-h urine, a procedure available in certain specialized endocrinologic laboratories.

### 11-Desoxycorticosterone (DOC)

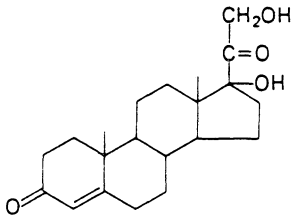


DOC

The object of the DOC assay, like the corticosterone assay, is to disclose enzyme defects of steroid biosynthesis. In Cushing's syndrome (adrenocortical carcinoma) and in ectopic ACTH production, elevated DOC levels are less significant diagnostically than patho-physiologically. The role of an isolated and varying DOC elevation in "low-renin" hypertension is not yet known. As to the possible importance of plasma DOC measurements in the differential diagnosis of hyperaldosteronism, see above, Preliminary remarks (p. 273).

DOC in the plasma can be determined, after paper-chromatographic or column-chromatographic separation, either by competitive protein binding analysis or by radioimmunoassay. High blank values, cited in numerous RIA studies, are an obstacle to accurate quantification. The normal range is 2 to 12 ng per 100 ml, with a mean childhood value of 10.2 $\pm$ 7.6 ng per 100 ml.[74]

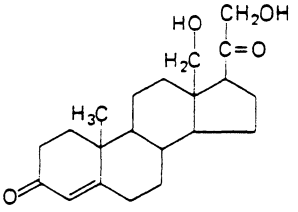
### Desoxycortisol (substance S)



Compound S

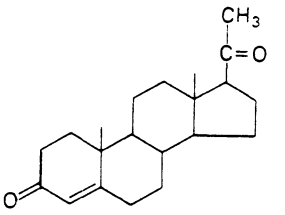
There is a strong compensatory elevation of 11-desoxycortisol in patients with 11-$\beta$-hydroxylase deficiency, as in the function test with metyrapone. RIA measurements after chromatographic separation are available,[74,81] as well as the measurement of tetrahydro-11-desoxycortisol in the 24-h urine. An 11-desoxycortisol excess can be recognized on determination of the 17-hydroxysteroids in the urine. The normal plasma level ranges from 0 to 0.8 ng/ml; in childhood an average value of 0.57 $\pm$ 0.26 (SD) ng/ml can be measured in the morning (9 to 10 A.M.).[74]

### 18-Hydroxy-11-desoxycorticosterone (18-OH-DOC)

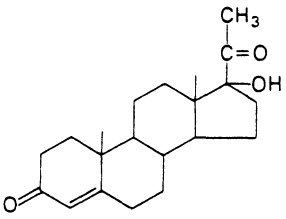



The measurement of this weak mineralocorticoid, which possesses only 1/175 of the action of aldosterone, is of no importance in the differential diagnosis of hypertension, although marked elevations have been demonstrated in essential hypertension of the low-renin type as well as in primary hyperaldosteronism.[49] The plasma analysis is done by radioimmunoassay. The highest levels are found around 8 A.M. with values between 3 and 16 ng per 100 ml. Specific antibodies are also available for the RIA measurement of 18-OH-tetrahydro-DOC in the 24-h urine.[34]

### Progesterone and 17-α-hydroxyprogesterone




Progesterone




17-α-Hydroxyprogesterone

The plasma progesterone is elevated in 17-α-hydroxylase deficiency, and 17-α-hydroxyprogesterone is correspondingly decreased. In 11-β-hydroxylase deficiency, the disinhibition of ACTH secretion as a result of the cortisol deficiency causes an excessive production of 17-α-hydroxyprogesterone. Progesterone may also be elevated in essential hypertension.[65] Both steroids can be measured by RIA with specific antibodies. The normal values for progesterone vary with the menstrual cycle. Mean values are as follows: follicular phase, 0.55 ± 0.103 (SD) ng/ml; midluteal phase, 8.6 ± 4.6 ng/ml;[1] prepuberty, 0.31 ± 0.19 ng/ml.[74]

The normal values for 17-α-hydroxyprogesterone are: follicular phase, 0.57 ± 0.21 ng/ml; prepuberty, 0.32 ± 0.13 ng/ml.[74]

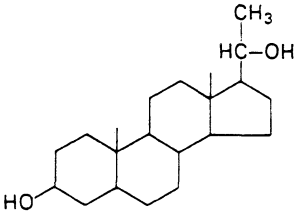
### 17-Hydroxysteroids

The analysis of 17-hydroxysteroids in the urine as a group test of adrenal steroids is still widely employed in the screening of adrenal disturbances. Cortisol, cortisone, 11-desoxycortisol, and their tetrahydro metabolites are detected in such analyses. In diagnostic programs for hypertensive patients, the main emphasis is on the demonstration of hypercortisolism. The method can also be used in function tests (dexamethasone, metyrapone), although numerous drugs interfere with the Porter-Silber color reaction (phenylhydrazine), such as phenothiazines, barbiturates, and digitalis preparations.[39,53] It is generally sufficient to precede the analysis with a 3-day medication-free period. Normal values vary with age and gender.

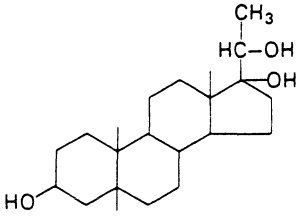
### 17-Ketosteroids

The urinalysis of 17-ketosteroids, often employed to estimate the androgenic activity of the adrenal cortex, encompasses the following steroids: etiocholanolone, dehydroepiandrosterone, androsterone, and additional trace steroids, but not testosterone or cortisol. In men, two-thirds to three-fourths of these steroids originate from the adrenal cortex; in women, 100%. In Cushing's syndrome (adrenocortical carcinoma, less frequently adrenocortical hyperplasia), elevated values may be present due to a dehydroepiandrosterone excess. Markedly low levels are found in 17-α-hydroxylase deficiency, and elevated levels in 11-β-hydroxylase deficiency as a result of increased androgen synthesis. Normal values vary with age and gender. A number of commonly used drugs interfere with the Zimmermann color reaction (coupling with methadinitrobenzene in alkaline milieu) on spectrophotometric analysis.[39]

### Pregnanetriol and pregnanediol




Pregnanediol

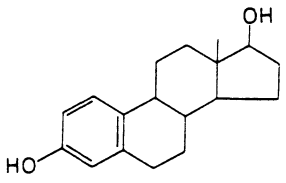



Pregnanetriol

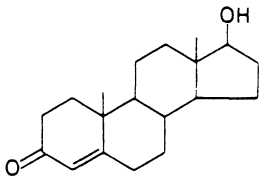
The measurement of pregnanetriol in the urine (as a metabolite of 17-α-hydroxyprogesterone) and pregnanediol (as a metabolite of progesterone and pregnenolone) has a limited diagnostic role in cases where the demonstration of plasma hormones is unavailable. Both spectrophotometric assay methods are quite laborious.[59] The normal range for pregnanediol in women is 0.4 to 1.8 mg per 24 h, and 1.5 to 4.8 mg per 24 h in the secretory phase; the normal range in men is 0.2 to 1.5 mg per 24 h.[52] The normal range for pregnanetriol is 0.42 to 3.2 mg per 24 h in women and 0.4 to 2.35 mg per 24 h in men.[52] It should be noted, however, that the values cited are subject to strong fluctuations, being age-dependent in both sexes and cycle-dependent in women. The

function tests are more important for diagnostic purposes.

### Estradiol and testosterone




Estradiol




Testosterone

Analysis of the sex steroids is helpful only in patients with hypertension associated with a defect of adrenal hormone production. The progressive virilization in 11-$\beta$-hydroxylase deficiency is accompanied by an excess of testosterone or its precursors. In 17-$\alpha$-hydroxylase deficiency there is a decrease of all androgenic and estrogenic steroids. The radioimmunoassay of these hormones belongs in the investigative program of every laboratory specializing in andrology and gynecologic endocrinology. The normal ranges vary as a function of age and sex, as well as with the menstrual cycle in women. The normal ranges show a distinct age-bracketing in children.[17,92]

## Additional Endocrinologic Techniques

### Preliminary remarks

The demonstration of pituitary hormones and "tissue" hormones and their enzyme components can offer only limited help in the differential diagnosis of hypertension and may not be justified at the present time. The technique for demonstrating *pituitary hormones* by means of RIA is (aside from ACTH) firmly established. Methods for quantitative determination of the various *prostaglandins* are still in the developmental stage and even today are practiced in only a few specialized laboratories, with substantial disparities in normal values. On the other hand, with the introduction of new synthetic, chromogenic substrates, the *kallikrein assay* in the urine could one day acquire diagnostic importance in the differentiation of primary aldosteronism and essential hypertension.

### ACTH

ACTH determinations in the plasma have not been widely used for differentiation of the various forms of Cushing's syndrome.[91] The reasons are mainly methodological: ACTH has a short half-life. The problem of preventing or retarding its degradation after collection of the blood sample has not yet been adequately resolved. Chilling of the blood and rapid centrifugation at 4°C are essential steps. The methods currently used vary both in terms of the extraction from the plasma and the antibodies used in the RIA. ACTH assays in the unextracted plasma are strongly influenced by the proteolytic breakdown of the tracer ACTH in the RIA preparation and so are not recommended. In view of the exacting methodology, the use of well-standardized kits appears advisable. In congenital defects in the biosynthesis of steroid hormones, elevated plasma ACTH levels[42] confirm the diagnosis, but need not be present. Mildly elevated ACTH levels in essential hypertension are of no diagnostic consequence and have been little studied from a pathogenic standpoint.[90] The diurnal variation is identical to that of cortisol. The normal values in adults (8 A.M.) are between 20 and 80 pg/ml.

### Somatotropic hormone (STH)

The observation of an increased incidence of hypertension in acromegaly implies no specific tasks with regard to hormone analysis. The RIA measurement of somatotropic hormone (STH) in the plasma is straightforward. It should be noted that STH basal values are not necessarily elevated in the acromegalic patient. The absence of a fall of STH following the oral administration of 100 g of glucose is of diagnostic significance. No correlation is present between the plasma STH and the blood pressure. The normal range for STH is 2 to 10 ng/ml.

### Prolactin

Prolactin determinations are of no importance in the diagnosis of hypertension, despite recent reports of alterations in juvenile hypertensives (elevated concentration profile at night).[78] According to studies by other authors,[51] the basal values of hypertensive patients are not altered relative to those of normotensive controls. The prolactin assay (RIA, double-antibody method) is uncomplicated. Numerous drugs influence the secretion of prolactin, and we have noted that an upright posture causes a decline. Strong elevations have been measured in renal failure with and without hypertension. The normal range is 5 to 15 ng/ml.

### Parathormone (PTH)

Hypercalcemia induced by increased autonomous PTH secretion can be proven by RIA which is one of the most intricate assays to work with. Difficulties are yet brought about by different (not human PTH) standards, various antibodies against PTH fragments and quality of the tracer PTH. Recently, a carboxy-terminal PTH fragment assay was introduced which indicates PTH excess accumulation of bioinactive split products in the circulation. Normal ranges vary from laboratory to laboratory.

### Prostaglandins

The importance of renal prostaglandins (PG) in the pathogenesis of hypertension is a subject of much current interest (see Chap. 13). As yet, however, they have found no role in practical diagnosis.

Hypertensives of the low-renin type apparently excrete significantly less E prostaglandins than do healthy controls and hypertensive patients with normal renin.[79]

The quantitative demonstration of prostaglandins of the E and F class in the urine reflects the synthesis rate in the kidney. Investigations in the renal venous blood are also informative. On the other hand, the interpretation of changes of the PG level in the peripheral venous blood is generally difficult owing to differences in the organs of origin and to rapid transformation during transit of the lungs. The bioassay of RIA requires various separation techniques (column chromatography in silicate columns or TLC). Despite relatively specific antibodies, RIA suffers from numerous nonspecific interference effects. PG determination by gas-chromatographic–mass-spectrometric analysis is time-consuming and requires elaborate technical facilities. The average normal range reported for $PGE_2$ is between 171 and 350 ng per 24\h with a sizable individual variation from 60 to 850 ng per 24 h. Extreme elevations reported in men (up to 20,000 ng per 24 h!) may be the result of contamination with seminal fluid.

### Kallikrein

The demonstration of quantitative differences in the renal excretion of the enzyme kallikrein in the various forms of hypertension has not yet acquired diagnostic importance. A breakdown of previous findings shows that patients with essential hypertension as well as those with renal hypertension may have a diminished kallikrein excretion.[44,50] The broad overlap with the normal range makes it doubtful, in any case, whether such a finding could be diagnostically helpful in the individual patient. On the other hand, the relatively high kallikrein excretion in primary aldosteronism (even compared to normotensive controls)[44] could be significant, provided the finding is confirmed in a larger patient population.

The new methods involving the esterolytic splitting of synthetic substrates by the addition of urine (radiometrically measured) are equivalent to the bioassay method. A new chromogenic tripeptide substrate, when incubated with fresh urine, liberates *p*-nitranilide, which then can be easily measured photometrically.[4]

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# Radiologic Methods of Diagnosis in Arterial Hypertension

# 27

H. U. Braedel, M. S. Polsky, H. Schieffer

Clinicians today differentiate primary or essential hypertension from the secondary or symptomatic forms. The etiology of the former is unknown, whereas secondary arterial hypertension can occur as a result of cardiac, renal, or endocrine abnormalities. Essential hypertension may be diagnosed only after the exclusion of all other forms.[48] On the other hand, every long-standing case of symptomatic hypertension has the potential of becoming self-sustaining even after the underlying lesions have been corrected. A prompt, intensive diagnostic work-up is essential, therefore.

## Hypertension due to Cardiovascular Causes

Cardiac-related hypertension is usually diagnosed during the clinical examination; radiologic studies confirm the diagnosis and dictate the therapeutic strategy.[10]

### Noninvasive Radiologic Studies

#### Chest teleroentgenogram in two planes

The X-ray focus and film are spaced 2 m apart in order that an approximately parallel beam is obtained. In this way an essentially distortion-free assessment of cardiac size can be made. Since the heart presents as a homogeneous organ in the usual roentgenogram, the different contours provide only a topographic impression of the individual heart chambers.[46] As a result, only the cardiac borders can be evaluated. In the posteroanterior chest film (Fig. 1), the following heart and vascular structures are visible as marginal features:

*From Upper Left Downward.* Distal portion of the aortic arch, proximal portion of the descending aorta, main branch of the pulmonary artery (the "pulmonary segment"), left atrial appendage, and left ventricle.

*From Upper Right Downward.* Superior vena cava, right atrium. The right ventricle is an anterior structure normally not delineated in the posteroanterior film.[94] In cases of long-standing arterial hypertension, the left ventricle enlarges toward the left, at times reaching the chest wall. The *lateral view* is routinely used for cardiac evaluation and is obtained by placing the left thorax against the film (dextrosinistral projection; Fig. 2). The structures seen anteriorly are, from above downward, the ascending aorta, main branch of the pulmonary artery, and the right ventricle. Normally a free space is present between the anterior heart border and the sternum—the retrosternal space. An enlargement of the right ventricle is seen as a protrusion of the upper anterior heart border into this space. (Figure 3 shows standard projections of the heart.)

*The posterior cardiac or vascular silhouette* is partially defined above by the superior vena cava, the descending aorta, the pulmonary vessels, and the left atrium. The left ventricle and inferior vena cava follow. The posterior cardiac contour and the spinal column bound the retrocardiac space. Enlargement of the left ventricle is recognized in this view by a posterior displacement of the visible contours; the so-called caval triangle is filled.[45]

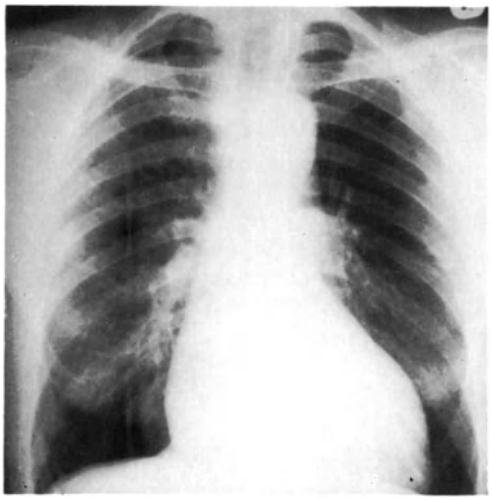


**Figure 1.** Posteroanterior chest teleroentgenogram, aortic configuration of the heart in hypertension. The heart is moderately enlarged to the left by left ventricular hypertrophy, the waist is preserved, the aorta is only mildly dilated, and there is evidence of hilar congestion (hypertensive heart).

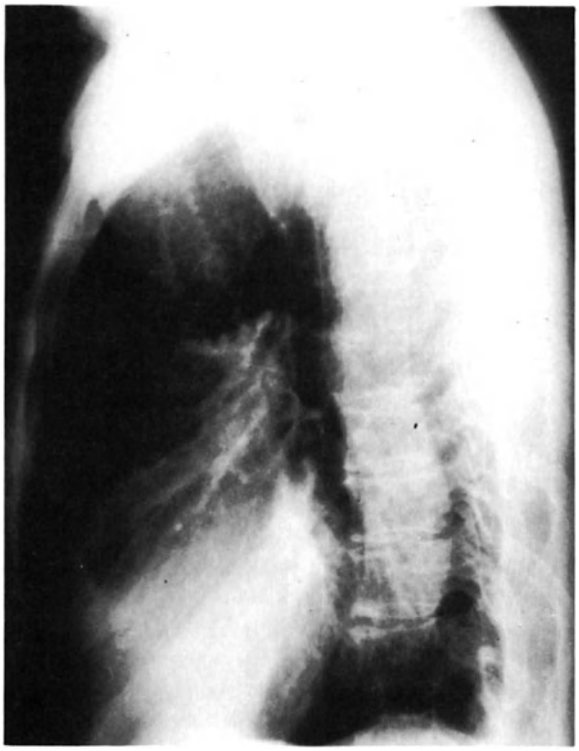


**Figure 2.** Dextrosinistral chest teleroentgenogram. "Elasticity hypertension." Dorsal protrusion of heart due to enlarged left ventricle. The mildly dilated aorta shows increased radiopacity throughout its course (hypertensive heart).

### Oblique chest teleroentgenogram

The posteroanterior and dextrosinistral views must be supplemented by right or left anterior oblique films in certain cases (congenital anomalies). These can provide additional information for assessing the posterior protrusion of the left ventricle, the anterior enlargement of the right ventricle and atrium, as well as the course and configuration of the thoracic aorta (left anterior oblique).

The right anterior oblique film can help in determining right ventricular enlargement (especially in the outflow tract) and posterior enlargement of the left atrium and ventricle.

### The kymogram

The kymogram provides a graphic record of the movements of the cardiac silhouette and great vessels. In this procedure, an X-ray–permeable lead grid is positioned between the patient and film. This grid has slits at regular intervals through which the film is exposed. Thus every image line moving perpendicular to the slits describes a curve. A synchronous evaluation of cardiac and vascular movements is possible to some degree. For example, aortic insufficiency will be demonstrated by vigorous marginal pulsations in all segments of the thoracic aorta, explained by the greater systolic-diastolic volume changes in this area. On the left heart border, one will also see the development of a lateral plateau with high tension peaks. The degree of pulsation changes does not necessarily correlate with the severity of the aortic insufficiency, however.[94,95]

## Invasive Radiologic Studies

### Cardiac catheterization

By catheterization of the heart and neighboring vessels, it is possible to measure the intra- and extracardiac pressures, determine cardiac and hemodynamic parameters, and radiographically visualize the heart and great vessels. Cardiac catheterization is the diagnostic procedure of choice in all the forms of hypertension listed in Table 1. Exceptions are "elasticity" hypertension, hypertension in complete A-V block, and the hyperkinetic heart syndrome, in which invasive methods should be avoided in establishing the diagnosis and determining therapy.

### Angiography of the heart and great vessels, ventriculography (levogram)

The contrast material is injected through a catheter into either the left or right ventricle with a mechanical syringe. Cinematography at 50 frames per second is usually employed. For the best anatomic detail, the AOT method (film magnification with automatic film changer) is preferred. A ventriculo-

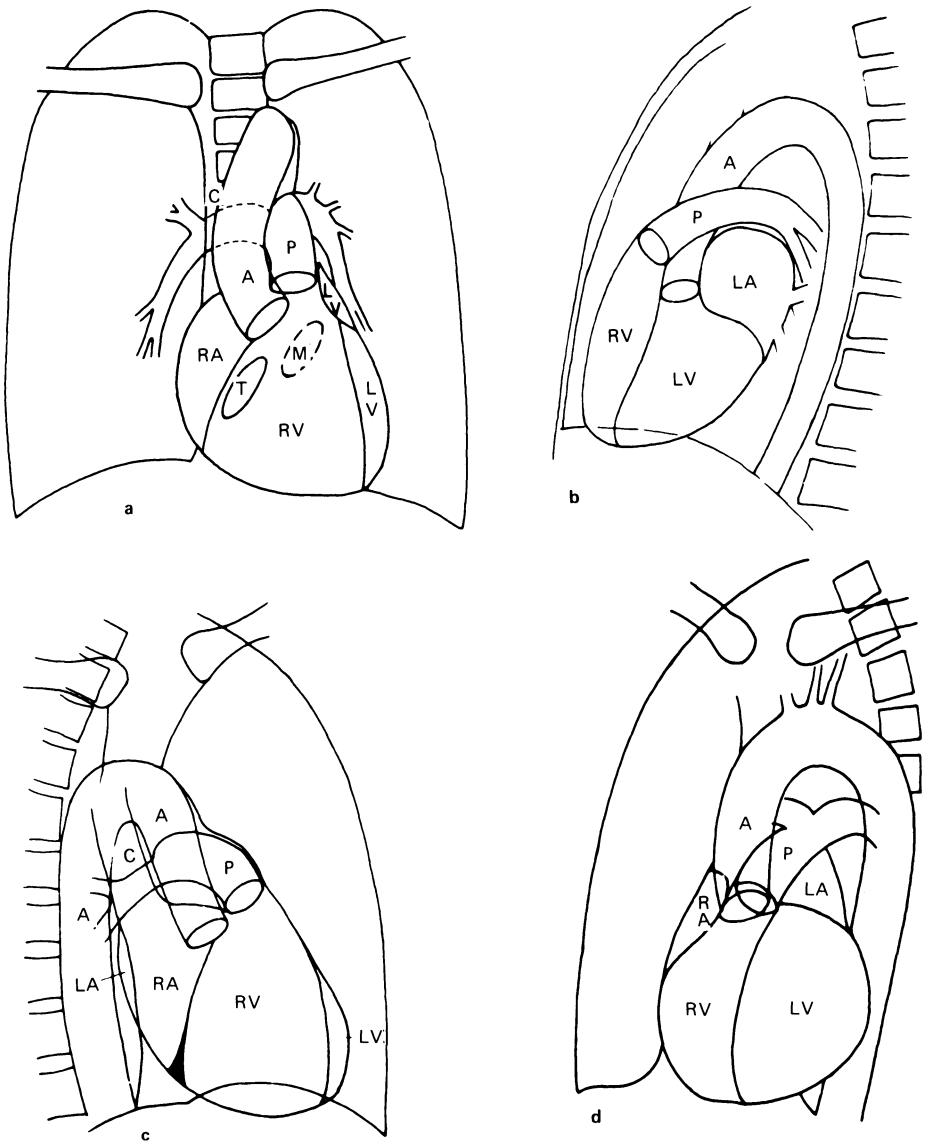



**Figure 3.** Standard projections of the heart. **a** Posteroanterior projection. **b** Left lateral projection. **c** Right anterior oblique projection. **d** Left anterior oblique projection. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; A, aorta; P, pulmonary artery; M, mitral valve; T, tricuspid valve; C, superior vena cava.

gram is necessary for the determination of ventricular form, size, and function.[77]

### Aortography

Aortography with visualization of the ascending aorta, the aortic arch, and the arteries arising from the aorta is accomplished by injecting contrast material in the area of the aortic root through a catheter inserted retro-grade through the femoral artery.[96] This procedure is contraindicated (danger of perforation) in the presence of aortic stenosis (e.g., coarctation of the aorta). To then demonstrate the stenosed vascular segment radiologically, access is gained via the brachial artery.[78] This procedure is performed in coarctation of the aorta as well as in aortic valve insufficiency, sinus of Valsalva aneurysm, and patent ductus arteriosus.

## Possible Complications of Invasive Diagnostic Studies[50]

### Vascular injury

Vascular injuries are possible at the site of catheter insertion (tears, hematomas, aneurysms, A-V fistulas). Passage of the catheter through the arteries and

**Table 1.** Survey of Forms of Arterial Hypertension due to Cardiovascular Causes

| |
|---|
| 1. Windkessel hypertension |
| Hypertension due to loss of aortic elasticity ("elasticity hypertension") |
| Hypertension in aortic valve insufficiency |
| Hypertension in patent ductus arteriosus and aortic-pulmonary window |
| Hypertension in perforated sinus of Valsalva aneurysm |
| 2. Other forms of hypertension from cardiovascular causes |
| Hypertension in coarctation of the aorta |
| Hypertension in complete A-V block |
| Hypertension in hyperkinetic syndrome |

veins can cause vascular wall injuries as well as dissections and perforations of arteriosclerotic vessels.

### Cardiac arrhythmias

Contact between the catheter and abdominal vessels may evoke vagus reflexes with resulting bradycardia and a fall in blood pressure. Endocardial contact with the catheter generally causes atrial or ventricular extrasystoles, and at times even persistent tachycardias (atrial and ventricular tachycardia; atrial and ventricular fibrillation).

### Endocarditis

Every invasive procedure carries a risk of bacterial endocarditis, especially in patients with acquired valve defects.

### Thromboembolism

Thromboembolic complications occur in 1.5% of catheter studies. Thrombi may form at the arterial puncture sites, or clots may dislodge from poorly rinsed catheters. Catheter manipulations can sometimes dislodge thrombi from the interior of the heart. Finally, air embolism may result from improper irrigation of the catheter.

### Allergic reactions

An intolerance to (usually iodinated) contrast materials can precipitate allergic reactions with urticaria, fever, and chills. Life-threatening reactions with bronchoconstriction are rare.

### Radiation exposure

The catheter is advanced under fluoroscopic control, and serial films are taken during angiography.

## Characteristic Radiographic Findings

### "Windkessel" forms of hypertension

Elasticity hypertension ("senile hypertension") secondary to a loss of aortic elasticity is a manifestation of arteriosclerosis of the great arteries. The resulting loss of "windkessel" (expansion chamber) function leads to a rise in systolic blood pressure with a concomitant fall of diastolic pressure.[90]

***Hypertension in Aortic Insufficiency.*** Aortic valve insufficiency may be a result of rheumatic or arteriosclerotic degenerative changes, bacterial endocarditis, or in rare cases a congenital malformation of the aortic valve. The incompetent valve permits the reflux of blood from the aorta back into the left ventricle during diastole, resulting in a fall of diastolic pressure. Also, the left ventricle must increase its output to expel the regurgitant blood and maintain a normal output to the circulation. This occurs primarily through an increase in the systolic pressure[90] (Fig. 4).

### Hypertension in patent ductus arteriosus and aortic-pulmonary window

The patent ductus arteriosus creates a communication between the aorta and left pulmonary artery. The aortic opening is situated immediately below the origin of the left subclavian artery. This congenital defect, which is life-sustaining during fetal life, remains open instead of obliterating during the first few days of life.[1] In the aortic-pulmonary window, there is a congenital opening in the septum between the aorta and pulmonary artery just above its origin from the heart.[13,27] In both forms there is a left-to-

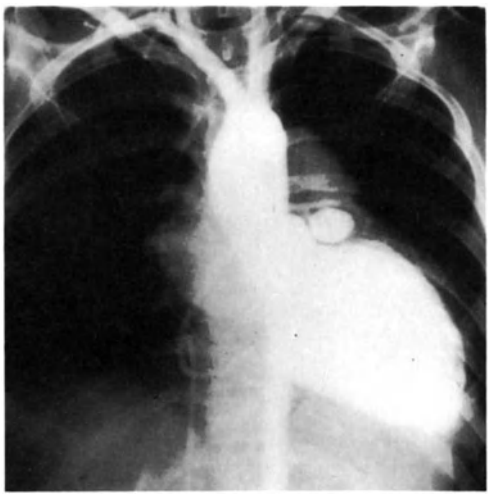


**Figure 4.** Aortic valve insufficiency and sinus of Valsalva aneurysm; retrograde thoracic aortogram. Reflux of contrast medium into dilatated, nonhypertrophic left ventricle (weak opacification of the slightly enlarged left atrium is seen in cases of relative mitral insufficiency). An aneurysm of the left sinus of Valsalva is filled with contrast material. The origin of the coronary arteries is normal.

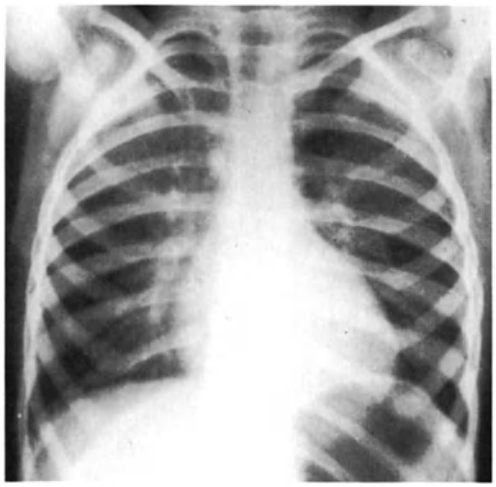


**Figure 5.** Patent ductus arteriosus in posteroanterior upright film. Narrow pedicle, aortic arch not prominent, left ventricular hypertrophy with radiographically visible enlargement as a result of left ventricular volume overload.

right shunt resulting from the pressure gradient and low resistance in the pulmonary circulation. In order to maintain a normal peripheral blood flow, the heart must increase its output, again via a rise in the systolic pressure. Because of the aortic leak, the diastolic pressure is descreased[90] (Figs. 5 and 6).

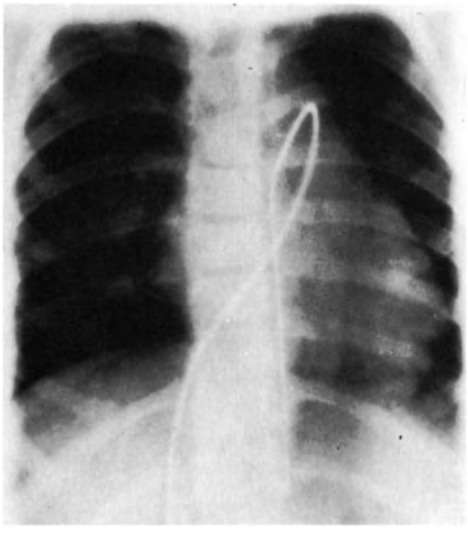


**Figure 6.** Patent ductus arteriosus in 8-year-old child. The catheter is advanced from the right femoral vein into the pulmonary artery. It makes an acute turn medially and caudally at the level of the pulmonary arch and displays a deltalike contour: course of the catheter through the patent ductus into the descending aorta (posteroanterior supine film).

### Hypertension in perforated sinus of Valsalva aneurysm

An aneurysm may arise in the sinus of Valsalva, located in the area of the aortic root. This can result from congenital or endocarditic weakness of the vascular wall. The aneurysm usually perforates into either the right atrium or right ventricle, creating a left-to-right shunt with consequences similar to those in patent ductus arteriosus (rise of systolic pressure, fall of diastolic pressure)[65] (Fig. 7).

In Figure 7 a transseptally placed catheter injects contrast material from the right ventricle into the left ventricle, revealing a ruptured aortic sinus perforating into the right ventricle.

### Hypertension due to other cardiovascular causes

***Hypertension in Coarctation of the Aorta.*** The coarctation forms as a result of congenital obstruction (or, more rarely, obliteration) of the aorta in its proximal descending portion. The extent and length of the change are variable. Depending on its anatomic relation to the ductus arteriosus or ligamentum arteriosum, the coarctation may be classified as preductal (infantile form) or postductal (adult form).[49] The collateral supply to the lower half of the body is by branches of the subclavian artery, especially the internal thoracic artery, which communicates with the thoracic aorta via the intercostal arteries. The costocervical trunk and thyrocervical trunk are also involved in the collateral supply. A pressure gradient develops at the site of the coarctation, with hypertension of the upper body half and hypotension of the lower half (Figs. 8–10).

***Hypertension in Complete A-V Block.*** In these cases there is extreme bradycardia with a very great increase in stroke volume. *Necessary hypertension* is the term sometimes applied to this state.[90]

***Hypertension in the Hyperkinetic Syndrome.*** Heightened stimulation of the $\beta$ receptors of unknown etiology may be encountered in juvenile patients. The result is a rate-dependent increase in the cardiac output with systolic hypertension.[66]

### Results and Diagnostic Value of Radiologic Studies

The chest teleroentgenogram can in itself be informative and diagnostically valuable, depending on the duration of the arterial hypertension. In longstanding cases, left ventricular hypertrophy is easily recognized. In the PA view, the ventricular contour protrudes to the left toward the chest wall (Fig. 1),

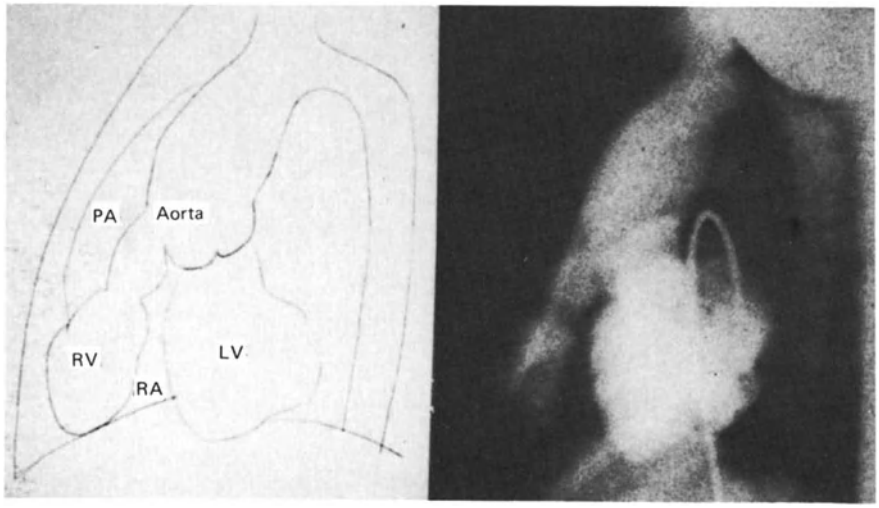



**Figure 7.** Perforated sinus of Valsalva aneurysm (into right ventricle); lateral film. Contrast medium injected into left ventricle via transseptally placed catheter. PA, pulmonary artery; LV, left ventricle; RV, right ventricle; RA, right atrium.

while the lateral film shows dorsal displacement (Fig. 3), occasionally to the point where the cardiac shadow overlaps the spinal column.[64] The aortic pedicle gives a particularly dense shadow in elasticity hypertension (Fig. 2), is sometimes ectatic, and often shows calcifications in the aortic knob.[88]

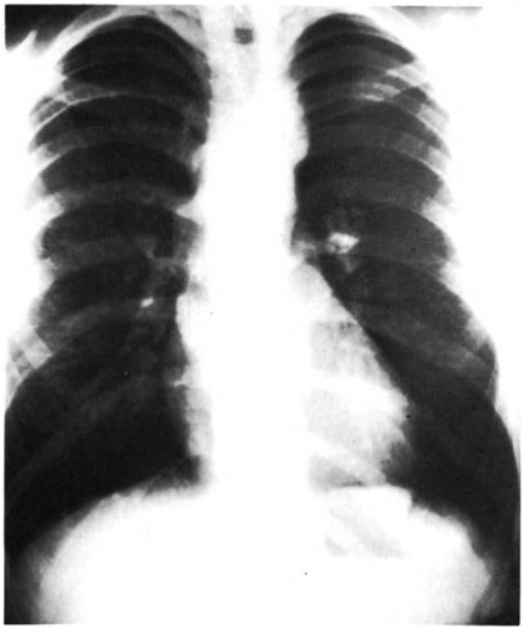


**Figure 8.** Coarctation of the aorta in 25-year-old man; posteroanterior chest teleroentgenogram. Marked indentation below aortic knob in typical location, rib notching.

The chest teleroentgenogram is also helpful in aortic insufficiency, for as hemodynamics become more severe, accompanying roentgenographic changes become evident. The typical "aortic heart" appears, as the left lower portion of the cardiac shadow elongates and enlarges to the left and caudally. The angle between the heart and pulmonary artery origin becomes more acute, the aortic knob is protuberant, and the rest of the aortic arch is dilated. The kymogram yields additional information from the more vigorous excursions of the ascending and descending aorta.[94,95]

Coarctation of the aorta shows a prominent left heart and in some cases cardiac enlargement. The aortic knob is usually prominent and sometimes displays a typical indentation (Fig. 8). The kymogram also provides information from the varying pulsations observed proximal and distal to the site of coarctation. The diagnosis is verified by the notching seen on the inferior margin of the third through eighth ribs due to pulsatile erosion by the tortuous and at times aneurysmically dilated intercostal arteries[68] (Fig. 9). A normal-size cardiac shadow is observed with the smaller shunt volumes that occur in patent ductus arteriosus and aortic-pulmonary window. With larger shunts the left atrium and ventricle are enlarged. the pulmonary arch is dilated, and the hilar image is intensified by the increased pulmonary blood flow (Fig. 5). Kymography discloses hilar pulsations.[13,27,51]

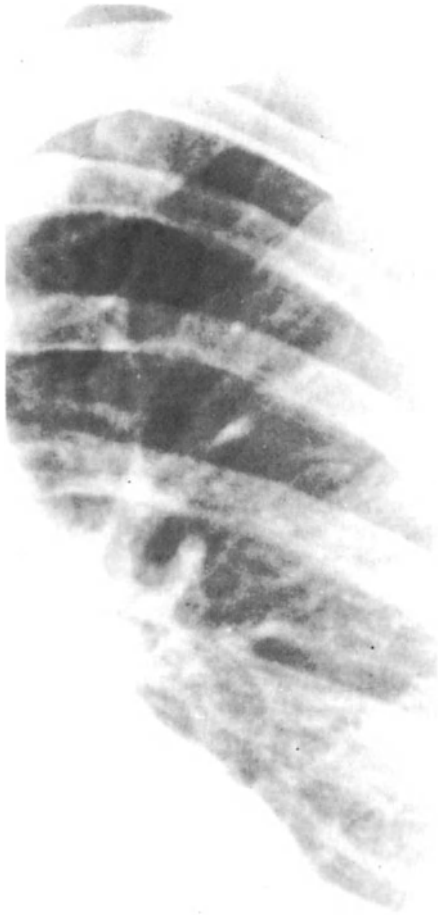


**Figure 9.** Notching of ribs (detail).

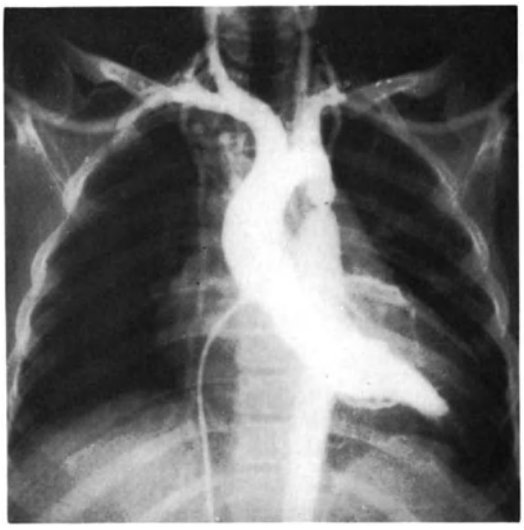


**Figure 10.** Coarctation of the aorta; transseptal levogram. The catheter is advanced from the right femoral vein transseptally via the right atrium into the left ventricle. The contrast medium opacifies the hypertrophied left ventricle and demonstrates an hourglass-shaped stenosis in the upper part of the descending aorta. Well-formed collateral circulation via the internal mammary artery.

Angiography and cardiac catheterization can be considered together in relation to their diagnostic utility.

Cardiac catheterization in aortic insufficiency makes it possible to measure the hemodynamic effects of the valve defect. The stroke and regurgitation volumes can be calculated from the ventriculogram. Aortography indicates the regurgitation volume. These findings, along with the clinical picture, will determine whether treatment should be operative or conservative.[9,63,91]

Right-heart catheterization is sufficient to establish a diagnosis of patent ductus arteriosus. The shunt volume can be calculated from the oxygen saturation gradient between the pulmonary artery distal to the ductus and the right ventricle. In about 80% of cases the ductus can be directly catheterized (Fig. 6). Angiography is advised only if coexisting anomalies are suspected.[51]

If coarctation of the aorta is present, cardiac catheterization enables one to determine the pressure gradient by measuring the pre- and poststenotic pressure. A coexisting aortic valve defect (in 5% of cases) must also be excluded. Futhermore, the angiographic demonstration of the location and length of the coarctation as well as the collateral supply to the lower body half is mandatory for operative correction[67] (Fig. 10). The diagnosis of coractation of the aorta constitutes an indication for surgery.

Cardiac catheterization and angiography are considered the method of choice in hypertension associated with cardiovascular defects. They not only permit an accurate diagnosis, but are extremely helpful in planning further therapy.

## Nephrogenic Hypertension

There are three main groups of nephrogenic hypertension: prerenal (vascular), intrarenal (parenchymato-vascular), and postrenal (urinary tract). The boundaries between these groups are indistinct. Changes in or effects on the vascular system are always the factor precipitating the hypertension. This is also true to some extent for the hydronephrotic

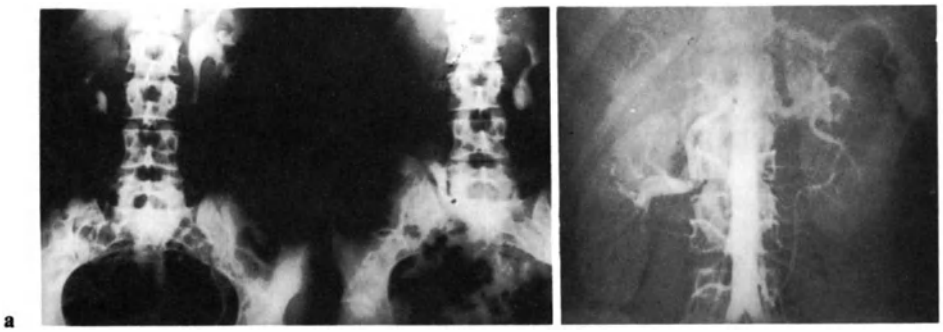



**Figure 11.** **a** Right-sided nephroptosis established by upright urogram. **b** Associated angiogram with marked renal artery stenosis on the side of the ptosis.

kidney, in which pressure on the renal parenchyma can result in intrarenal circulatory impairment.

The *excretory urogram* (plain film, early and late contrast films) is at the forefront of the radiodiagnostic repertoire. It is used in the demonstration of:

1. Pathologic calcifications in the kidneys or urinary outflow tract (stones, parenchymal calcifications associated with tuberculosis or tumors, calcified cysts, vascular or aneurysmic calcifications, trauma effects) as well as irregularities in the size or location of the kidneys.
2. Outflow obstructions (acquired, congenital) with reflux in the ureter (hydroureter, megaureter) and renal calyces (hydronephrosis,[12] pyonephrosis) associated with prostatic disorders and other lower abdominal diseases, ureteroceles, subpelvic constrictions, multiple small[41] or large solitary cysts, horseshoe kidneys, and other malformations.

The exact size and form of the kidneys can be determined by *zonography* or *nephrotomography*. A decrease in the length of the right kidney by 2 cm or more as compared to the left kidney, or of the left kidney by 1.5 cm or more relative to the right kidney, is considered significant.[16,93] In thin patients, upright films should be obtained (Fig. 11a,b).

In the rapid-sequence method,[6,24,29,47,71,73,93] early films are made 1, 2, 3, and in some cases 4 and 5 min after injection of the contrast medium, followed by late films taken at 8, 15, and 30 min. Generally the results obtained with the late films can also be observed in the 5- and 6-min films (Fig. 13b). The contrast material should be rapidly injected as a bolus. If venous conditions permit, one ampule of contrast medium is injected with a tourniquet affixed, and a

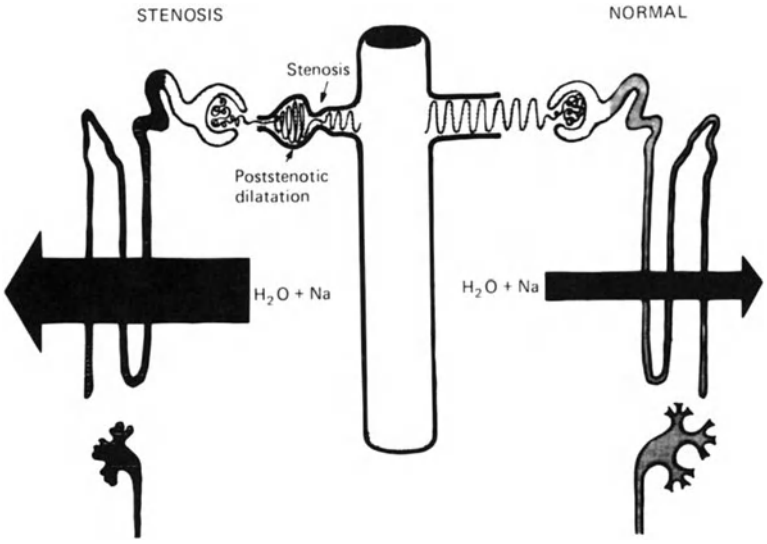



**Figure 12.**

second ampule is injected after the tourniquet is released. As an alternative, each ampule can be injected simultaneously into both cubital veins. In the presence of a functionally significant unilateral renal artery stenosis with a diminution of renal blood flow and glomerular filtration, the contrast material will appear earlier and will be more concentrated on the unstenosed side than on the stenosed side in the 1- or 2-min film. On the stenosed side the contrast medium reaches the renal pelvis more slowly as a result of the slower flow of the primary urine. Because the percentage water reabsorption is greater than on the healthy side, the nonreabsorbed materials, including the contrast medium, appear somewhat later in hyperconcentrated form in the collecting system (see Fig. 12). These processes are demonstrated by the *late films* of the excretory urogram, which show normal drainage of the contrast medium from the calyceal system on the healthy side and hyperconcentration of the medium on the stenosed side (Fig. 13a–d).

This effect can be accentuated with "washout" pyelography, in which the patient is given an infusion of physiologic saline or 40 g of urea (not in patients with impaired renal function and high BUN) in 500 ml of distilled water or saline. This will accelerate the excretion of contrast medium on the healthy side. A similar effect can be achieved by administering a diuretic.

It should be mentioned that rapid-sequence urography is an object of growing criticism.[61,93] Stolle et al.,[93] for example, evaluated the IVPs of 402 randomly selected hypertensive patients, 80 of whom subsequently underwent arteriography. They found an accuracy rate of 58% in cases of proven unilateral renovascular disease. Urographic signs suggestive of renal artery stenosis were found in 6.5% of the overall group. Renal artery stenoses smaller than 60% of the vascular diameter rarely showed urographic signs. Correctly positive findings were obtained in 18.5% of cases; The urogram was positive in 33% of patients with 20% to 50% stenosis, 55% with 50% to 80% stenosis, and 77% with stenosis greater than 80%. The percentage of false-positive results in this study was remarkably high: 17.5%.

The early films increased the number of correct tentative diagnoses only moderately. On the other hand, there was a greater than average number of false-positive results in the early phase. Thus, one should not be too optimistic regarding the value of early films in the excretery urogram.

Consideration of the pole-to-pole diameter of the kidneys is of great importance despite the fact that it is not an exact measure of renal size.[36] Marked renal size disparities combined with hypertension should always prompt radionuclide studies, which are discussed elsewhere in this book. The results of these studies will determine in large measure whether to proceed with angiography, assuming the patient is operable.

*Renal angiography*[3,30,98] involves the injection of a contrast material into the aorta *(abdominal survey aortography)* or into the renal artery itself *(selective renal arteriography)*. With abdominal aortography it is possible in various projections to accurately assess the proximal renal artery (Fig. 14) and to detect any collateral vessels that may arise from the aortic branches. Selective arteriography provides a high-contrast image of the intrarenal arterial system and intrarenal collaterals which is free of overlapping shadows. *Magnification angiography* can yield additional information in some cases.

Selective catheterization of the renal artery is also necessary in cases where it is desirable to *determine the pressure gradient* across a stenosis. In this procedure a very thin polyethylene catheter with an outer diameter less than 1 mm is threaded through the selective renal catheter past the site of the stenosis. The angiographic catheter itself is then withdrawn into the abdominal aorta under fluoroscopic control. The pressure distal and proximal to the stenosis is then measured. Hemodynamic significance is assumed if the pressure gradient is greater than 40 mm Hg.[7,8]

Abrams, Baum, and Stamey describe a simple method for determining the hemodynamic significance of a renal artery stenosis.[2,4] Fifteen milliliters of a renally excreted contrast medium is injected directly into the renal vein with a pressure injector within three-fourths of a second. The time required for the medium to disappear from the renal veins is called the *washout time.* (Small amounts of medium remaining in the dorsally located veins are disregarded.) In normal subjects the washout time is 1.25 to 4.5 s. In the presence of 50% to 80% stenosis, it is 1.5 to 6 s; in stenoses exceeding 80% the washout time is considerably prolonged and averages 6 to 11 s. Prolonged washout times are also associated with the increased resistance in the smaller renal arteries and arterioles seen in advanced nephrosclerosis.

According to Wolf, the increase of renal size after the infusion of vasodilators in *vasodilated excretory urography* provides a suitable means of detecting clinically significant renal artery stenosis. A size increase of 10% or more indicates an absence of significant stenosis, while an increase of 5% or less is interpreted as clinically significant.[102,103] Raust et al.[79] tested this method in 1032 kidneys, 84 of which were also studied angiographically, and compared it with the rapid-sequence excretory urogram. They

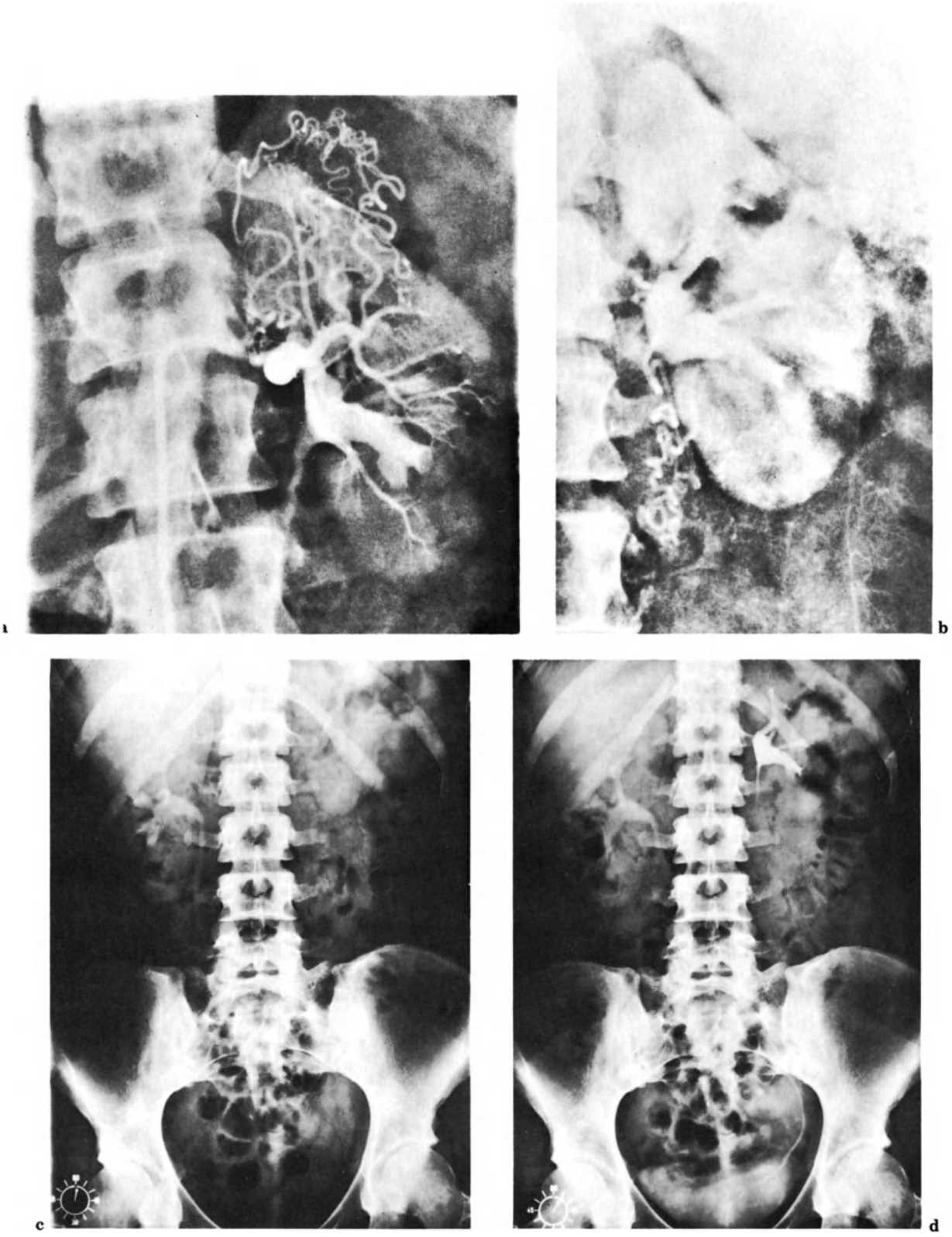


**Figure 13. a–d** Twenty-year-old woman: left renal artery stenosis with collateral supply via adrenal and capsular arteries; **a** at 1 min; **b** collateral above the ureteral arteries; **c** at 6 min contrast medium excreted only on right side; **d** much stronger opacification on left than on contralateral side.

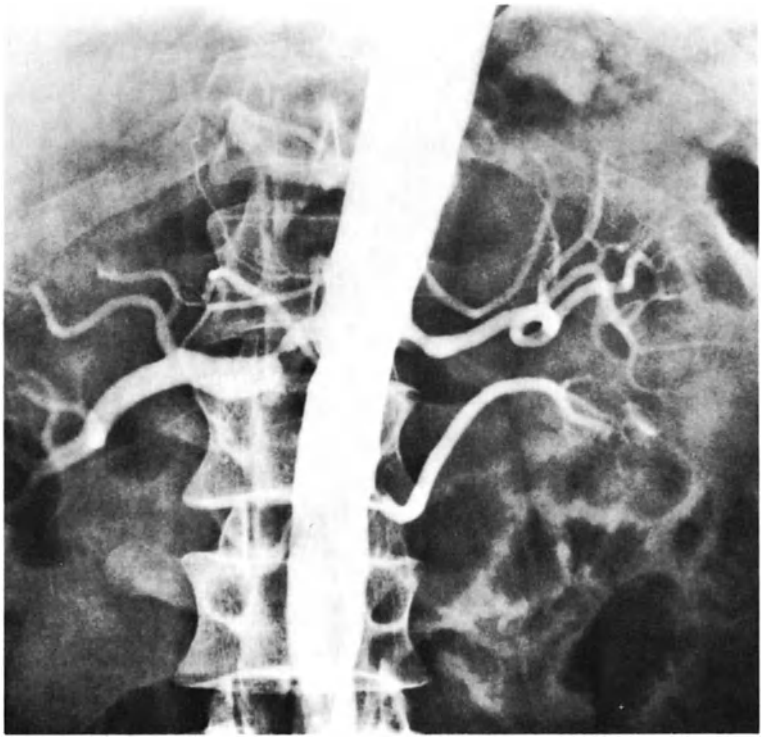


**Figure 14.** Survey angiogram of 50-year-old hypertensive man with marked proximal renal artery stenosis, mainly on right side, where poststenotic dilatation is also seen.

found it to be of less diagnostic value than represented by Wolf et al. and state their preference for the urogram.

The possible causes of renovascular hypertension are as follows:

1. Causes primarily affecting the renal vasculature
   a. Arteriosclerosis of the renal artery and intrarenal arteries
   b. Fibromuscular disease
   c. Neurofibromatosis
   d. Segmental hypoplasia (Ask-Upmark)
   e. Arterial thrombosis (secondary to arteriosclerosis, fibromuscular disease, inflammation, arteritis of varying etiology, renal artery aneurysms, polycythemia, trauma)
   f. Embolism (heart defect)
   g. Arteriovenous fistula (trauma, biopsy, surgery, tumor)
   h. Aneurysms of the renal artery and its branches[14]
   i. Various arteritides
      (1) Thromboangiitis obliterans
      (2) Periarteritis nodosa[22]
      (3) Takayasu's disease
   j. Renal transplantation
2. Causes secondarily affecting the renal vasculature
   a. Severe arteriosclerotic changes of the supra-, inter-, and infrarenal abdominal aorta
   b. Coarctation of the aorta
   c. Compression from without (hematoma, Page kidney,[32,70,89] cysts, malignant tumor)
   d. Tension from abnormally positioned fibrous tissue (diaphragmatic insertions)[57]

While the experimental work of Goldblatt has established renovascular lesions as a possible cause of hypertension, it must be borne in mind that only about 5% of all hypertensives have a renovascular cause for their disease.[16]

A large proportion of patients with renal artery stenosis are normotensive.[33] This is especially true of arteriosclerotic stenoses, which account for the majority of such lesions.[3] Arteriosclerotic stenoses are found primarily in the proximal third of the renal artery and are often associated with poststenotic dilatation even to the point of aneurysm. As the disease progresses, the renal artery may become completely obstructed.

*Fibromuscular disease*[34,72,83,97] is most prevalent in the middle and distal thirds of the renal artery. Intrarenal branches may also be affected, however. The angiographic changes show a "string of beads" pattern and are usually localized on one side. The disease may affect the intima, media, adventitia, or

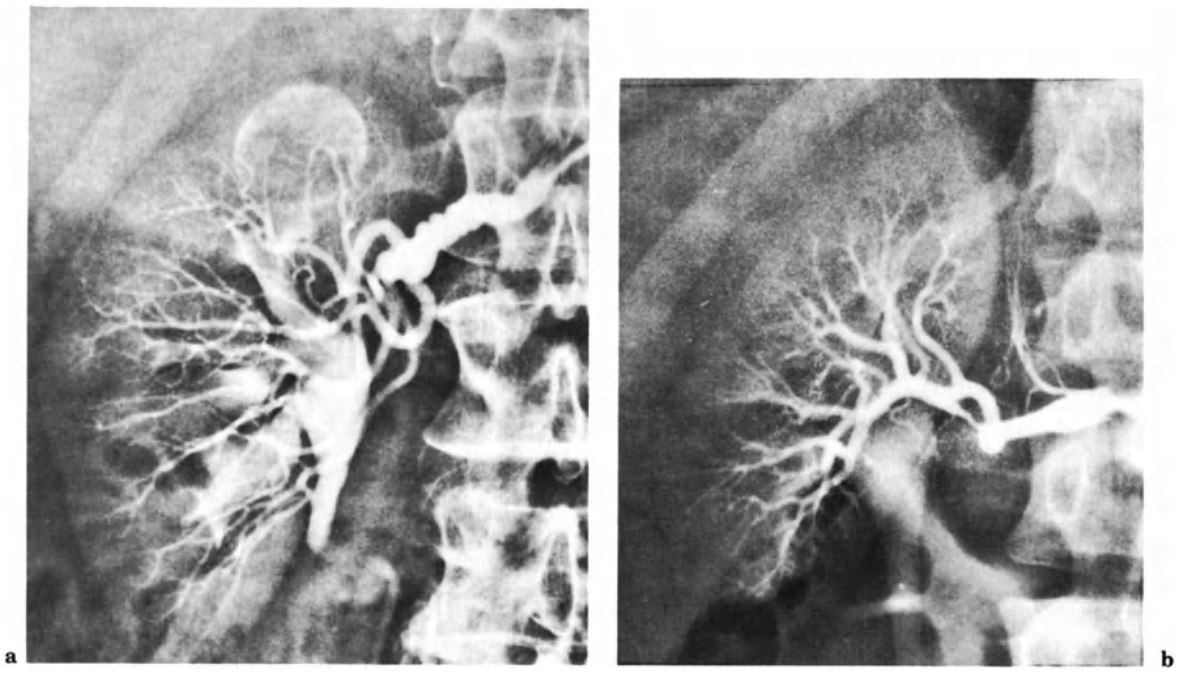



**Figure 15.** **a** Fibromuscular hyperplasia of the right renal artery. The hypernephroma in the upper renal pole is 3 cm in diameter (histologically proven). **b** Twenty-year-old hypertensive man with stenosis of distal half of right renal artery and significant, nearly threadlike constriction of a renal artery segment branch. Probable fibrous stenosis of intima or adventitia; no operation.

even periarterial tissue. The most common form involves the media, and this constitutes true *fibromuscular hyperplasia* (Fig. 15a). The intima[19] and adventitia are very rarely involved. A higher than average proportion of patients with fibromuscular disease are reported to have nephroptosis or hypermobile kidneys.[57] While the aforementioned string-of-beads appearance of medial fibrosis is pathognomonic, circumferential stenosis with no diverticulum-like dilations is the main finding in fibrous stenosis of the intima and adventitia (Fig. 15b). Besides the main renal artery, accessory renal arteries may also be affected by fibrous dysplasia. In contrast to the localized stenoses in arteriosclerosis, collaterals are frequently observed in fibromuscular dysplasia.[57] Fibromuscular dysplasia also differs from arteriosclerosis in that the abdominal aorta is free of changes. In *segmental hypoplasia* (Ask-Upmark kidney),[39,84] the arteries demonstrate medial hyperplasia and a fibroelastic hyperplasia of the intima.[5]

The vascular changes of *fibromuscular dysplasia* cannot be distinguished angiographically from stenoses caused by *neurofibromatosis*.[42] Rosenbusch et al. found in the literature 72 cases of neurofibromatosis associated with renovascular hypertension.[83] They reported on three further patients, two of whom displayed unilateral renal artery stenoses with small aneurysms. The third patient had a coarctation of the abdominal aorta.

It is virtually impossible to distinguish angiographically a renal artery *thrombosis* from an *embolism* (Figs. 16 and 17). Complete occlusion of the main renal artery by thrombosis or embolism does not automatically lead to hypertension, unless a collateral circulation has developed.

*Arteriovenous fistulas* may be congenital or acquired. Congenital fistulas are seen with arteriovenous angiomas, while acquired fistulas can result from trauma, biopsy, surgery (Fig. 18), arteriosclerosis, severe inflammatory processes and, most commonly, hypernephromatic disease (Fig. 19). An important cause of A-V fistulas is the common ligature of an artery and vein during nephrectomy. A-V fistulas may also form from the rupture of an *aneurysm*. These are usually true aneurysms. They may be congenital, traumatic, arteriosclerotic, mycotic, or inflammatory in origin, the arteriosclerotic type being the most common.

*Fibromuscular disease* as well as *periarteritis nodosa* can lead to microaneurysms.[35] The majority of the aneurysms are of the saccular type (Fig. 20). Fusiform aneurysms are poststenotic dilatations seen distal to high-grade stenoses. Usually the aneurysms

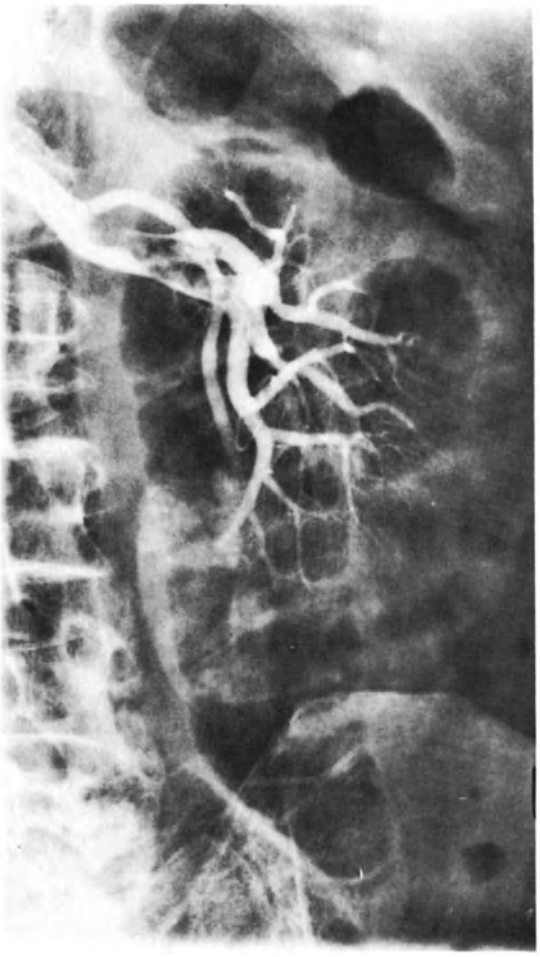


**Figure 16.** Recent renal artery thrombosis of single left kidney with general arteriosclerosis; no hypertension.

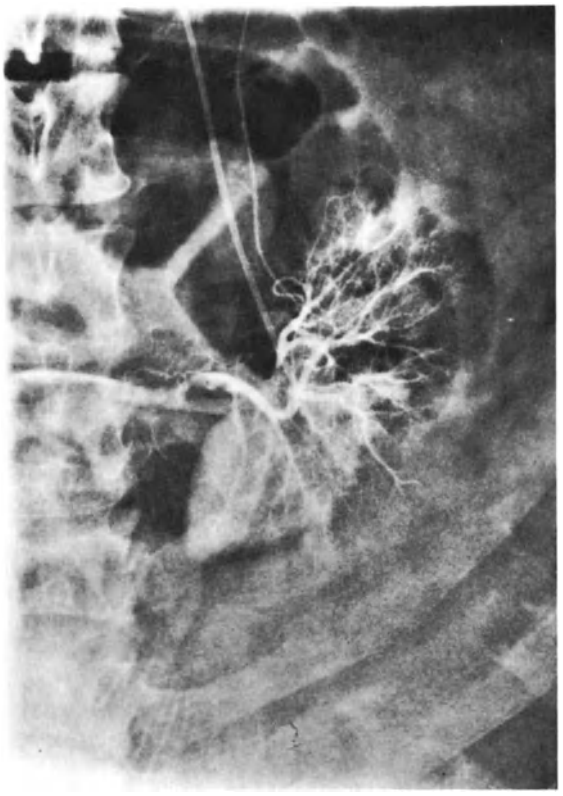


**Figure 17.** Acute right renal artery embolism in 53-year-old man with pacemaker (due to heart block and arrhythmia); no hypertension.

are isolated and localized in the main artery. Calcifications of the aneurysmal wall are not uncommon. The cause of hypertension with aneurysms is related to decreased blood flow as a result of turbulence, thrombosis within the aneurysm, and consequent narrowing of the flow channel, pressure of the aneurysm on neighboring vessels. Aneurysms may also be multiple (Fig. 21), and they are bilateral in about 50% of cases.

The renal vessels are commonly involved in the various *arteritides*. In periarteritis nodosa, for example, 80% of patients will have renovascular involvement, typically with microaneurysms in the renal periphery (Fig. 22).[57]

Hypertension after renal transplantation is seen in 37% of cases (Doyle in ref. 61). Various causes have been suggested: (1) renovascular processes, (2) immunosuppressive therapy, and (3) rejection responses.

**Figure 18.** Hypertension in patient with arteriovenous fistula after right upper polar resection. Photo: Prof. Dr. W. Wenz, Institute of Radiology, University of Freiburg.

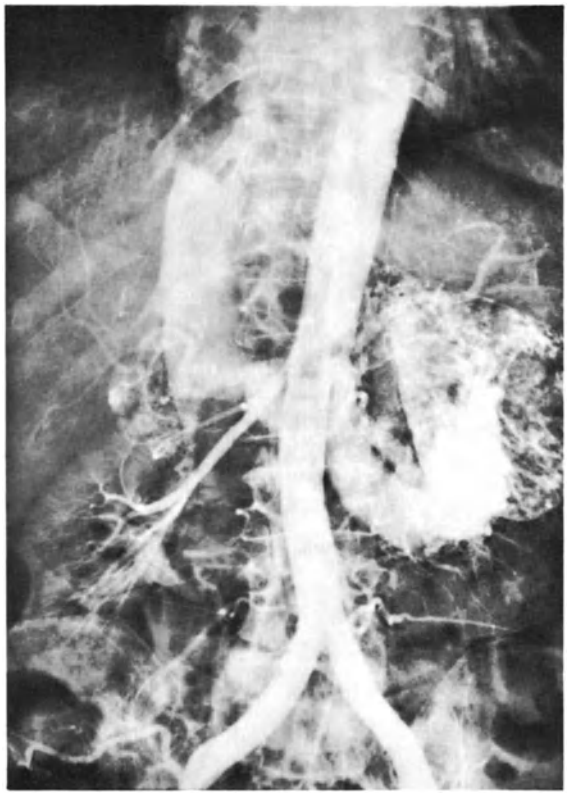


**Figure 19.** Hypertension in massive arteriovenous fistula secondary to left-sided hypernephroma. Opacification of inferior vena cava seen during arterial phase of survey aortogram. Patient became normotensive after surgery.

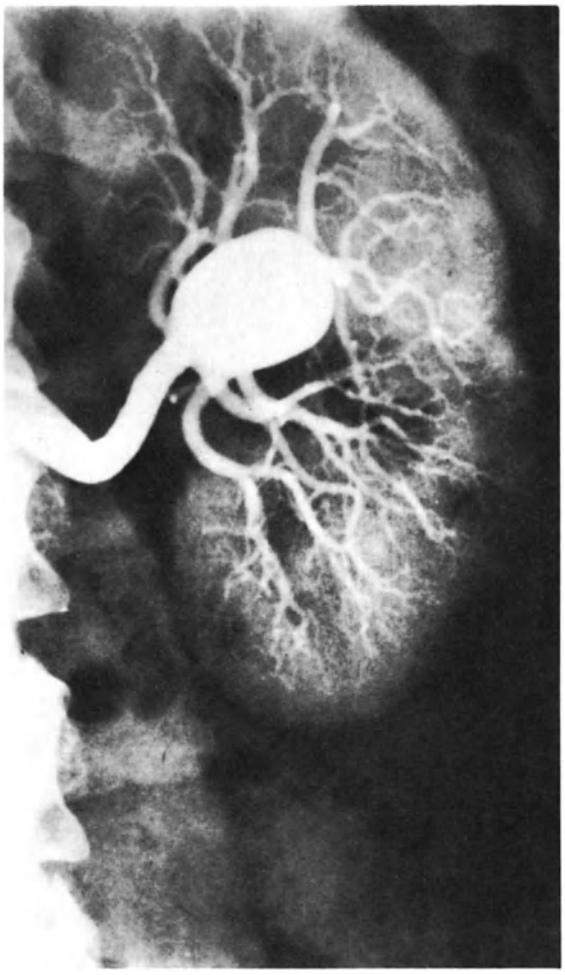


**Figure 20.** Large saccular intrarenal aneurysm in adolescent female hypertensive patient.

Angiography, which is performed through the femoral artery on the side opposite the transplant,[59] can demonstrate thromboses or constrictions in the area of the vascular anastomosis. Often the patient must be rotated in various oblique views in order to demonstrate the stenoses. A slight decrease in the renal artery diameter is frequently observed, but this may be of no significance. In rejection episodes a rarefaction of the parenchymal vessels is seen, and the usually constricted intrarenal arteries appear to be unduly straight; the flow rate is reduced.[106]

Of course *changes in the supra-, inter-, and infrarenal portions of the lower abdominal aorta* can lead to impairments of renovascular flow.

An extremely rare cause of flow reduction in a renal artery is described by Kincaid:[57] *tension on the renal arteries* by atypically located muscle fibers of the diaphragm and psoas muscle (films made during inspiration and expiration[3]).

A further possible cause of *constriction of the renal artery and its branches* is *compression* from a perirenal or subcapsular hematoma with consequent fibrosis, or as a result of cysts or malignancies.

*Angiographs* are indicated after stenosis surgery[58] if clearance studies suggest a flow reduction or if hypertension recurs. Possible complications of venous bypass surgery include stenoses, obstructions, infarctions, and especially dilatations, which at times take the form of aneurysms (Fig. 23a,b). The dilatations, which tend to be progressive, make radiologic follow-up imperative[31] (Fig. 24a,b).

The *collateral circulation*[38] in renal artery stenosis can take various forms (Fig. 25). In general, the demonstration of a collateral circulation implies that the stenosis is hemodynamically significant. Bookstein and Ernst, by changing the flow direction in the distal, nonparenchymatous branches of the renal artery by the infusion of vasodilators or vasoconstrictors, were able to establish the existence of

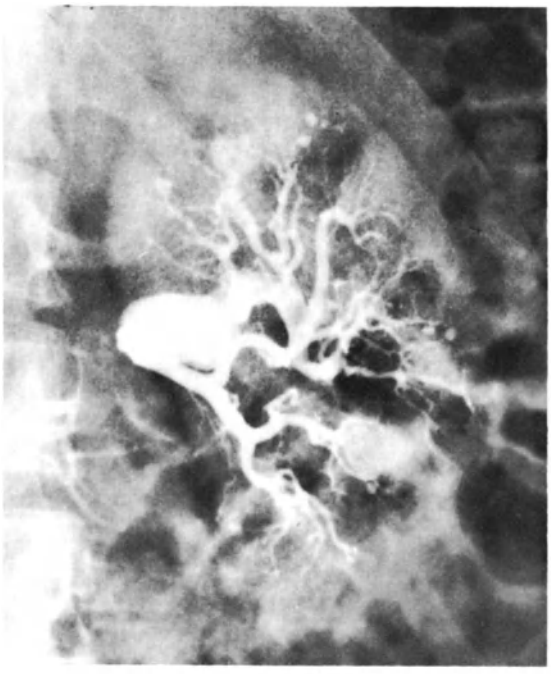


**Figure 21.** One large and multiple small left renal artery aneurysms in a 26-year-old hypertensive man. BP 220/110 before surgery, 145/85 14 days after nephrectomy.

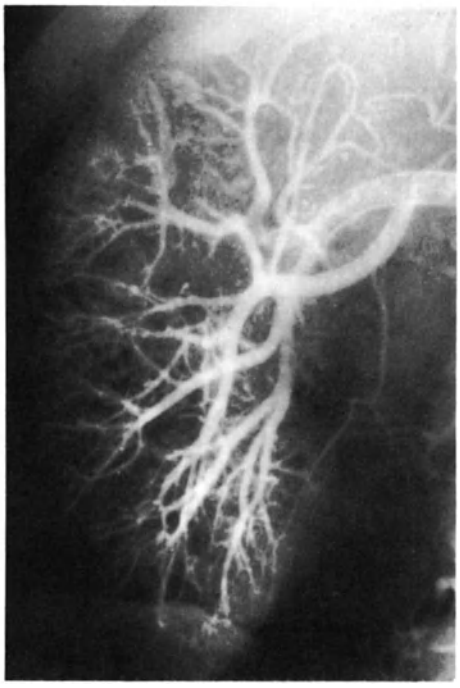


**Figure 22.** Fifty-year-old man with hypertension in histologically established periarteritis nodosa (biopsy material). Selective right renal arteriogram demonstrating multiple small renal artery aneurysms.

collaterals and thus the presence of a significant stenosis.[16,18]

## Technique

1. Infusion of acetylcholine, 80 μg/min for 5 min, followed by angiography 10 s later, or
2. Epinephrine, 3–4 μg, again followed 10 s later by angiography

A stenosis is also considered significant if it reduces the vascular lumen to less than 1.5 mm. However, the spatial configuration of the stenosis cannot always be accurately determined angiographically, especially in the case of fibromuscular dysplasia.

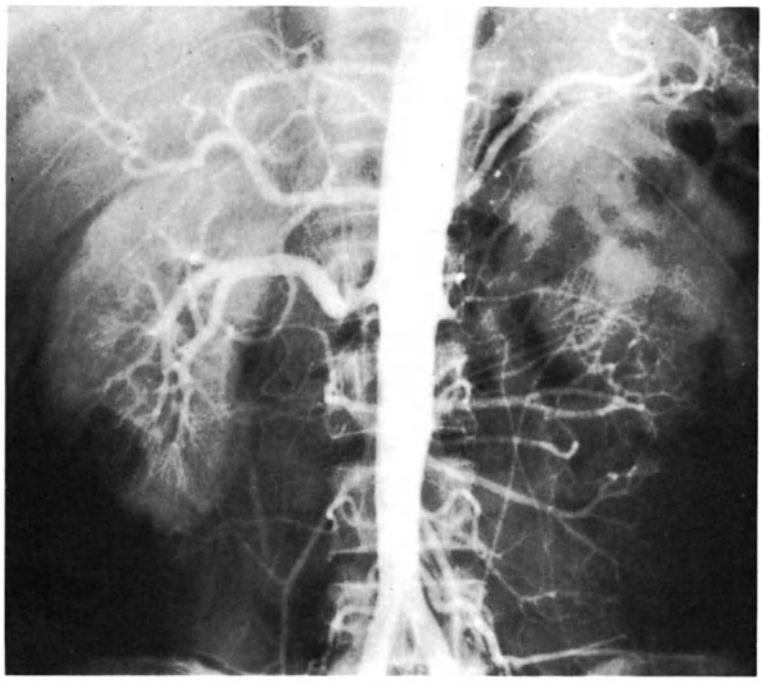
*Renal parenchymal changes* are the most frequent cause of nephrogenic hypertension.

The radiologic diagnosis of *chronic interstitial nephritis,* which may be *bacterial* (various forms of pyelonephritis) or *nonbacterial* (e.g., analgesic abuse, hyperuricemia, gout, radiation injury[92]), is based upon urography.

Kröpelin describes irregular contrast opacification in the collecting system, a hypotonic collecting system, and a loss of caliceal concavity as being characteristic of chronic pyelonephritis.[61] In the late stages, parenchymal destruction, scarring, atrophy, and even calcification may be present.

The diagnostic investigation of bacterial interstitial nephritis (pyelonephritis) should include the *reflux test* (Fig. 27) which must always be performed before urography. The reflux test is done after retrograde bladder filling under fluoroscopic control. Since some patients demonstrate reflux only during micturition, it is necessary to obtain a film during voiding. It is customary to differentiate vesicoureteral from vesicorenal reflux.

Angiography is rarely indicated in the evaluation of the hypertensive patient with chronic interstitial nephritis. In cases of advanced pyelonephritis, angiography usually shows a rarefaction of the peripheral arterial branches, which appear straightened and have a narrow lumen. The outer vascular contour may display irregularities, and thromboses of the smaller branches are present. The medullary-cortical boundary is indistinct, and the overall renal contour is irregular (Fig. 28). The main angiographic signs of severe primary malignant nephrosclerosis (Fig. 29a,b) are nonvisualization of the arcuate arteries and a marked delay of the arterial transit time (normally 1.5 to 2.5 s; in extreme cases over 20 s). Less pronounced flow delays are found in arterio-ar-



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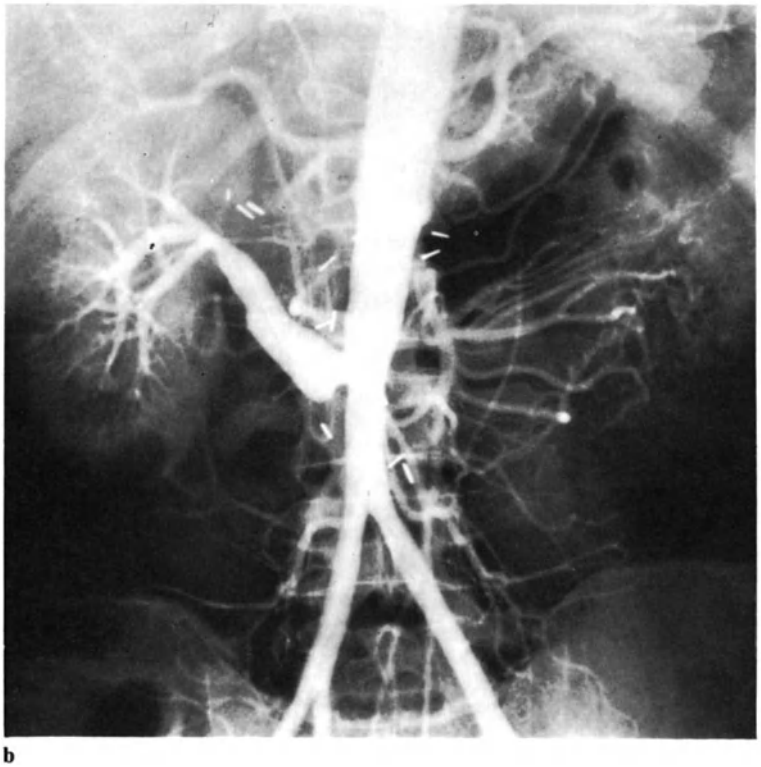


b

**Figure 23.** **a** Stenosis in initial part of right renal artery following left nephrectomy. **b** Condition 4 months after arterial reconstruction by venous interposition. Aneurysmatic dilatation of venous graft. BP 280/170 before surgery, 145/100 after surgery.

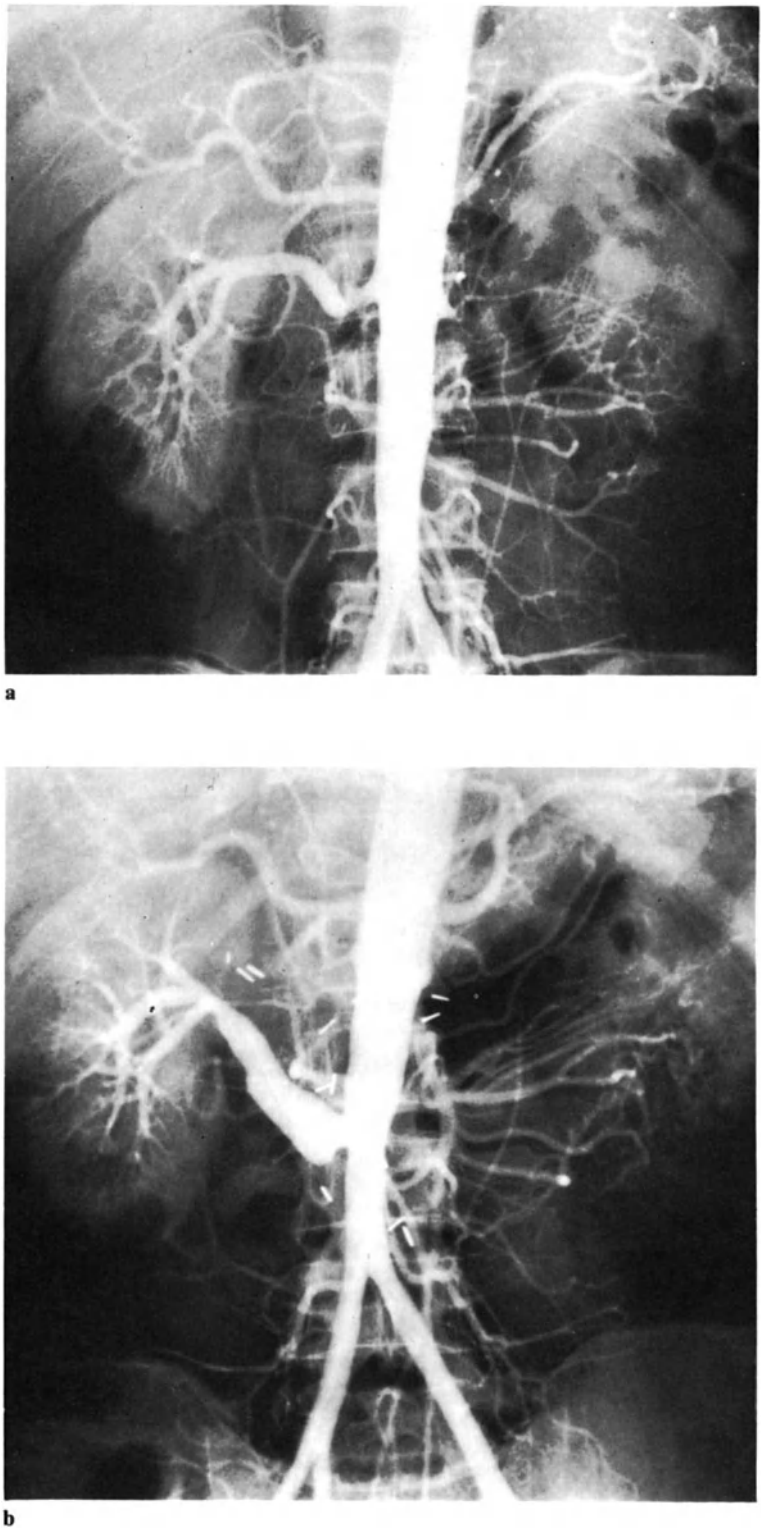


**Figure 24. a** Narrowing of right renal artery with poststenotic dilatation and collateral supply via ureteral artery. **b** Condition after placement of somewhat overlong Velour prosthesis.

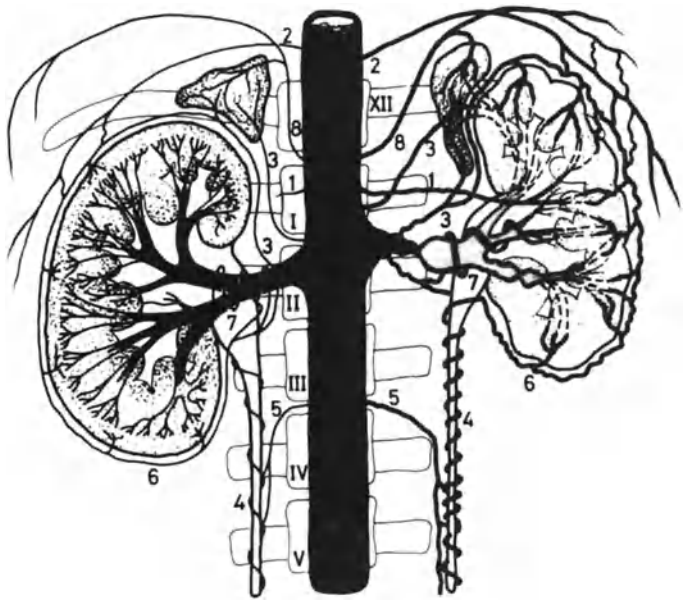



**Figure 25.** Collateral supply of the kidney. 1, lumbar arteries; 2, intercostal arteries; 3, adrenal arteries (Figs. 13a, 26b): 4, ureteral arteries (tortuosity of ureter, notching, scalloping); 5, gonadal arteries, mesenteric arteries; 6, renal capsular arteries; 7, renal pelvic arteries (Fig. 26a); 8, diaphragmatic arteries.

teriolosclerosis, chronic pyelonephritis, and chronic glomerulonephritis.

In contrast to chronic pyelonephritis, the renal contours are generally less irregular in arterio-arteriolosclerosis, and the medullary-cortical boundary may even be greatly accentuated.[40] The intrarenal arteries up to the arcuates are more or less ectatic, and only in advanced cases is there a marked luminal difference between the renal artery and the interlobal arteries and more distal vessels ("pruned-tree" sign). As the glomeruli and arterioles are destroyed, the cortex becomes thin. Lucent areas in the cortex are further evidence of the nonuniformity of the disease process. Because the cortex shows little contrast filling, a marked delineation appears between the medulla and cortex. The capsular arteries are dilated and show increased flow, but, unlike the findings in chronic inflammation, they usually exhibit little tortuosity. The capsular arteries are frequently seen to join with the perforating arteries.

In most forms of *glomerulonephritis,* intensive radiologic studies are unnecessary. If renal angiography is done in chronic glomerulonephritis (e.g., to exclude a suspected tumor), one is impressed by the relatively homogeneous vascular reduction. The renal contours are generally smooth and the medullary-cortical boundary indistinct. The arcuate vessels become unidentifiable only in the late stages of the disease. The capsular arteries appear well formed.

Hypertension associated with membranous or perimembranous glomerulonephritis may at times necessitate further angiographic studies. For example, Barbiano et al. evaluated 112 cases and found a nephrotic syndrome in 57 and hypertension in 43.[11] The arteriograms are essentially normal except for nonvisualization of the renal vein in the venous phase. Venous drainage via the capsular vessels, on the other hand, may be quite pronounced. The findings can be substantiated by venography (Fig. 30).

In rare cases hypertension may be caused by a renin-secreting tumor, called also a *juxtaglomerular cell tumor.*[110] Because of its small size (up to 4 cm) and relatively poor vascularity, it can easily be overlooked in the angiogram. The condition of primary reninism produced by this tumor is also called the Robertson-Kihara syndrome, after the authors who first described it.

## Hypertension due to Endocrine Causes

The recognition of endocrine-related hypertension is based principally on clinical and laboratory findings. If the cause is *adrenal* (which is usually the case), radiologic methods can show the morphologic aspects (tumor or hyperplasia) and localization.[21]

### Anatomy and Vascular Supply of the Adrenal Glands

The size of the adrenal glands varies considerably. Reschke found in his seriographs of normal adrenals (with no allowance for the 21% magnification factor) a variability of 220 to 994 $mm^2$ for the right

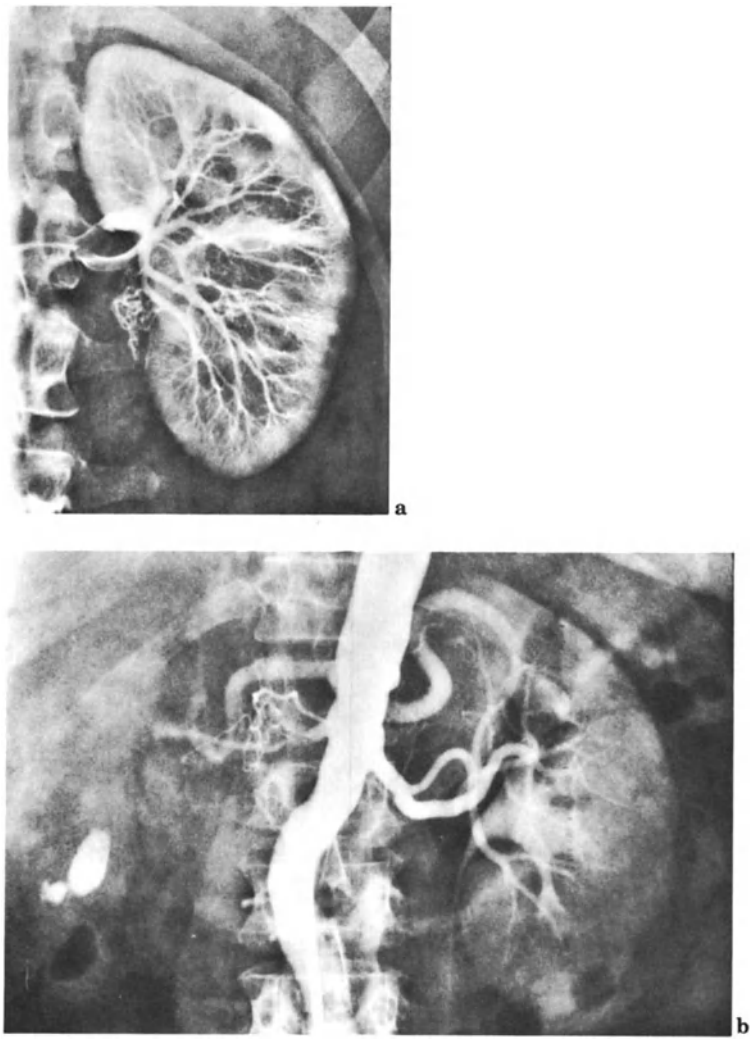


**Figure 26.** **a** A 22-year-old hypertensive woman with stenosis of a left renal artery segment branch, poststenotic flow reduction and collateral supply via renal pelvic arteries and arteries of the renal sinus. **b** A 63-year-old man with high-grade right renal artery stenosis and collateral supply via the inferior suprarenal artery (see also Fig 28.).

adrenal, 273 to 1188 $mm^2$ for the left adrenal, and 850 to 1717 $mm^2$ for both.[80] The adrenals consist of 80% to 90% cortex and 10% to 20% medulla. The right adrenal has the shape of a triangle whose lower surface abuts on the upper border of the kidney. The inferior vena cava takes a course medial and anterior to this gland. The left adrenal gland may be triangular but may also be crescentic or elliptical in shape. It is usually situated somewhat lower than the right and abuts on the upper medial border of the kidney. The adrenals receive their blood supply from three arteries:

1. The superior suprarenal artery arising from the inferior phrenic artery
2. The middle suprarenal artery, which almost always arises directly from the aorta
3. The inferior renal artery, which is a branch of the renal artery. The adrenal also receives blood from the ovarian-testicular arteries, the superior mesenteric, the celiac trunk, and one of the lumbar arteries.

The left adrenal drains mediocaudally into the renal vein, normally in common with the inferior phrenic vein. The two vessels may drain the adrenal separately in some cases, however. On the right, the adrenal vein drains directly into the inferior vena cava. In rare cases two or three veins arise from the gland. The adrenal vein reaches the vena cava ap-

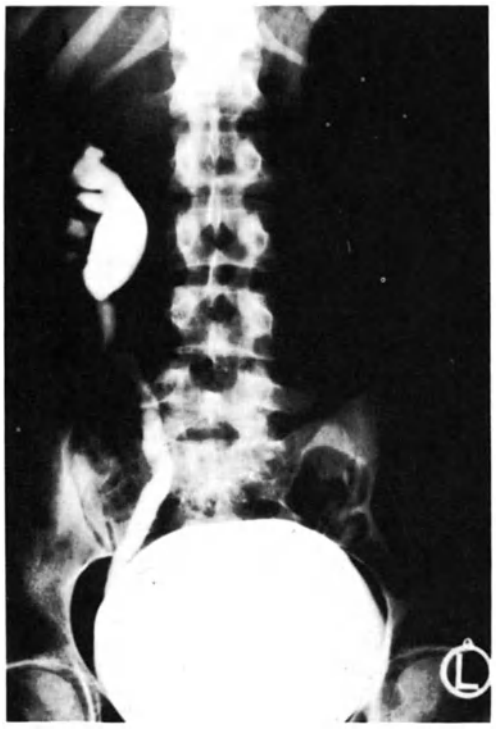


**Figure 27.** Massive right-sided vesicorenal reflux.

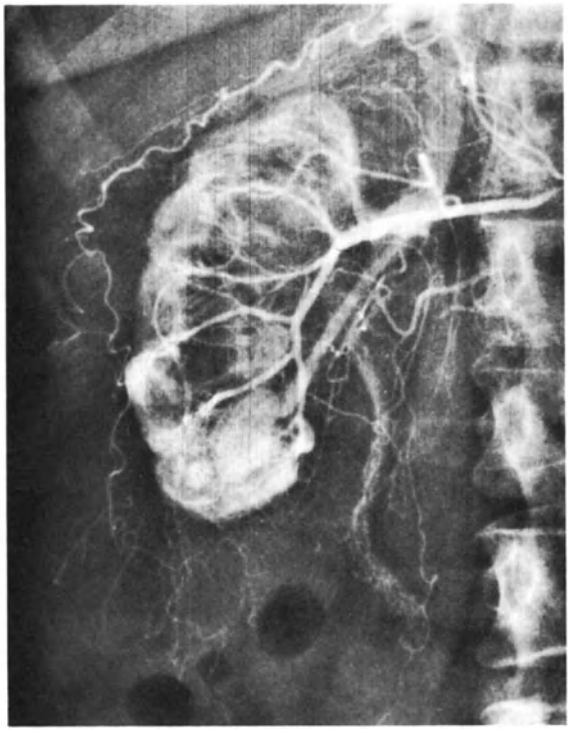


**Figure 28.** Same patient as in Fig. 26b on selective right arteriography. Advanced pyelonephritis with nephrolithiasis, constriction, and rarefaction of the arterial vascular tree. Medullary-cortical boundary indistinct, irregular contour of small kidney, premature venous filling.

proximately at the level of the inferior border of the twelfth rib, 3 to 4 cm above the right renal vein. Hepatic veins also enter the inferior vena cava in immediate proximity to the adrenal vein; this fact must be considered during attempts to catheterize the right suprarenal vein. It is reported that in 10% to 15% of cases, the venous drainage of the right adrenal gland is into a hepatic vein.[53] The right adrenal vein has a maximum length of 10 mm; the left is in the range of 20 to 40 mm.

## Radiologic Methods of Diagnosis

### Abdominal scout film, urography, and tomography

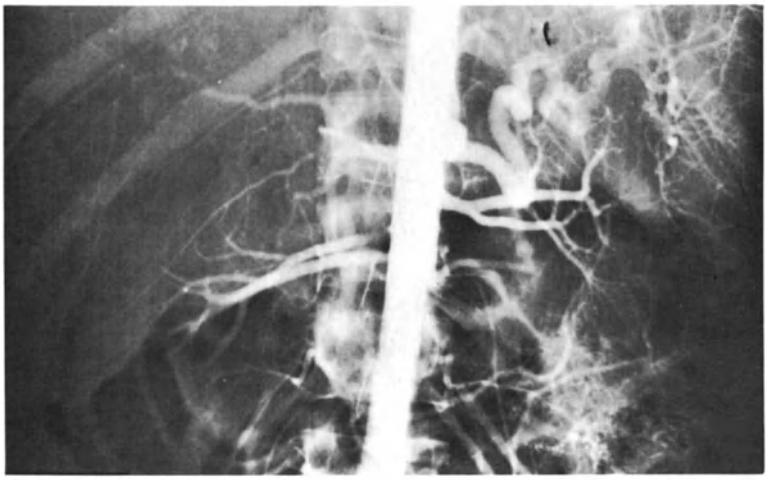
The radiologic examination of the adrenal glands begins with the plain abdominal film. Calcifications in a nonenlarged adrenal are usually based on tuberculosis but may also be related to hematomas that occurred at birth and later calcified. Streak and eggshell calcifications are indicative of a cyst. Irregular calcium deposits may be present with large adrenal tumors. Calcified mesenteric lymph nodes, pancreatic calcifications, or calcified rib cartilage should also be considered in the differential diagnosis. The plain film is followed by urography and, if necessary, tomography. Adrenal tumors 2 cm or more in diameter are capable of affecting neighboring organs. Indirect evidence of an adrenal tumor is provided by an off-axis position of the kidney (Fig. 31) as well as by an overlapping of the psoas shadow by a soft-tissue mass (lateral or caudal displacement of the kidney, Fig. 32).

### Invasive methods of diagnosis

***Retroperitoneal Pneumography.*** Unlike most authors, Deininger et al. continue to use retroperitoneal pneumography in adrenal diagnostics.[26] In this procedure a maximum of 1000 ml of either nitrous oxide or carbon dioxide, both easily absorbed, is insufflated retroperitoneally. The distribution of the gas is monitored fluoroscopically; frontal and sagittal films taken in either the supine or upright position are recommended.

### *Angiography*

*Arteriography.*[23,54,55,80] The arteriogram should be done in two planes if possible, with the selective visualization of at least one adrenal artery. The infe-



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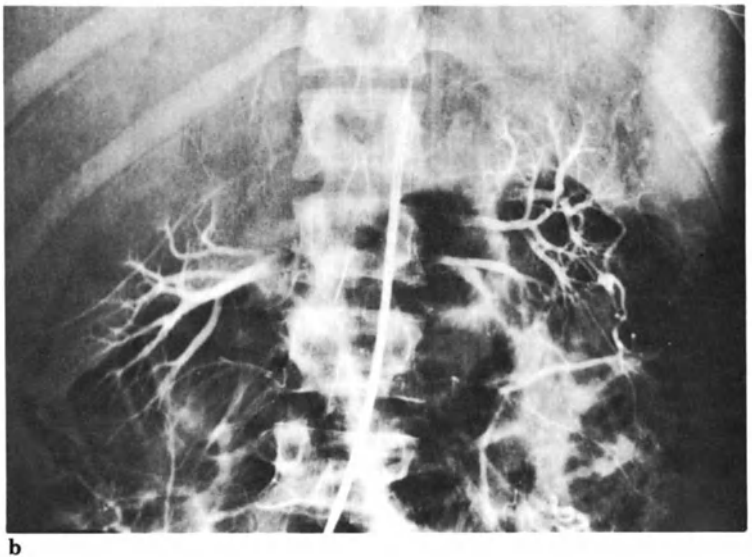

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**Figure 29. a,b** A 22-year-old man with BP of 260/130. Renal biopsy material showed grade IV primary malignant nephrosclerosis (Institute of Pathology, Mainz, West Germany). **a** Survey aortogram showing splenic artery with intrasplenic branches; the hepatic artery and renal arteries are also demonstrated, but not to the periphery. **b** Stagnation of contrast medium in the renal arteries; the area supplied by the celiac trunk is already free of contrast medium.

rior suprarenal artery, which ordinarily arises from the renal artery, is best visualized by the prior injection of 10 μg of suprarenin into the renal artery followed by the injection of 10 to 12 ml of contrast material into this vessel. Although adrenal arteries have been reported to arise from a lumbar artery, injection of the lumbar artery should be avoided because of the risk of spinal artery lesion with resulting paralysis.[20] Since pheochromocytomas can also occur outside the adrenal, selective procedures should be supplemented by survey aortography of the abdomen including the urinary bladder and perhaps the thoracic space and cervical region if such a tumor is suspected. Subtraction films can yield additional information in some cases. The amount of contrast material to be used varies; normally 2 to 4 ml is required for the inferior and middle suprarenal artery, 5 to 6 ml for the inferior phrenic artery and the ovarian or testicular artery, and up to 10 ml in the case of large tumors.

*Venography.*[25,37,54,55,74–76,81,100] As in arteriography, adrenal venography is done via the femoral vein using the Seldinger technique. Anatomic conditions require that different catheter shapes be used for the right and left adrenal glands. To visualize the right adrenal gland, 3 to 4 ml of contrast medium is needed, and 6 to 8 ml to visualize the left. Up to 10 to 12 ml may be required for tumors.

The optimum quantity of contrast material for a particular situation can be determined by a test injection of 1 to 2 ml. A preliminary injection is also

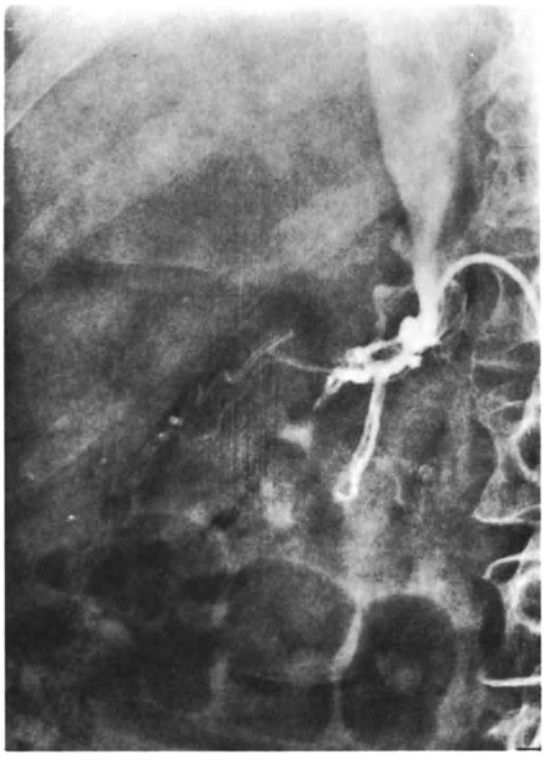

**Figure 30.** A 71-year-old woman with perimembranous glomerulonephritis and bilateral renal vein thrombosis. BP prior to treatment 210/100; BP after antihypertensive medication 150/85. Diagnosis of immune complex nephritis established by renal biopsy.

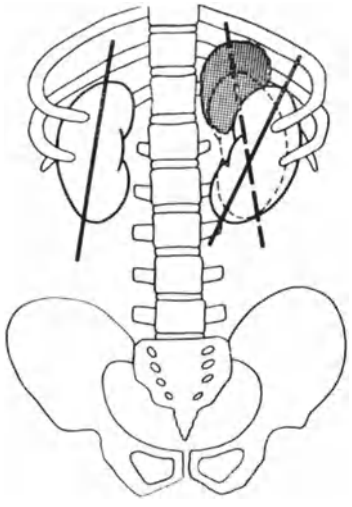

**Figure 31.** Change in the long axis of the left kidney by an extrarenal tumor.

recommended before drawing blood from the adrenal gland for hormone analyses, especially on the right side, in order to verify the position of the catheter in the adrenal vein.

## Noninvasive methods of diagnosis

***Computed Tomography.***[28,43,56,60,82,107–109] Adrenal diagnostics have been substantially improved in recent years by increasing experience with *computed tomography*. As a noninvasive procedure, it should precede angiography.

Tomography shows the *normal adrenal gland* as a triangular (Fig. 33) or elliptical structure. Vascular structures (e.g., hepatic veins) may be a source of deception, especially on the right side, and so it is good practice to render these identifiable by injecting 20 ml of a renally excreted contrast material (60%). This will increase the density of the vessels from 40 to about 100 Hounsfield units, while increasing that of the remaining tissues by only about 20 units. Adrenal *hyperplasia* may be assumed if the limb of the organ is more than 2 cm in length.

If a rapid scanner with a scan time of 2 to 4 s and attainable shadow density of 4 mm is available, tumors as small as 10 mm in diameter can be detected (Fig. 34) (K. H. Hübener, Tübingen, personal communication).[108]

***Sonography.*** While Davidson et al.[25] and Lecky et al.[62] report that the minimum tumor size for adenoma detection by *sonography* is 30 mm, tumors as small as 13 mm[104] or 15 mm[44] can be demonstrated with the use of modern ultrasonic instruments with gray-scale display[44,69,85–87,104,105,111,113] and focusing transducers. The normal adrenal gland can be demonstrated in about 85% of cases.[44] The accuracy of the procedure is about 95%.[104] Transsonancy indicates cysts, complex echo structures may occur in necrosis.[44,105] The differential diagnosis of adrenal neoplasms with a solid echo structure is not possible (Fig. 35).

A correct examination technique is of prime importance with sonography. This should include transverse scans in the supine position, sagittal scans in the prone position and, if necessary, subcostal longitudinal scans in the supine position (for the right side).[44] The type of transducer used depends on the patient's body size (slender: 3.5 MHz, 13-mm crystal diameter, medium focus; obese: 2.25 MHz, 19-mm crystal diameter, long focus).[44] Errors may arise from masking effects by the liver, pancreas, or lymph nodes.

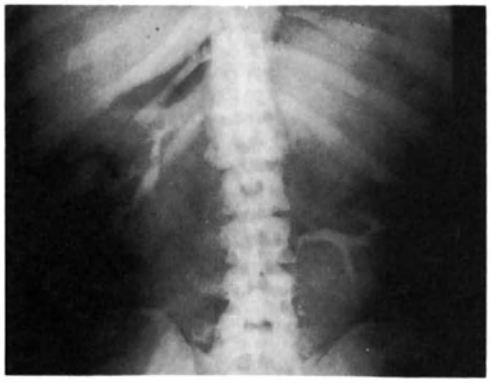

**Figure 32.** Displacement of the left kidney by a highly differentiated adrenal cortical carcinoma (histologically verified).

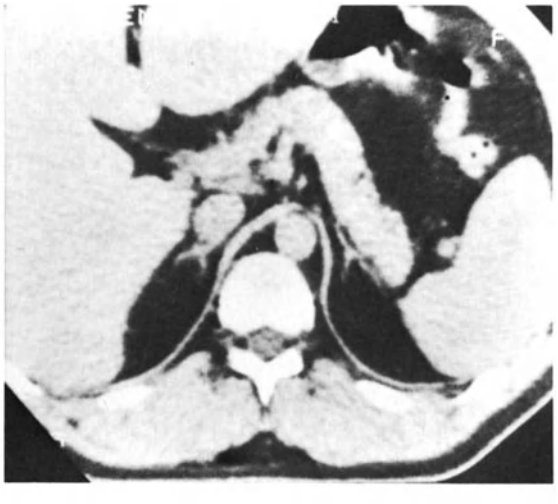

**Figure 33.** Normal-size triangular right adrenal gland. Photo: Prof. Dr. G. Friedmann, Institute of Radiology of the Cologne University Clinics.

**Complications of invasive diagnostic procedures**

The greatest danger in angiography is extravasation.[17,52] This can be avoided if the recommended amount of contrast medium is not exceeded and if the injection itself is not forced. Vascular thromboses are not a real threat as long as the catheter is removed from the adrenal artery or vein immediately after injection.

To avoid hypertensive crisis during contrast visualization of a pheochromocytoma, careful premedication is required. The usual regimen is to administer an $\alpha$ blocker (Dibenzyline) intravenously,

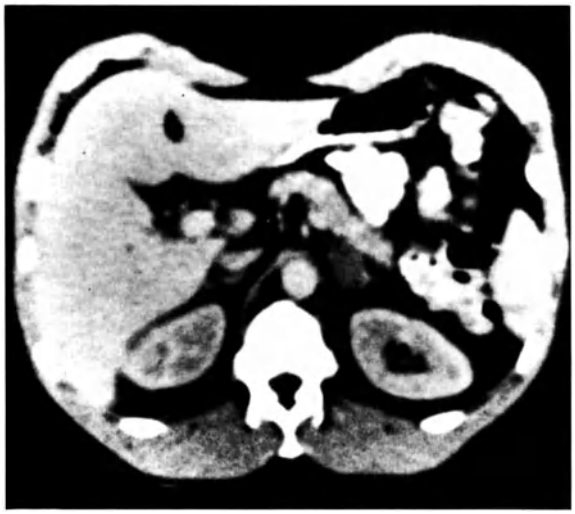

**Figure 34.** Adrenal tumor of left side, 2.5 cm in diameter, verified at operation. Photo: Prof. Dr. G. Friedmann, Institute of Radiology of the Cologne University Clinics.

**Figure 35.** Ultrasonogram in prone position. Longitudinal section of right kidney. Pheochromocytoma of adrenal gland in 10-year-old child with excessive hypertension. Reflections at center of tumor caused by central calcification. Photo: Prof. Dr. G. van Kaick, Heidelberg.

beginning at least 3 days prior to the procedure, in doses of 1 mg/kg body weight, until normalization of blood pressure is achieved. Opinions vary at present as to the advisability of using $\beta$ blockers when tachycardia is present (40 mg of propranolol by mouth until the pulse rate has fallen below 80).[61,99]

In retroperitoneal pneumography, complications can be avoided by making certain that the needle tip is not within a vessel and by using no more than 1000 ml of a rapidly absorbed gas.

### Results and value of radiologic investigations

Plain abdominal films and urography with tomography are limited in their diagnostic value. To be detected, tumors must be at least 2 cm in diameter on the right and 4 to 5 cm on left owing to the localization of the adrenal gland.[99] Additional difficulties are encountered on the left—even in retroperitoneal pneumography—in that the fluid-filled gastric fundus can mimic an adrenal tumor.

Before the advent of computed tomography, the method of choice was venography. It can demonstrate tumors as small as 10 mm in diameter and thus provides a diagnostic accuracy of 80% in the usually small adenomas of Conn's syndrome.[21] Overall demonstration of the adrenal gland is also easily done with venography, since generally the venous drainage is by only a single main vein, and the veins communicate with one another. The right adrenal vein is more difficult to catheterize than the left, Voegeli and Käser reporting a success rate of 65% on the right vs. 96% on the left.[99] Other investigators report similar results.

The diagnosis of hyperplasia is often difficult owing to the variability in the form and size of the adrenals. It is most easily accomplished by venography. According to Lecky et al., the adrenal venogram demonstrates gland enlargement with increased distances between the contrast-filled veins.[62] Reschke feels that the adrenal must be at least 1000 $mm^2$ (both 1300 to 1500 $mm^2$) in order for adrenal hyperplasia to be diagnosed.[80] It is not unusual for the hyperplastic adrenal to lack a distinct border.[53] Nodular hyperplasia caused by the presence of multiple small adenomas gives the gland a perforated appearance.

Arteriography, which can demonstrate only a portion of the gland via one of the adrenal arteries, is employed when venography is unseccessful (usually on the right side). However, if clinical and laboratory findings clearly point to adrenal disease, it may be assumed even without angiography that if findings are normal on one side, a pathologic process will be present on the opposite side. In cases where pheochromocytoma is suspected and adrenal findings are normal, venography of the adrenals should be followed by survey aortography of the abdomen, chest, and neck. If X-ray studies fail to demonstrate the pheochromocytoma, localization may be attempted by staged blood sampling from the vena cava and determination of catecholamine levels from the blood samples.

The radiologic procedures serve to preoperatively localize and outline the type of adrenal pathology present. Whereas adrenal hyperplasia is bilateral, adenomas tend to be unilateral, are multiple in 5% to 10% of cases, and affect the left adrenal more frequently than the right.[80,99] With large adenomas, the opposite side is usually hypoplastic.[37]

It is difficult or impossible to deduce the *character* of an adrenal process from the *vascular architectonics*. Thus, the adenoma of Conn's syndrome, which seldom exceeds 3 cm in diameter, the adenoma in Cushing's syndrome, and pheochromocytoma are all relatively hypovascular and are often impossible to differentiate from one another.

There are criteria, however, which may enable a more specific diagnosis to be made. It is reported, for example, that the Conn syndrome adenoma causes the arteries to separate in candelabrum fashion (Fig. 36). In the late arterial phase, increased

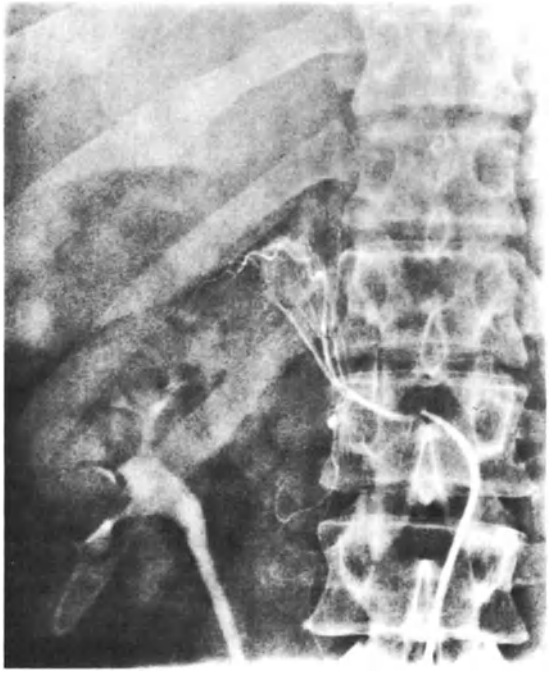

**Figure 36.** Selection visualization of the right middle suprarenal artery in a 40-year-old male hypertensive patient with right-sided Conn adenoma (histologically verified); patient became normotensive after surgery.

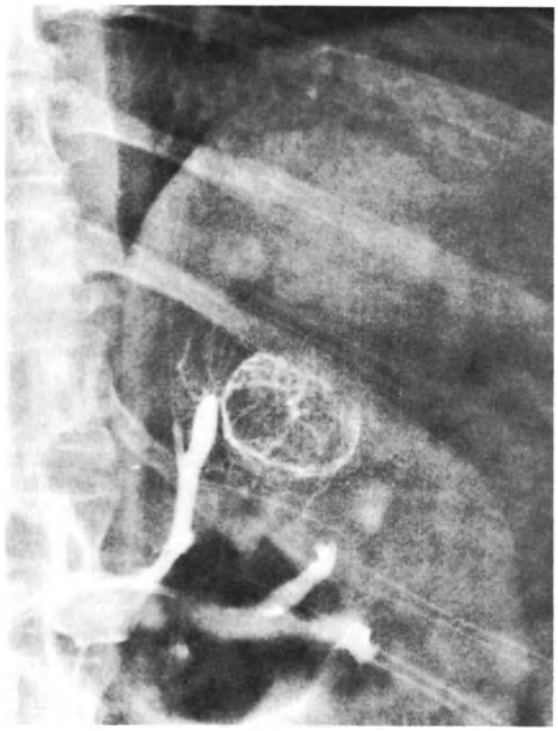

**Figure 37.** Selective visualization of the left suprarenal vein. Histologically verified adenoma of left adrenal in Cushing's syndrome; surgery resulted in remission of hypertension.

marginal vascularity is seen,[80] and the veins are displaced toward the periphery;[37,53] the site of predilection is the organ periphery.[37]

A venous network within the tumor itself, in addition to the opacification of the peripheral veins, is more a sign of Cushing adenoma than of any other tumor[53] (Fig. 37). The vascular picture of *pheochromocytoma*[15,101] is highly variable (Fig. 38a–c). Hypovascularity[37] as well as hypernephroma-like vascularity[26] has been reported. In 90% of cases pheochromocytomas are unilateral, and 10% are extra-adrenal,[26] in which case they are usually hypervascular.[62] Bilateral adrenal pheochromocytomas or adrenal hyperplasia associated with medullary thyroid carcinoma constitute the Sipple syndrome.

*Malignant pheochromocytoma* is characterized by the osseous type of metastasis.

The *adrenal carcinoma* is better vascularized than the adenomas, but it, too, is relatively poorly vascularized. It is mentioned here because it is occasionally associated with hypertension.

Avascular space-taking lesions which cause stretching and displacement of the arteries and veins are usually *adrenal cysts;* they are a relatively uncommon cause of hypertension.[62]

Angiography can show whether an adrenal tumor is *benign or malignant* only if extension is sufficient to indicate malignancy.

Today, the noninvasive procedures of sonography and computed tomography have almost completely replaced angiography in adrenal diagnostics. Sonography is particularly important as a screening test

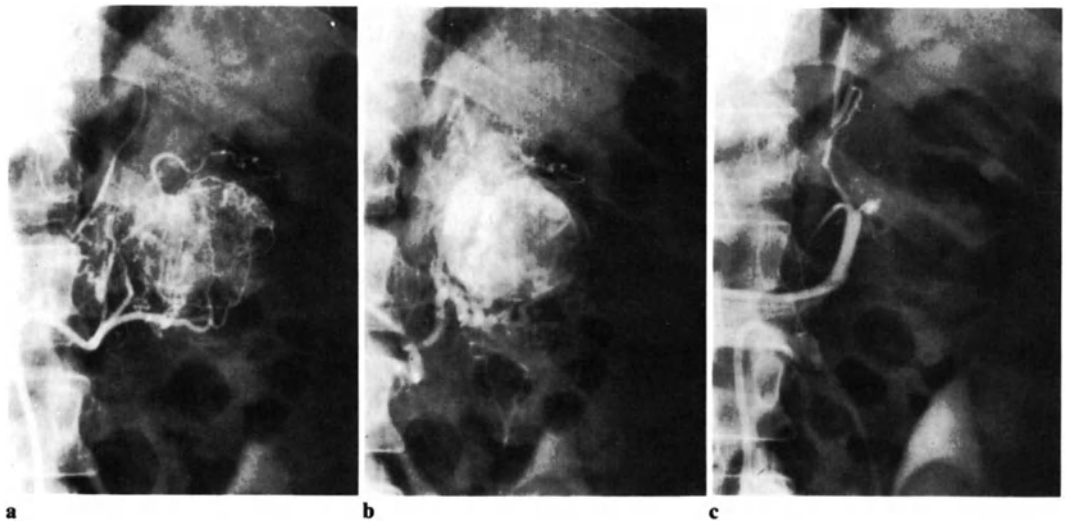


**Figure 38. a–c** Histologically verified pheochromocytoma of left adrenal gland with hypertensive crises and postoperative normalization of blood pressure. **a** Rich arterial supply. **b** Visualization of a dense venous capsular plexus. **c** Weak venographic visualization of a sparsely developed intratumoral venous system with good filling of the left adrenal vein.

for the detection of gross changes.[108] With computed tomography, the organ can be demonstrated, and a diagnosis made, in 90% to 95% of patients.[107,108] A lack of retroperitoneal fatty tissue can make it difficult to delineate the adrenals. Misinterpretations can result from enlarged lymph nodes, among other things, but these can be largely eliminated by contrast enhancement.

### Summary

In summary, it can be said that after excretory urography, the noninvasive procedures of sonography and computed tomography are the methods of choice in the radiologic diagnosis of adrenal disease. Foremost among the invasive procedures is venography, especially since it affords an opportunity for selective blood sampling. Arteriography may be necessary in pheochromocytoma diagnosis; it is also indicated if venography proves to be unfeasible, particularly on the right side. For the recently developed therapeutic approach to renovascular hypertension with percutaneous transluminal angioplasty see Chapter 16.

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# Radionuclide Methods in the Diagnosis of Arterial Hypertensive Disease

# 28

E. Oberhausen, R. Berberich

Many hypertensive diseases are based upon disorders of organs and organ systems and, conversely, hypertension has secondary damaging effects, especially on the kidneys, the heart, and the vessels. Therefore, for the diagnostic evaluation of hypertension, of its possible causes, and of its secondary consequences, extensive diagnostic procedures must be undertaken in some cases. This need is sometimes met by the use of suitable radioactive drugs for functional diagnosis and scintigraphic studies. How often the different radionuclide methods are used is determined, on the one hand, by the contribution of the pathologically altered functions of the various organs to the genesis of the arterial hypertension and, on the other hand, by the probability of secondary organ damage. It is further influenced by the wide variations in the value of diagnostic radionuclide methods for different organs and organ systems. It may be stated in general that nearly all radionuclide studies involve minimal inconvenience and risk to the patient. Thus, they are useful not only for the actual diagnosis but especially for observing the course of a disease which may require follow-up examinations at more or less regular intervals. The following discussion of radioisotope examination techniques employed in arterial hypertensive diseases is subdivided according to the organs examined.

## Kidneys

### Isotope Clearance Studies

Determinations of radioisotope clearance have become increasingly important in recent years. This is mainly because these methods are much easier to carry out and place less stress on the patient than classic methods having about the same accuracy. Like all determinations of renal clearance, radioisotope methods are based on the fact that elimination of the clearance substance is proportional to its plasma concentration $C_p$. If the substance $m$ is excreted exclusively by the kidneys, the following formula applies:

$$\frac{dm}{dt} = -C_p \times Cl \qquad (1)$$

That is, the amount of substance ($dm$) eliminated per unit time ($dt$) is equal to its plasma concentration multiplied by the plasma volume ($Cl$) cleared in that time. This plasma volume cleared per unit time is defined as clearance. Equation (1) is the basis of all clearance determinations. The various methods employed to date can be distinguished according to whether Eq. (1) is used in differential or (as in the classic methods) in integrated form. A further distinction arises from the question of whether additional assumptions concerning the distribution volumes of the substances employed are required besides Eq. (1). Finally, the importance of a method depends in large measure on whether it is suitable for clearance determinations in the separate kidneys.

Among the radioactive agents available for clearance studies, the excretory mechanism of $^{131}$I-iodohippurate is very similar to that of para-aminohippuric acid (PAH). Comparative studies have shown that the extraction of $^{131}$I-iodohippurate is only about 86% that of PAH.[6,49] However, this is no obstacle to the use of $^{131}$I-iodohippurate as a clearance substance as long as the different extraction values are kept in mind. The chelating agents EDTA or DTPA, tagged with $^{51}$Cr, $^{169}$Yb, or $^{99m}$Tc, are handled

by the kidneys in a manner similar to inulin.[11,19,27] These substances are suitable for the determination of the glomerular filtration rate. $^{51}$Cr-EDTA has been used most extensively, and comparative measurements with inulin[57,61] have shown maximum differences of about 5%.

### Measurements with the partially shielded whole-body counter

By measuring the retention curve with a partially shielded whole-body counter, clearance determinations can be carried out according to Eq. (1), without additional assumptions regarding the distribution volumes of the clearance substance. If $^{131}$I-iodohippurate is used as the clearance substance, a retention curve and isotope renogram can be obtained simultaneously, and a split renal clearance determination becomes possible. Figure 1 shows the arrangement of the partially shielded whole-body counter with two NaI crystals, coupled to an on-line electronic analyzer.[37,43] With this system it is possible to measure the total amount of labeled clearance substance as a function of time. Since the activity already eliminated by the kidneys should no longer influence the measurement, the gamma rays from the kidney and bladder region are screened out by a lead shield so that they cannot reach the crystals. From the retention curve measured by this arrangement, it is possible to determine the differential quotient at the times when blood samples are drawn for measurement of plasma concentration. The clearance is then calculated in accordance with Eq. (1) by the formula

$$Cl = -\frac{dm/dt}{C_p} \qquad (2)$$

While the retention curve is being measured, the activity over each kidney can be simultaneously recorded in an isotope renogram by means of collimated external gamma-ray detectors. The different counting geometries in various patients prevent the isotope renogram from yielding quantitative results by itself: but if the total clearance of both kidneys is known, it is possible to compare both sides and thus to determine the portion of the total clearance accounted for by each kidney. The form of the renogram depends on a number of factors which interact in such a way that the renogram over the left kidney is determined in part by the function of the right kidney, and vice versa. The renogram represents essentially the sum of the following two components:

1. The retention curve, which is determined by the presence of activity within the field of view of the detector and parallels the retention curve of the whole body
2. The component defined by the excretion of the radiolabeled substance into the collecting system of the kidney and by the time necessary for passage through the collecting system

Because of the overlapping of the different components, the individual phases of the renogram curve cannot be ascribed to individual factors. It is best, therefore, to employ a neutral subdivision into three parts, as shown in Figure 2. Part 2 is best suited for comparison of the two kidneys; its course is dictated by the following parameters: the selective accumulation of iodohippurate in the kidney, its decreasing concentration in the plasma, and its diffusion into the part of the extracellular space "seen" by the de-

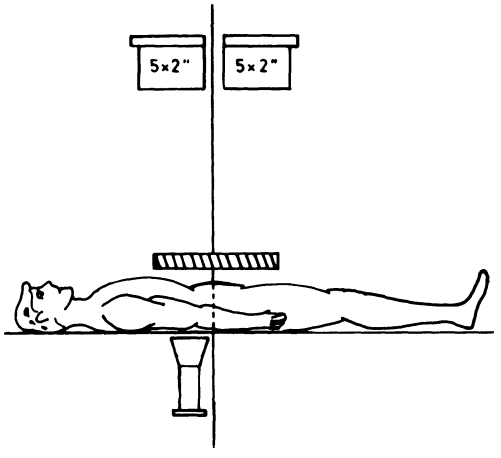



**Figure 1.** Arrangement of partially shielded whole-body counter.

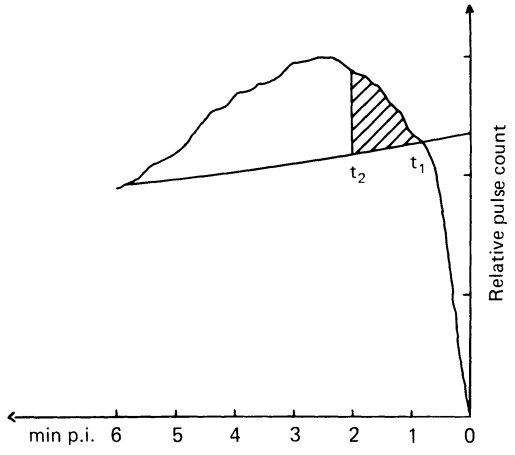



**Figure 2.** Isotope renogram and normalized retention curve.

tector. The sum of the latter two parameters takes the same course as the retention curve measured over the whole body. If the retention curve is projected onto the renogram curve, as shown in Figure 2, the area $F$ between the two curves and the abscissas $t_1$ and $t_2$ is a measure of the selective accumulation of iodohippurate in the kidney. The following equations express the relation between the two areas $F_L$ and $F_R$:

$$A_R = \frac{F_R}{F_L + F_R} \qquad A_L = \frac{F_L}{F_L + F_R} \tag{3}$$

where $A_L$ and $A_R$ designate the respective portions of iododohippurate clearance accounted for by the left and right kidneys. If the total clearance has also been determined, the values for the separate kidneys are obtained by multiplying the total clearance by $A_L$ and $A_R$.[31,36]

Part 3 of the renogram is usually a good indicator of outflow conditions. However, it must be kept in mind that part 3 is always prolonged when renal function is impaired, even if no outflow obstruction is present. Furthermore, prolongation may be caused by protracted retention of the iodohippurate in the renal parenchyma or in the collecting system. These two possibilities cannot be differentiated by measurement with simple probes.

Figure 3 shows the results of a split clearance determination with $^{131}$I-iodohippurate. The retention curve and the determination of the plasma activity concentration yield a total clearance of 210 ml/min, which is already indicative of renal function impairment. Evaluation of both renograms indicates that the reduction is more severe in the left kidney than in the right one, which also shows a reduced clearance of 119 ml/min. Thus, the study indicates a bilateral disease process that is more advanced on the left side than on the right.

Figure 4 demonstrates that the split clearance determination is possible even with severe outflow obstruction—an advantage not obtained with the classic method. The rise in the activity curve for the right kidney throughout the test is indicative of a right-sided outflow obstruction. For calculating the split clearances, however, only the initial part of phase 2 is used, since it is not yet influenced by the obstruction.

Figure 5 shows how a marked reduction of $^{131}$I-iodohippurate clearance is also present in the case of functionally significant renal artery stenosis. The patient, a female, was shown angiographically to have bilateral renal artery stenosis which was more severe on the left side than on the right. In their statistical study, Maxwell et al. showed that of 693 cases of angiographically proven renal artery stenosis, 86% also demonstrated a corresponding change in their isotope renograms.[30] Since not all angiographically demonstrable renal artery stenoses are functionally significant, it remains unclear whether the 14% without renographic changes had functionally insignificant stenoses. This possibility would at least be consistent with our own experience, which indicates that functionally active stenoses generally cause a marked reduction of iodohippurate clearance. In several angiographically proven renal artery stenoses with normal clearance in the involved kidney, no change of clearance or improvement of hypertension was found after surgical correction of the stenosis. Heidenreich et al. were able to show that simultaneous determinations of the $^{131}$I-iodohippur-

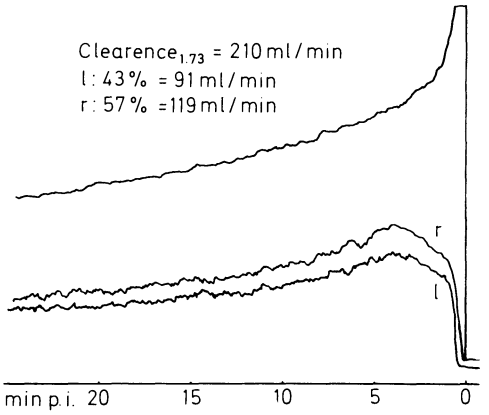



**Figure 3.** Retention curve and isotope renogram in impaired, lateralized renal function.

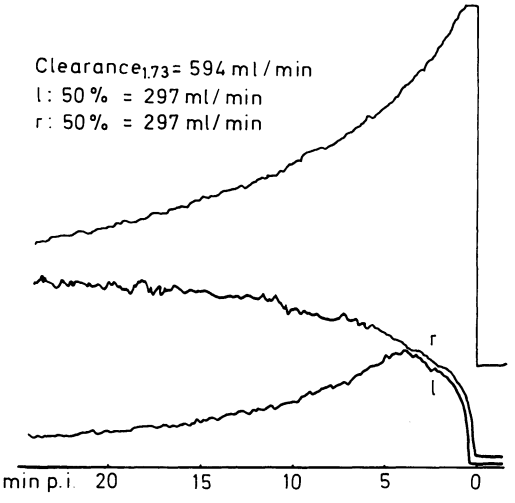



**Figure 4.** Retention curve and isotope renogram in right-sided outflow obstruction.

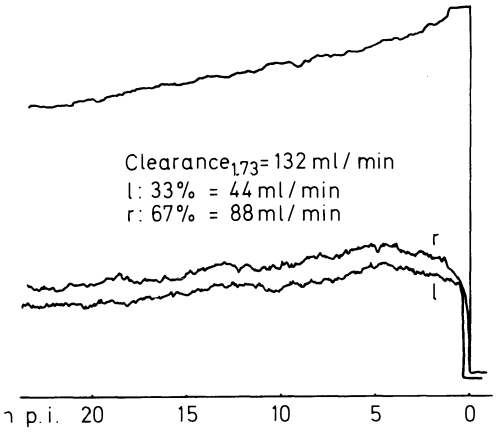



**Figure 5.** Retention curve and isotope renogram in bilateral renal artery stenosis.

ate clearance and $^{99m}$Tc-DTPA clearance (which corresponds to the inulin clearance) can be performed with the partially shielded whole-body counter.[17,20] The two radionuclides $^{131}$I and $^{99m}$Tc satisfy the requirement that their gamma energies be sufficiently far apart to permit resolution during measurement. This combination also affords the opportunity of simultaneously determining the filtration fraction.

In general, determination of the split $^{131}$I-iodohippurate clearance represents a valuable addition to the diagnosis of hypertension, making it possible to verify a suspected renal cause even in complicated cases. The importance of clearance studies in follow-up examinations is particularly stressed. They are easy to perform, involve minimum patient stress, and in most cases yield important prognostic information.

### Measurements with the Anger camera and computer system

In some cases it is necessary to know the clearance of different segments of kidney, for otherwise conventional collimators cannot be adjusted to the renal tissue if one kidney is dystopic or if developmental anomalies (horseshoe kidney, cake kidney) are present. In all these cases, relative clearance values can be determined by renal function scintigraphy with the Anger camera and an on-line computer system. With the Anger camera, incident gamma rays from the total field of view (26 to 40 cm in diameter) are localized electronically according to their absorption site in the detector. By use of a parallel-hole collimator, a graphic image of the activity distribution is created which can be stored in the computer system for retrieval and analysis.

Because renal function scintigraphy requires considerably more equipment than does isotope renography, it should be reserved for cases in which the individual renal clearance must be supplemented by more detailed data, or when renal shape or location require it. For the examination, the patient is placed in either the prone or supine position. Approximately 300 $\mu$Ci of $^{131}$I-iodohippurate is injected, on the average. The total duration of the examination is about 30 min. The computer system linked to the Anger camera must have the capability of continuously storing individual images on a magnetic disk or tape. It must also have the capability of plotting "region of interest" time-dependent activity curves for more than five regions in the field of view either simultaneously or consecutively. After the injection, the individual images are recorded on disk or tape at 20-s intervals. To determine the relative clearance values, regions of interest are assigned over the right and left kidneys and a tissue area containing neither renal parenchyma nor efferent collecting ducts. The time-activity curves are plotted for these regions from the individual images. An example of the selection of regions of interest and the corresponding time-activity curves is shown in Figure 6.

If the relative clearance of renal segments is also to be determined, additional "regions" must be assigned accordingly.[39,47] The evaluation is done according to the same procedure described above for the four-channel system, using the time-activity curve over the area free of renal parenchyma (tissue curve) instead of the whole-body retention curve.

Figure 7 shows the results of such an examination.

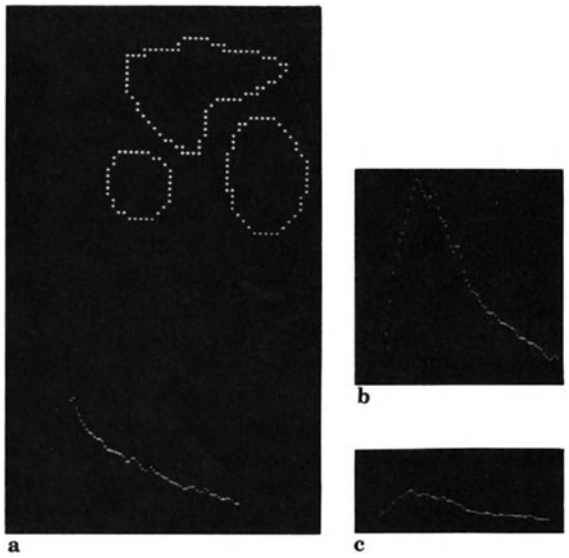



**Figure 6.** Example of the selection of regions of interest and the computed time-activity curves. **a** Tissue curve; **b** left kidney; **c** right kidney.

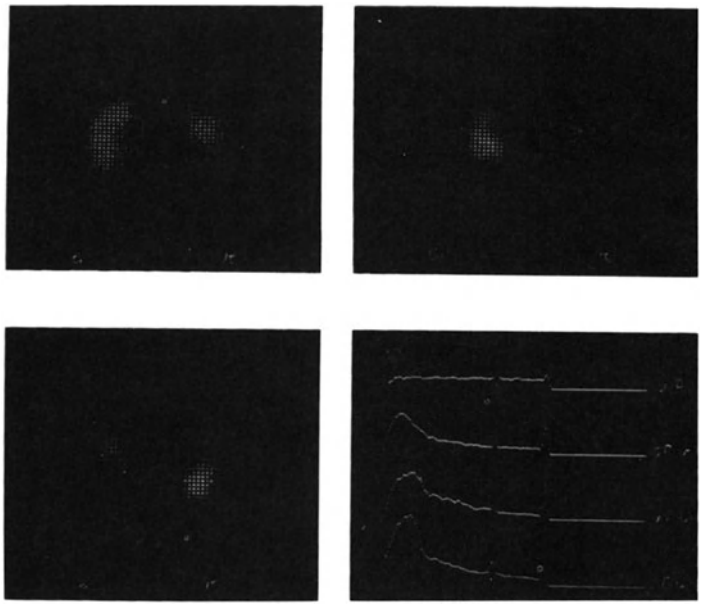


**Figure 7.** Renal phase scintigram for studying the clearance of renal segments.

A previous split clearance determination with a partially shielded whole-body counter had demonstrated a reduction on the right side. Also, pyelonephritic changes in the right caudal area were seen in the urogram. On the picture showing the accumulation of iodohippurate between 1 and 3 min, it can be seen that the caudal part of the right kidney takes up practically no iodohippurate. The renograms of the corresponding cranial and caudal pole are normal for the entire left kidney and for the cranial pole of the right kidney. For the caudal pole of the right kidney, however, a marked function impairment is demonstrated. Thus it can be concluded that the reduced clearance of the right kidney can be attributed entirely to its caudal part.

Comparative measurements between the iodohippurate clearance determination by the four-channel apparatus, on the one hand, and the Anger camera with on-line computer system, on the other, showed very good agreement in terms of lateral distribution.[41] At the same time, it was found that the total clearance determination from the tissue curve is subject to a sizable error. This is a further reason for considering the split clearance determination with the four-channel system a standard method and using the Anger camera with computer system only for the study of special problems.

### Clearance determination from the fall of plasma activity

In their search for a simple method of assessing renal function, a number of authors have attempted to calculate renal clearance from the fall in the plasma concentration of substances eliminated by the kidneys after iv injection.[35,52] In this approach it must be assumed that the behavior of the substance in the organism can be described by a two-compartment system (Fig. 8), or in approximation by a one-compartment model, in addition to Eq. (1).

In a two-compartment model, the changes in the serum concentration can be described by the sum of two exponential functions:

$$C_p = A \cdot e^{-\lambda_1 t} + B \cdot e^{-\lambda_2 t} \qquad (4)$$

The serum concentration curve for $^{51}$Cr-EDTA, a substance filtrated only by the glomeruli, corresponds closely to this model (Fig. 9). In routine applications, usually only the monoexponential part of

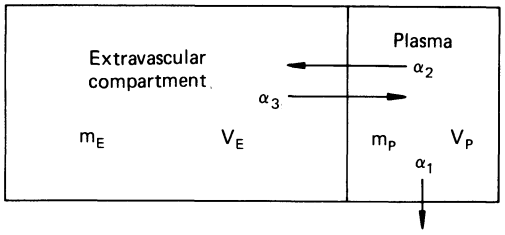



**Figure 8.** Two-compartment model for calculating the clearance from the fall of plasma activity. $m_P$, Quantity of substance in the plasma; $V_P$, plasma volume; $m_E$, quantity of substance in extravascular compartment; $V_E$, extravascular compartment.

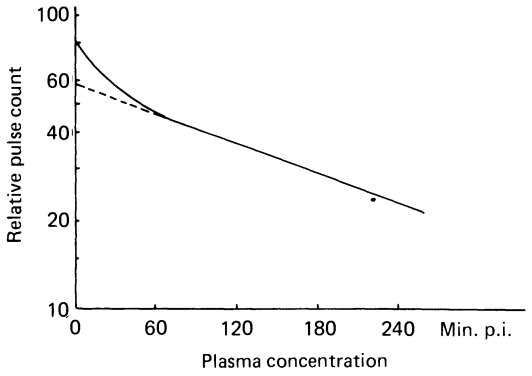



**Figure 9.** Fall of plasma activity for substances handled by glomerular filtration.

the curve, reached after about 60 min, is used. The clearance is then calculated according to the formula

$$Cl = V\frac{0.693}{T_{1/2}} \qquad (5)$$

where $V$ is the extrapolated distribution volume computed from the ratio of injected activity to extrapolated initial plasma concentration and $T_{1/2}$ is the half-life computed from the fall of the plasma concentration.

This simplified method neglects the initial part of the curve and is therefore necessarily subject to a systematic error of about 10% that varies individually to some degree. This method cannot, therefore, replace the accurate determinations of glomerular filtration by the whole-body counter or the classic method, but it is certainly far superior to the simple serum creatinine assay and to the endogenous creatinine clearance.

Measurements of renal plasma flow have also been attempted from the fall of plasma iodohippurate activity. For this substance, however, a two-compartment model is insufficient, and the plasma concentration curve is not monoexponential in any time interval.[38] Therefore, major deviations occur in individual cases compared to the accurately determined clearance values, although good correlations are still obtained in large-scale studies.[51]

## Blood Flow Scintigraphy

A further radioisotope method for the diagnosis of perfusion disorders is renal blood flow scintigraphy.[45,46] This study requires the same equipment as the renal function scintigram, i.e., a gamma camera linked to a data processor. It is done with either $^{99m}TcO_4$ or $^{99m}Tc$ compounds suitable for renal scintigraphy. When the latter is used, a static image can also be obtained.

In the blood flow scintigram, 10 to 15 mCi of the radioactive agent is injected intravenously, preferably as a bolus. This is best achieved by using a two-chamber syringe,[7] which is automatically post-rinsed with physiologic saline. During the first 30 s after injection, the changing activity pattern is photographed in individual exposures of 0.25-s duration, thus permitting an evaluation of the perfusion of the kidneys, aorta, and iliac arteries. Especially in the case of pronounced stenoses, this is apparent even in corresponding cumulative images. For a more detailed assessment, especially of renal perfusion, time-activity curves can be generated. Figure 10 shows such curves for a patient with lateralization of renal function. While a distinct "peak" is demonstrable on the left side owing to the high renal perfusion, only a normal rise of activity is present on the right side, similar to that seen over a less well perfused body region. For comparison, Figure 11 shows a single image from the blood flow scintigram taken in the same patient as well as the renograms derived from the scintigram. Like the blood flow scintigram, the individual image indicates a reduction of renal parenchyma on the right side; the ren-

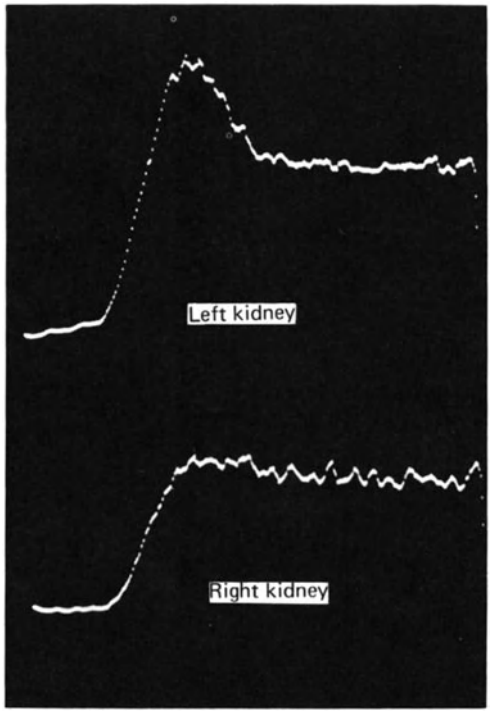



**Figure 10.** Time-activity curve in lateralized renal perfusion.

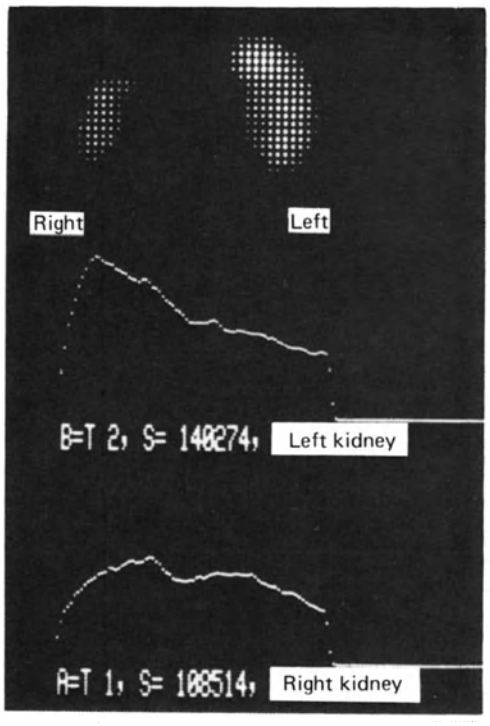



**Figure 11.** Renal phase scintigram of same patient as in Figure 10.

ogram shows a markedly reduced secretion on the right side.

While the $^{131}$I-iodohippurate clearance is a measure of effective renal plasma flow only when secretion of this substance in the tubular cells is undisturbed, the blood flow scintigram reflects the perfusion of the kidneys independent of other aspects of renal function and thus represents an important method (particularly in the absence of urine flow) of ascertaining whether the kidney is perfused or not. It is only a qualitative procedure at present, however, since a quantitative evaluation of the blood flow scintigram has not yet been described.

## Imaging

The static renal scintigram is a two-dimensional representation of the spatial distribution of gamma-radiating radionuclides in the kidney, using radioactive substances which alter their distribution pattern very slowly. The most important radioactive agents used are $^{197}$Hg-labeled chlormerodrin and especially the $^{99m}$Tc-labeled compounds DTPA and dimercaptosuccinate.[18] The distribution of the gamma-radiating nuclides can be recorded with either the scanner or the gamma camera. In the case of the scanner, a collimated detector scans the field of interest, and the distribution is plotted as a line scintigram. With the gamma camera, gamma rays are registered simultaneously from the entire image field, assigned to corresponding points in the image, and displayed on the oscillograph screen. The scintigrams are documented with a Polaroid camera. The advantage of gamma cameras over scanners lies in their much higher recording speed and their greater spatial resolution.

Whereas the urogram visualizes the renal collecting system, the renal scintigram gives a picture of the functioning renal parenchyma. Thus, the urogram and scintigram do not compete with each other but are mutually complementary.

The scintigram is particularly important in detecting parenchymal diseases that originate in the area of the renal cortex, i.e., at a distance from the collecting system. In these cases radionuclide methods are often the only means of establishing an impairment of function and determining the localization and extent of the focus. An example is shown in Figure 12. With relatively discreet inflammatory changes in the right collecting system, $^{131}$I-iodohippurate clearance fell to 152 ml/min and thus to 36% of the total function, and the scintigram demonstrates the corresponding reduction of functional parenchyma in the right kidney. Thus, in cases mainly with parenchymal involvement, radionuclide studies can demonstrate disease processes before serious alterations become visible in the urogram.

With staghorn calculi in the renal pelvis or renal calyces, the reduction of function is usually the result of secondary pyelonephritis as well as urinary stasis. It is therefore important to know not only the degree of function impairment but also the location of still healthy as well as nonfunctioning tissues. This is achieved by combining the split renal clearance with the scintigram. Figure 13 shows the examination results of such a case. The clearance of the right kidney is plainly reduced relative to the left but is such that the organ should be preserved.

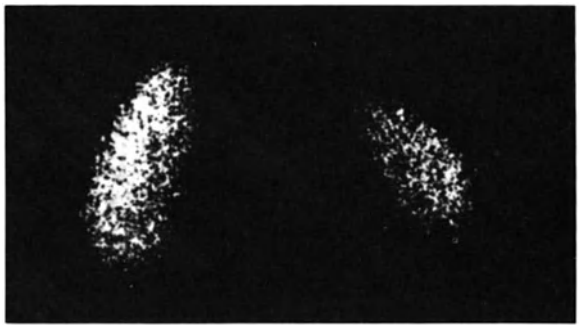
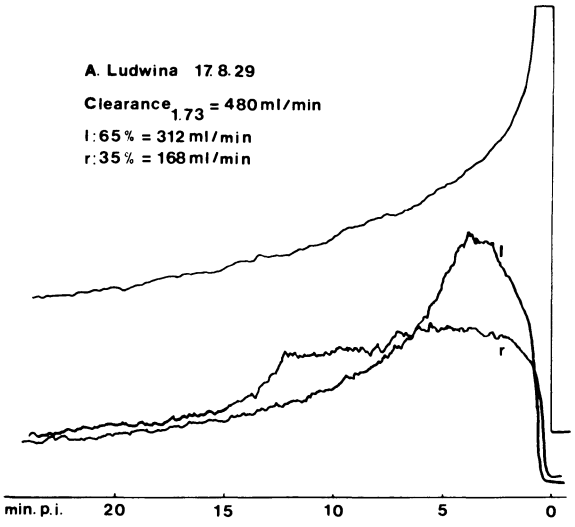
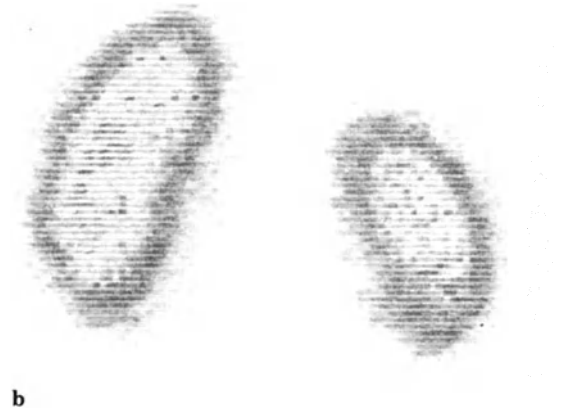


**Figure 12.** Static renal scintigram in right-sided pyelonephritis.




a



b

**Figure 13.** Retention curve, renograms, and static scintigram in right-sided secondary pyelonephritis.

The scintigram shows that primarily the medial part of the caudal section is nonfunctioning. Such findings help in the decision whether a lithotomy or a nephrectomy is indicated. Since partial nephrectomies are often necessary with staghorn calculi, the scintigram may indicate which parts of the kidney should be spared if possible, or whether a partial renal resection appears justified owing to localized storage defects.

## Adrenal Glands

### Determination of Total Electrolyte Content

Total potassium content as well as the content of exchangeable sodium can be determined by dilution measurements. For potassium, $^{42}K$ with a half-life of 12.4 h is administered orally or intravenously in an activity of about 100 $\mu$Ci. The total urine excreted until equilibrium is achieved is collected and its activity determined. After about 24 h, an equilibrium develops between the $^{42}K$ and the potassium present in the body. The total potassium content can now be determined from urine samples by the determination of $^{42}K$ and the potassium concentration in the urine according to the equation

$$^{39}Ke = \frac{(^{42}Ki - {}^{42}Ka) \cdot {}^{39}Ku}{{}^{42}Ku} \qquad (6)$$

where $^{39}Ke$ = total potassium content in mEq; $^{42}Ki$ = injected activity of $^{42}K$ in $\mu$Ci; $^{42}Ka$ = activity of $^{42}K$ in $\mu$Ci excreted before collection of equilibrium urine sample; $^{42}Ku$ = concentration of activity in urine in $\mu Ci/cm^3$; and $^{39}Ku$ = potassium concentration in urine in $mEq/cm^3$.

This method yields the total potassium content, for after 24 h the exchange between the administered $^{42}K$ and the natural potassium present in the body is practically complete.[25,50] In this method the total potassium and exchangeable potassium coincide within the limits of error of the determination method. The situation is different for sodium. Here only 70% to 76% of the sodium present in the body is exchanged within 24 h.[29] Thus, if an analogous method is used that involves the administration of $^{22}Na$ or $^{24}Na$, it is possible to calculate the exchangeable sodium. Table 1 presents the values measured

**Table 1.** Normal Values of Exchangeable Sodium and Potassium

| Subject (Age) | Sodium (mEq/kg) | Subject (Age) | Potassium (mEq/kg) |
|---|---|---|---|
| Men | | Men | |
| 18–33 | 41.4 ± 21% | 16–30 | 48.1 |
| 34–50 | 41.4 | 31–60 | 45.1 |
| 51–70 | 40.1 | 61–90 | 37.3 |
| Women | | Women | |
| 16–33 | 39.2 ± 16% | 16–30 | 38.2 |
| 35–72 | 41.4 | 31–60 | 34.2 |
| | | 61–90 | 29.7 |

in normal persons for total potassium by Moore et al.[33] and for exchangeable sodium by Edelmann.[12] While the exchangeable sodium remains largely constant, the total potassium shows a clear dependence on age and sex, attributable to differences in fat content. This was confirmed particularly clearly by the determination of total potassium content from the gamma radiation of $^{40}K$, which is present in natural potassium in a concentration of 0.0118 wt %.[28,42] Thus, with sufficiently sensitive detectors, called whole-body counters,[34] it is possible to measure the total potassium content without administering any radioactive agents. By an additional injection of about 0.2 $\mu$Ci of $^{22}Na$, total potassium and exchangeable sodium can be determined simultaneously with the whole-body counter.[26]

Figure 14 shows the gamma-ray spectrum recorded in one patient after the injection of 0.2 $\mu$Ci of $^{22}Na$. Measurement in both energy channels $E_1$ and $E_2$ makes it possible to determine $^{22}Na$ and $^{40}K$ at the same time. For $^{40}K$, measurement with the whole-body counter yields the total potassium content directly, while the determination of exchangeable sodium depends on knowledge of the ratio between the $^{22}Na$ activity and the sodium content of a urine specimen. Repeated measurements in normal persons over a 30-day period showed that $^{22}Na$ as well as $^{40}K$ can be determined with 3% accuracy during a 30-min measuring period.

Figure 15 shows the results for total potassium and exchangeable sodium obtained in a female patient after a single injection of 0.2 $\mu$Ci of $^{22}Na$ before and after surgical removal of an adrenal adenoma. Before surgery, the total potassium was clearly subnormal, while exchangeable sodium was just as clearly elevated. In a measurement 12 days after surgery, the potassium had increased above normal levels while the sodium had correspondingly decreased.

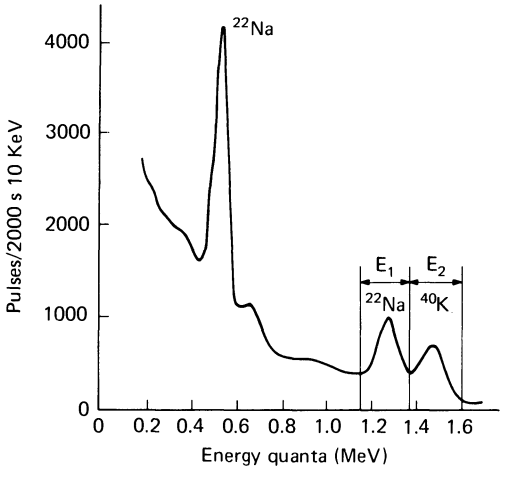



**Figure 14.** Gamma radiation spectrum after injection of 200 nCi of $^{22}Na$.

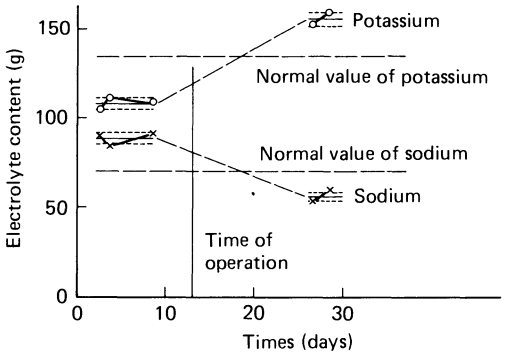



**Figure 15.** Total potassium and exchangeable sodium before and after removal of an adrenal adenoma.

## Studies of Steroid Metabolism

A large number of $^{14}C$- or $^{3}H$-labeled hormones with a relatively high specific activity are available for such studies. Their high specific activity ensures that the endogenous steroid hormone pool in in vivo studies remains essentially unchanged, thus meeting an important methodological prerequisite for metabolic examinations. To date, radiolabeled substances have been used almost exclusively as a tool for pathophysiologic research, rather than in diagnosis. It must be kept in mind, however, that kinetic data in particular, which can be obtained only with radiolabeled steroids, provide further insights into the function and significance of the endocrine glands as well as the steroid hormone metabolism in various diseases.

The plasma concentrations of certain steroids or their elimination in the urine are a relatively poor index of the amount of steroid secreted by an endocrine gland, as these values are influenced by the function of the liver, kidneys, and thyroid. Much more precise is the secretion rate determined according to the dilution principle.[48] In this method a radiolabeled steroid of known activity is injected, and the specific activity is determined for a metabolite of this steroid isolated from the urine. If the conditions listed below are satisfied, the secretion rate $S$ is given by the formula

$$S = \frac{A}{a \cdot t} \tag{7}$$

where $A$ = injected activity; $a$ = specific activity of

the metabolite, mmol/activity; and $t$ = collecting time.

The conditions necessary for the validity of this simple relation[29,59] are:

1. The injected radiolabeled steroid and endogenous steroid must have the same distribution area.
2. The amount of steroid injected must be minute compared to the amount of endogenous steroid present.
3. The injected steroid must correspond to the endogenous hormone in its chemical and biological properties.
4. The isolated metabolite must originate exclusively from the steroid hormone to be determined.
5. The collecting period must be as long as the period during which the radiolabeled metabolite is excreted.

These conditions can be met in the determination of the secretion rates of cortisol, corticosterone, and aldosterone. The following secretion rates were found for these three steroids in normal persons:

Cortisol: 11.0–22.0 mg/day[9]
Corticosterone: 2.1–4.0 mg/day[21]
Aldosterone: 0.04–0.18 mg/day[56]

Figure 16 shows how the secretion rates for cortisol and corticosterone in a female patient with Cushing's syndrome change in different tests.[22]

Some steroids do not originate entirely from the secretion of an endocrine gland but are partially formed as precursors in the liver. In this case measurement by the simple principle of isotope dilution yields the production rate, which is made up of the secretion rate as well as the synthesis rate in the liver. Further difficulties in measurement may arise

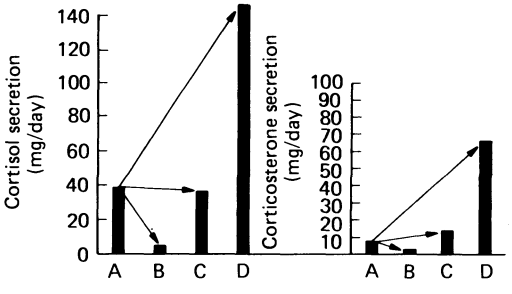



**Figure 16.** Secretion rates of cortisol and corticosterone in a female patient with Cushing's syndrome. *A*, initial value; *B*, dexamethasone test; *C*, metyrapone test; *D*, ACTH test.

because (as in the case of progesterone) no metabolite is known to derive exclusively from a single steroid hormone.[1] A further parameter for characterizing steroid metabolism is the "metabolic clearance rate," which is the plasma volume that is completely cleared per unit time of a particular steroid. It can be measured by the injection of the radiolabeled steroid and the subsequent measurement of the fall in plasma activity. The following relation applies:

$$\text{MCR} = -\frac{dc}{dt} \cdot \frac{P}{c} \qquad (8)$$

where MCR = metabolic clearance rate; $c$ = plasma concentration of radiolabeled steroid; and $P$ = plasma volume.

The following relation exists between the metabolic clearance rate and the production rate: production rate = MCR × hormone concentration in the plasma. Thus, the metabolic clearance rate can be obtained by dividing the production rate by the hormone concentration, and vice versa. Furthermore, by measuring both variables it is possible to determine whether the proposed simple model applies or whether more complicated multicompartment models must be employed.

## Scintigraphic Imaging of the Adrenals

In the various states of adrenal hyperfunction, it is often difficult to decide from laboratory data whether the condition involves a primary pituitary process with secondary adrenocortical hyperplasia or an adenoma or carcinoma of the adrenal gland. Hence, morphologic visualization of the adrenal is necessary for further evaluation. Besides roentgenologic studies, an important means of accomplishing this is by scintigraphic imaging.[5,8,10] 19-Iodocholesterol and 6-$\beta$-iodomethylcholesterol, both labeled with $^{131}$I, and 6-Se-cholesterol labeled with $^{75}$Se have been used as radioactive agents for adrenal imaging. The biological half-life of cholesterol in the adrenal is about 8 days and thus considerably longer than in the other organs, where its half-life is about 2 days.Therefore, scintigrams taken after the fifth day following intravenous injection usually show no interfering activity due to background in the gastrointestinal tract. With 19-iodocholesterol, most authors have used an activity of 1 mCi for adrenal scintigraphy. According to Trage et al., 6-$\beta$-iodomethyl has a much greater tissue affinity and so only 250 $\mu$Ci of this substance is sufficient.[60] This activity should not be exceeded in order to avoid excessive radiation exposure for the patient. Since $^{131}$I is released during breakdown of the compounds labeled with it, the

thyroid gland has to be blocked. Montz et al. indicate that the probability of detection is better with $^{75}$Se-cholesterol than with 19-iodocholesterol and that useful scintigrams can be obtained after only 2 to 3 days.[32] Normal adrenals are visualized as elliptical areas measuring 2–3 × 3–4 cm in size. The storage intensity of the labeled compounds is symmetrical. Slight size differences between the two adrenal cortical areas are physiological. In adrenal hyperplasia, measurable enlargements are frequently visible in the scintigram and can be differentiated from autonomous tumors by the scintigraphic dexamethasone test. Only one adrenal is visualized in unilateral destructive processes or in cortical adenomas and carcinomas, which form excessive glucocorticoids and suppress the function of the normal adrenal cortical tissue by inhibiting corticotropin-releasing factor and the release of ACTH.

Figure 17 illustrates the fact that demonstrable accumulations can also occur in the metastases of adrenocortical carcinomas. After surgical removal of the carcinoma, a normal liver-spleen scintigram was obtained with $^{99m}$Tc-sulfur colloid. The posterior view shown in the left of the figure reveals two sites of reduced storage in the liver and one in the spleen. The right portion of the figure shows a cumulative liver-spleen scintigram along with the adrenal scintigram subsequently obtained. It can be seen that the three areas consist of tissue which stores 6-$\beta$-iodomethyl. Another storage area is seen caudal to the spleen.

The adrenals cannot be visualized in hypercorticism or when corticoids are administered. In secondary hypocorticism, imaging (storage) can be achieved by stimulation with ACTH; this is not possible in primary hypocorticism. Adrenal scintigraphy is also capable of detecting residual tissue after surgery, demonstrating regeneration or recurrences, and locating ectopic adrenal tissue, thereby obviating the need for more stressful diagnostic procedures.

## Thyroid Gland

Diagnostic procedures for the identification of hyperthyroid states are of particular interest in evaluation of the hypertensive patient. Besides the radionuclide methods of localization and functional diagnosis discussed below, the measurement of thyroid hormone concentration is one of the most important basic examinations. Questions of method and related problems are discussed in Chapter 26.

### Localization Studies

Scintigraphic imaging of the thyroid can be performed with the two iodine isotopes $^{123}$I and $^{131}$I or with $^{99m}$Tc. Iodine isotopes have the advantage that both scintigraphy and function studies can be carried out at the same time. With $^{131}$I, however, it must be considered that the thyroid receives a radiation dose of about 2 rad/$\mu$Ci of $^{131}$I administered, resulting in a thyroid radiation exposure of about 50 rad for a normal examination. For this reason, and owing to its better gamma energy for scintigraphic imaging, $^{123}$I is much preferred. When this isotope is used, the radiation dose to the thyroid is comparable to that obtained with the $^{99m}$Tc thyroid scintigram, and the gonadal dose is smaller. Thyroid scintigrams with $^{99m}$Tc largely preclude simultaneous function studies, and so the evaluation must be based on scintigrams and in vitro tests.

The scintigram discloses the size of the thyroid and indicates whether the activity is uniformly distributed over the tissue or whether the storage is patchy.[2] Areas of abnormal storage should be coordinated with palpation findings. In diffuse hyperthyroidism, the scintigram is very often unremarkable. If nodular goiter occurs, differentiating it from autonomous adenoma can be difficult, especially when still compensated; for even with euthyroid goiter one often finds functionally heterogeneous areas

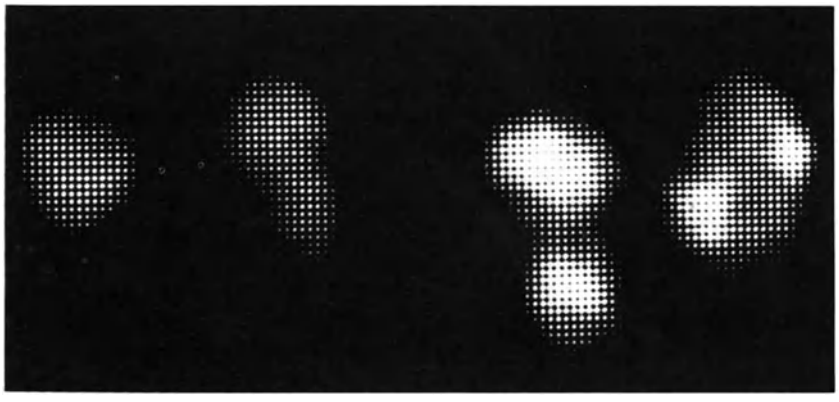


**Figure 17.** Metastases of an adrenocortical carcinoma.

which are usually the result of regressive cystic changes in individual tissue segments. Since the serum levels of the thyroid hormones frequently remain normal for some time in cases of autonomous adenoma, repetition of the scintigraphy after thyroid suppression with 3 mg of thyroxine is often necessary in order to delineate autonomous tissue whose storage function is still undiminished.

### Function Studies

Still the most widely used function test is the two-phase radioiodine study with measurement of iodine uptake in the thyroid over a 48-h period, and the determination of plasma concentrations of radiolabeled substances after 48 h. The test thus discloses the iodine affinity of the thyroid. Because the labeled substances present in the plasma after 48 h are almost exclusively thyroid hormones, the test also provieds a measure of how rapidly the thyroid releases the iodine in hormonal form. In hyperthyroidism, an increase in iodine storage is usually seen after 24 h and a marked decrease between 24 and 48 h. The plasma concentration of the radioactive iodine after 48 h is also elevated compared to the assumed limit of 0.27% of administered activity per liter of plasma. Because such changes of the iodine metabolism may also result from reductions of the thyroid iodine pool due to other causes, diagnostic conclusions should be drawn only in connection with the scintigram and only if the plasma thyroxine concentration is known. In borderline cases, a determination of the tri-iodothyronine concentration will usually be necessary as well, since this is the only hormone to be elevated in some forms of hyperthyroidism.

A further possibility in difficult-to-diagnose cases is repetition of the radioiodine test together with the scintigram after suppression of the thyroid.

Difficulties in the radioiodine test are associated mainly with the prolonged duration of the examination. A much more easily handled function test is the thyroid iodide clearance.[3] It is derived from the uptake of radioactive iodine per unit time and the plasma concentration in accordance with Eq. (9):

$$Cl = \frac{dA/dt}{C_p} \qquad (9)$$

where $dA/dt$ = radioactive iodine uptake in the thyroid per unit time and $C_p$ = plasma concentration.

Thirty minutes is sufficient for measurement, during which time the rise of activity over the thyroid is measured. A roughly linear relation exists between stored activity and time. With suitable calibration, the slope of this line yields the uptake per unit time. The blood sample for the determination of plasma activity is drawn at about the midpoint of the measuring period. Figure 18 shows the typical complex of findings in hyperthyroidism. With a largely normal scintigram, the iodide clearance is 370 ml/min (normal: 30–60 ml/min), and the thyroxine concentration is 18 $\mu$g per 100 ml; both are markedly elevated. Large scale studies[58] have shown a significant difference between euthyroidism and hyperthyroidism in terms of iodide clearance, thus ensuring a relatively high degree of diagnostic certainty. By use of $^{123}I$, thyroid clearance and scintigraphy can usually be performed within 2 h after administration of the radioiodine,[23] thus providing an easy-to-handle test of thyroid function disorders.

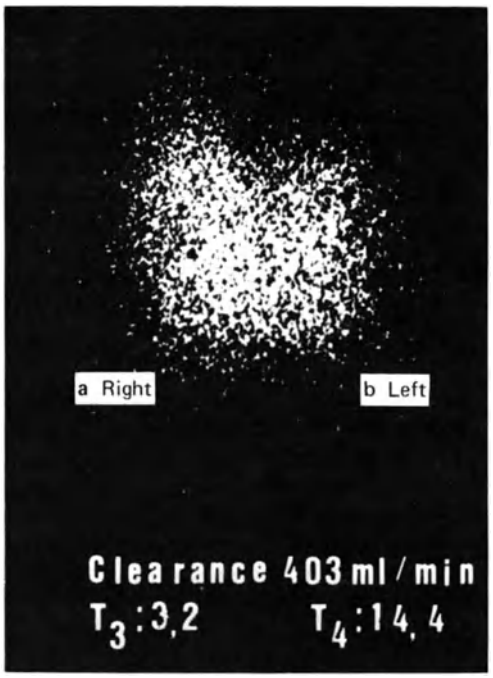



**Figure 18.** Typical complex of findings in hyperthyroidism.

## Heart and Circulation

Stenoses of the aorta and larger arteries can be demonstrated relatively easily by the method of blood flow scintigraphy described earlier in this chapter. A sharply decreased rise of activity is observed distal to the stenosis.

The cardiac changes that commonly result from

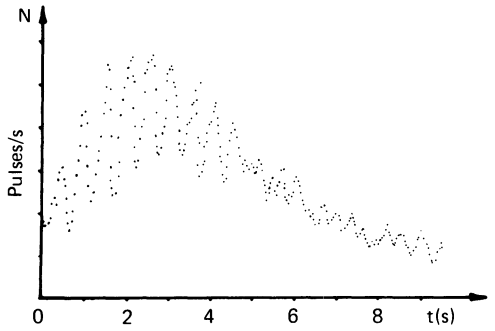



**Figure 19.** Time-activity curve over left ventricle during first passage of tracer.

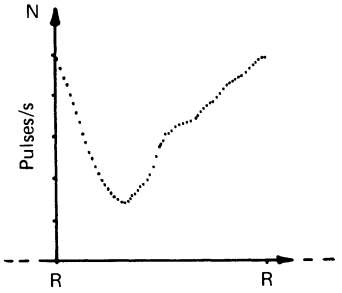



**Figure 20.** Time-activity curves after uniform distribution of tracer.

long-standing hypertension can also be demonstrated with radionuclide methods. The agents used must remain in the bloodstream for some time. Albumins or erythrocytes tagged with $^{99m}$Tc are most commonly used, but $^{113m}$In has also been recommended by some authors. The studies are usually done with the gamma camera linked to a data processor with time-activity curves generated for the selected regions of interest. Thus, the examination technique is similar to the arrangement in renal-phase scintigraphy, but the imaging frequency must be much higher, ranging from 4 to 20 frames per second. With a bolus injection, the minimum[24] or mean[16] transit time can be determined for the first passage of the tracer through the heart. These two parameters in themselves permit a global function assessment to be made.[40,44,62] With a suitably high temporal resolution, it is possible to determine the left ventricular ejection fraction from the fluctuations of the time-activity curves recorded over the left ventricle during the cardiac cycles.[54,63] One such time-activity curve is shown in Figure 19.

As soon as the radiolabeled substance has become evenly distributed in the circulatory system, each cardiac cycle is associated with the same pattern of pulse counts measured over the heart. In order to obtain time-activity curves that are as free as possible from statistical variations, the pulse counts for some 200 cardiac cycles are added together by phase. This in-phase addition is accomplished by using the R wave of the ECG as the starting point for imaging in each cardiac cycle.[14] From these images, time-activity curves like those shown in Figure 20 are generated. They reflect the change in the pulse counts and, thus, in a quantity analogous to the ventricular volume. From the course of the summed individual images, it can be determined whether contraction of the left ventricle is regular or whether localized disturbances of motility are present. If the contribution of tissue activity is subtracted from the pulse counts of the end-diastolic and end-systolic images, the ejection fraction of the left ventricle is obtained from the ratio of the net pulse counts.[4] Figure 21 shows the end-diastolic and end-systolic cumulative images for a patient in whom the ejection fraction was determined.

If the radioactive material is injected not as a bolus but by continuous infusion for about 10 to 12

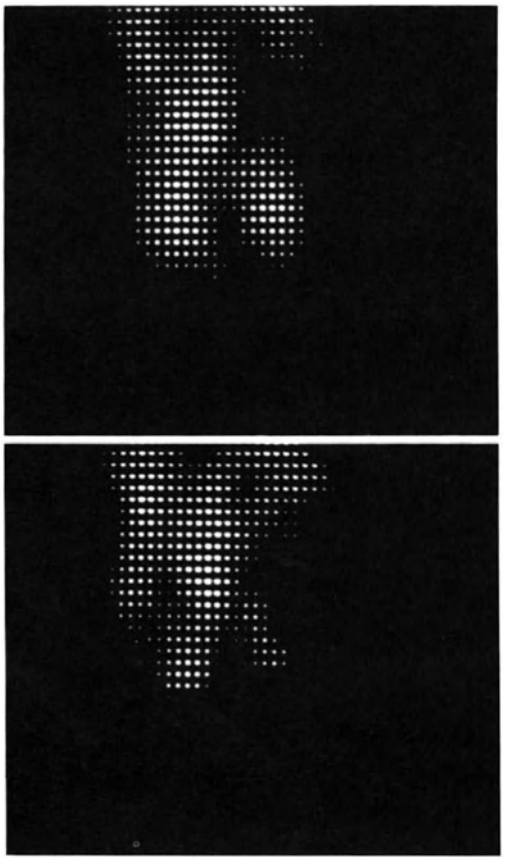


**Figure 21.** End-systolic and end-diastolic cumulative image.

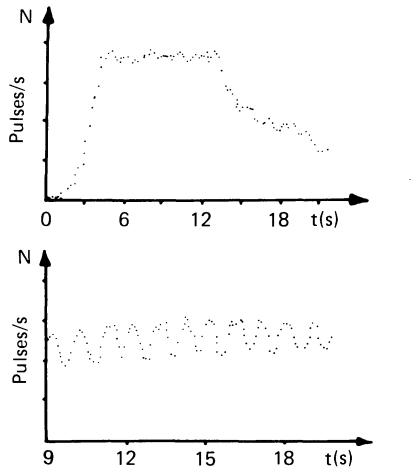



**Figure 22.** Time-activity curves over the vena cava and left ventricle during uniform infusion.

s, it becomes possible to determine a patient-specific calibration factor in order to calculate the corresponding volumes from the measured pulse counts.[13] Several seconds after the start of the continuous infusion a constant activity is measured over the vena cava (Fig. 22), while activity fluctuations due to cardiac actions are recorded over the ventricles. Since after several seconds the variations of pulse count correspond to the inflowing activity during one cardiac action, a correlation can be established between infused activity and the measured pulse count. If, after uniform distribution, the activity concentration in the blood is also determined, all variables necessary for converting the ordinate of the curve in Figure 20 into unit volume are known. Then in addition to the ejection fraction the cardiac output and maximum volume differential can be evaluated. Inasmuch as the radioactive substances used remain in the bloodstream for some time, the parameters important for assessment of cardiac function can be determined both at rest and during exercise, thereby gaining further important diagnostic information.

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# Therapy of Hypertension

# The Early Treatment of Mild Hypertension

# 29

K. O. Stumpe

Mild blood pressure elevations are observed relatively frequently and in all age groups. There is no generally accepted definition of *mild hypertension,* however, nor is there agreement as to the level of pressure at which treatment should commence. Theoretically, antihypertensive therapy should be initiated at the level which carries an excess risk for future morbidity and mortality.

At present only isolated prospective studies are available which demonstrate the benefit of early treatment in mild hypertension. For example, the Veterans Administration Cooperative Study Group reported on the effect of treatment in patients with diastolic blood pressures between 90 and 114 mm Hg.[29] Statistical evaluation showed that the 5-year incidence of typical hypertensive complications such as heart failure, cerebral hemorrhage, hypertensive encephalopathy, and aortic aneurysm was only 7% in patients who received antihypertensive treatment, while it was five times higher (35%) in the untreated control group.

There is also evidence that a correlation exists between blood pressure level and life expectancy even within the so-called normotensive range. For example, a man in his midthirties with a blood pressure of 130/90 mm Hg has a shorter life expectancy than a man of equal age with a blood pressure of 120/80 mm Hg.[16] A comparison of 35- and 55-year-old men shows that the effect of rising blood pressure on remaining life expectancy decreases with age and that persons over 65 may no longer experience the consequences of hypertension. Thus, the younger the patient, the more potentially serious the hypertension, and the earlier antihypertensive therapy should be instituted, even if the blood pressure elevation is mild.

By utilization of statistics on the distribution of blood pressure in a large sample of the adult population and morbidity data,[5] it is possible to define normotensive, hypertensive, and borderline hypertensive values for various age groups[10] (Table 1).

The term *mild hypertension* should be reserved either for borderline values accompanied by signs of cardiovascular changes (ECG, chest X-ray, funduscopy) or for values which are consistently within the hypertensive range but do not exceed 105 mm Hg diastolic in the 18 to 60 age group. As for the systolic cutoff point, there is considerable uncertainty owing to a lack of corresponding studies on the benefit of antihypertensive therapy in pure systolic hypertension. This applies in particular to patients over age 60.[6]

As long as the definition of hypertension is based upon the demonstration of an improved prognosis with antihypertensive therapy, the cutoff points are variable and may have to be lowered in the light of current or future prospective studies.

Owing to the extreme variability of the blood pressure, it is often difficult to differentiate borderline hypertension from mild established hypertension, especially if no organ damage is present. The transitions are fluid. The significance of mild as well as borderline hypertension lies in the fact that they may represent the initial stage of a later significant hypertension and may be accompanied by excess cardiovascular morbidity and mortality.[11,13–15] On the other hand, in view of the frequency of mild blood pressure elevations, the incidence of future hypertension of moderate severity is not overwhelming. The average prevalence is between 15% and 20%.[23,24] Consequently, in 10 to 20 years, 80% to 85% of young patients with mild and borderline hy-

**Table 1.** Classification of Blood Pressures

| | | 17–40 | 41–60 | >60 Years |
|---|---|---|---|---|
| Normotension | | ≤140/90 | ≤150/90 | ≤160/90 |
| Hypertension | | ≥160/100 | ≥160/100 | ≥175/100 |
| Borderline hypertension | (a) | >140/90 | >150/90 | >160/90 |
| | | <160/100 | <160/100 | <175/100 |

or (b) Some levels hypertensive, some normotensive. No cardiovascular changes.

pertension will not develop significant hypertension. Thus, since only a small percentage of patients would benefit from antihypertensive therapy, the question arises: Should all patients with mild hypertension receive treatment in order to prevent complications in a minority of the whole group? This question can be answered in the affirmative only if the curative or preventive effects of treatment outweigh the possible harmful side effects of the medication in the overall group.

On the basis of available data and previous experience, it does not appear that all patients with mild or borderline hypertension should receive antihypertensive treatment. An effort should be made to identify the hypertensive subgroup which is at highest risk of developing significant hypertension leading to vascular complications. It is this high-risk group which should be treated. Low doses of drugs which produce as few subjective or chemical side effects as possible are indicated.

The identification of this "high-risk group" can be undertaken with the aid of certain diagnostic measures (Table 2). Besides the question of family history, the physician must be alert for cardiovascular changes. If the optic fundus, ECG, chest X-ray, or renal function parameters (serum creatinine) indicate the presence of vascular changes or left ventricular hypertrophy, initiation of treatment is indicated in both borderline and mild hypertensives.

The presence of *risk factors* is also important. There are basically two types of risk factors: those leading to the development of atherosclerotic disease and those predisposing to later development of hypertension (Table 3). In the presence of a mild blood pressure elevation, factors which are likely to predispose to a progression of the hypertension are of special interest. These are the blood pressure level, family history, tachycardia, and race.

The *blood pressure level* is by far the strongest factor predisposing to the development of significant hypertension,[23] even in the very narrow borderline and mild hypertensive range. It is, therefore, very important to obtain multiple and representative blood pressure readings in patients with mildly elevated blood pressures. The therapeutic decision, estimation of the effect of treatment, and monitoring of blood pressure trends can be based only on reliable blood pressure measurements. It is therefore recommended that the mildly hypertensive patient perform regular blood pressure self-determinations at home in addition to the determinations performed in the physician's office. When the patient has learned the technique, a cuff should be prescribed or lent for home use. Optimally, the home and office measurements should supplement each other. Studies by Julius,[10] as well as personal experience, have shown that the blood pressure measured in the office or clinic does not always coincide with the values measured under "usual" circumstances. Thus, while most borderline and mild hypertensives have lower blood pressure readings at

**Table 2.** Minimum Diagnostic Program for Mild Hypertension

| Family History | Laboratory Tests |
|---|---|
| Physical examination | Serum creatinine |
| Weight | Serum cholesterol |
| Funduscopy | Serum glucose |
| Left ventricular hypertrophy | Urinalysis |
| | ECG |
| | Chest X-ray |

**Table 3.** Differentiation between Risk Factors Influencing Development of Arteriosclerosis and Hypertension

| |
|---|
| →*Arteriosclerosis* |
| 1. Hyperlipidemia |
| 2. Hyperglycemia |
| 3. Hyperuricemia |
| 4. Nicotine |
| 5. Lack of exercise |
| →*Hypertension* |
| 1. Blood pressure level |
| 2. Family history |
| 3. Race |
| 4. Tachycardia |
| 5. Obesity |
| 6. High-salt intake↑ |

home than in the office or clinic, higher home readings are obtained in about 30% of cases.

*Family history* is also of considerable importance.[28] If one or both parents had hypertension or died from the complications of hypertension, the offspring with mild or borderline hypertension has a three times higher chance of developing significant hypertension than in the absence of a family history.

Another indicator of the risk of future significant hypertension is *tachycardia.*[13] An increase in the pulse rate cannot always be considered a benign symptom. It is frequently and erroneously assumed that tachycardia in the physician's office or outpatient clinic is a sign of temporary anxiety and as such is innocent.[10] As early as 1945, Levy et al. showed that tachycardia carries a significantly higher risk for future significant hypertension, even if the blood pressure values are normal.[13]

Another important factor is *race.* It is known that blacks with borderline and mild hypertension are three to four times as likely as white individuals to develop significant hypertension.[5]

When and how should mild hypertension be treated? The fact that drug therapy is not immediately indicated in every case does not free the physician from the obligation to manage all patients with mild or borderline hypertension. The patient should be educated about the importance and risks of high blood pressure and made aware of the need for frequent blood pressure measurements. If the diastolic blood pressure is below 100 mm Hg and no apparent risk factors are present, blood pressure trends can be monitored by measurements at 6-month intervals, and general nonpharmacologic measures adopted to normalize the blood pressure. If the baseline increases by 10 mm Hg in 1 year, drug therapy should be instituted. Treatment should produce few side effects, and the regimen should be easy to follow.

Because the antihypertensive drugs currently in use can cause subjective complaints as well as unfavorable biochemical changes, the treatment of mildly hypertensive patients should begin with *nonpharmacologic measures* (Table 4), particularly if there is no organ damage and no more than one of the aforementioned risk factors is present. Two such measures are of particular benefit in mild hypertension: weight reduction and restriction of salt intake. Reisin and his group have recently shown that a weight reduction of 10 kg without salt restriction in overweight hypertensives leads to a marked reduction or even normalization of blood pressure.[21] It must be realized, of course, that only about one of three obese patients will succeed in achieving a long-term weight reduction. For this reason one should not wait for the possible benefits of weight reduction in mild hypertensives if the diastolic pressure is consistently above 100 mm Hg but should supplement weight control with simultaneous pharmacologic therapy. If weight reduction is successful, the drug regimen can be reduced or discontinued in stages. It should be remembered that the obese patient with mild hypertension is jeopardized less by his obesity than by his high blood pressure.

**Table 4.** General Therapeutics for Mild Hypertension

| | |
|---|---|
| 1. | Correction of: |
| | Obesity |
| | Hyperlipidemia and hyperglycemia |
| | Excessive salt and nicotine intake |
| 2. | Physical exercise |
| 3. | Frequent blood pressure measurements including blood pressure determinations by patient |

Another nonpharmacologic measure is the limitation of salt intake. Although salt restriction is not of proven value in the long-term reduction of blood pressure, a significant association between salt intake and prevalence of hypertension is frequently found.[7] The patient should be discouraged from consuming salt-rich foods or adding salt to already prepared foods. Recent studies have shown that the blood pressure can be lowered by a moderate restriction of salt intake to about 5 to 8 g/day.[17]

Besides these two important general measures, other risk factors such as elevated plasma lipids, disturbances of sugar and purine metabolism, and excessive smoking should be corrected either by dietary modification or pharmacologic therapy. Exercise should also be recommended in the form of running, bicycling, swimming, ball-playing, etc. Such physical activity aids in weight control and contributes to the patient's feeling of well-being.

If adequate blood pressure reduction cannot be achieved by the nonpharmacologic measures mentioned, we institute drug therapy (Fig. 1) in patients under 40 if multiple measurements indicate an *average* blood pressure of 145/95 mm Hg or higher, or if the average pressure fluctuates between 140/90 and 150/95 mm Hg or higher and there is a family history and one risk factor, or if there is no family history and two risk factors. These patients should be treated over a 2-year period. After this period, treatment may be discontinued for 2 months. If the blood pressure rises, therapy is reinstituted. If the patient remains normotensive, blood pressure measurements, ECG, and creatinine assay are performed every 6 months. The patient should not obtain the impression that he or she is "cured" of hypertension and must understand the need for continued supervision.

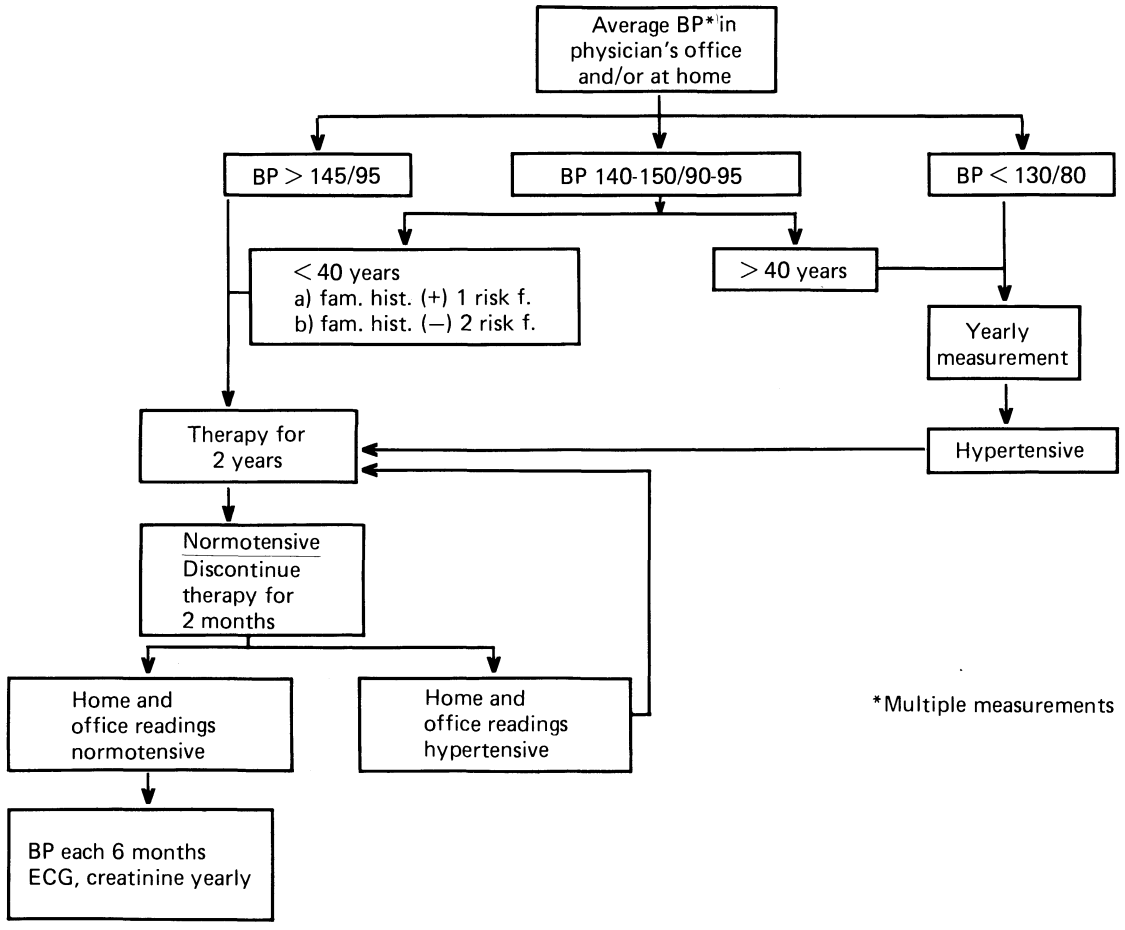


**Figure 1.** Indications for therapy in mild hypertension.

The question of whether elderly patients (over age 65) with pure systolic hypertension (systolic blood pressure above 165 mm Hg and diastolic pressure less than 95 mm Hg) should receive antihypertensive treatment cannot be answered at present, owing to a lack of corresponding prospective studies. The systolic blood pressure increase in these patients may be the result of the often extensive vascular sclerosis occurring in this age group.

In elderly patients with diastolic values of 105 mm Hg and higher, treatment is definitely indicated. Judged by available data, such treatment can significantly reduce the incidence of stroke and heart failure.[18,20]

With regard to the *pharmacologic treatment* of mild hypertension, two classes of antihypertensive drugs are preferred owing to their efficacy and mild side effects. These are the β-blocking drugs and the diuretics. Each type of drug may be administered singly, since they cause no significant sodium and fluid retention and thus do not promote the development of resistance. The question of which of the two drug types is superior cannot yet be answered. The antihypertensive effect is approximately the same in an unselected patient group, and the rare subjective side effects are tolerated equally well. However, β-blocking drugs may one day prove superior to the diuretics owing to their fewer *biochemical* side effects. We refer not to the changes in potassium, glucose, or uric acid metabolism that occur with diuretics, but to the recently observed disturbances of lipid metabolism, notably the increase in plasma triglycerides and β-lipoproteins.[1,3] Such changes may increase the risk of coronary heart disease.[2,8] Meanwhile, there is evidence that the incidence of heart attack is reduced in hypertensive patients treated with β-blocking drugs;[12,25] future confirmation of these findings would shift the decision in favor of the β-blockers. More prospective studies are needed before this question can be resolved.

We consider the β-receptor blocking agents to be

**Table 5.** Drug Therapy for Mild Hypertension

1. β-Receptor blocking drugs, e.g., 3 × 20–40 mg of Inderal daily, not exceeding 2 × 30 mg/day

If above is contraindicated:

2. Thiazide diuretics combined with $K^+$-retaining diuretics

Indicated only under some circumstances: reserpine, clonidine, α-methyldopa, and guanethidine

the drugs of first choice in the treatment of mild hypertension (Tables 5 and 6). This applies even to elderly patients, provided there are no contraindications such as obstructive syndrome or second-degree A-V block. Therapy should start with relatively low doses of the β-blocking drug, e.g., 20 to 40 mg of Dociton three times daily. Doses higher than 2 × 80 mg of Dociton or equivalent doses of other β-blocking drugs are seldom necessary.

At present, about 20 β-receptor blocking drugs are available in the Federal Republic of Germany. These drugs are entirely equivalent with regard to their antihypertensive efficacy at comparable doses.[4,9,26,27,30] However, there are considerations which might favor a particular β-blocking drug under certain circumstances. A distinction is made between cardioselective and noncardioselective β-blocking drugs. This cardioselectivity is only relative, since all β-blocking drugs increase the bronchial resistance at adequate doses and are therefore contraindicated in asthmatics and patients with severe obstructive bronchitis.[22] Nevertheless, if mild bronchospasm occurs during treatment with a noncardioselective blocking drug, changing to a selective drug might enable the continuation of therapy.[30] If a low pulse rate is present before start of treatment or marked bradycardia develops during the course of treatment, a β-blocking drug with intrinsic sympathicomimetic activity, such as pindolol, oxprenolol, or acebutolol, may be used. These drugs have a negligible effect on pulse rate in some patients. β-Blocking drugs with intrinsic sympathicomimetic activity are also indicated if peripheral circulation is impaired (cold extremities). If the drug possesses cardioselectivity as well, the cold-extremities symptom is even less common, and the drug may be used even in mild cases of Raynaud's disease.[30]

On the other hand, β-blocking drugs with intrinsic sympathicomimetic activity can cause palpitations, restlessness, sweating, and even blood pressure elevation, especially at higher doses. In these cases a change to a β-blocking drug without intrinsic sympathicomimetic activity is advised. Finally, the central nervous system side effects of some β-blocking drugs, such as sleeplessness, nightmares, or fatigue, can often be relieved by changing to a β-blocker which is less apt to cross the blood-brain barrier, such as atenolol or sotalol.[30]

If β-blocking drugs are contraindicated, low doses of a thiazide preparation, either alone or in a fixed combination with a potassium-retaining diuretic, are recommended (Table 7). If moderate doses of a β-blocking drug are insufficient to lower the blood pressure, combined treatment with a β-blocking drug and a diuretic may be tried (Table 8). These combinations need be administered only once daily in most cases.[19]

Reserpine, clonidine, α-methyldopa, or guanethidine should not be the drug of first choice in mild hypertension. These drugs almost always cause side effects and necessitate concurrent diuretic therapy. Reserpine, moreover, increases the appetite.[10]

**Table 6.** Differential Therapy with β-Receptor Blocking Drugs for Mild Hypertension†

| | Preparation | mg | ISA* | Receptor Affinity | Lipophility | Dosage (mg) |
|---|---|---|---|---|---|---|
| Propranolol | Inderal | 80 | 0 | $\beta_1 + \beta_2$ | ++ | 2–3 × 40–2 × 240 |
| Timolol | Temserin | 10 | 0 | $\beta_1 + \beta_2$ | + | 2 × 5–2 × 10 |
| Nadolol | Corgard | 120 | 0 | $\beta_1 + \beta_2$ | ++ | 1 × 60–120 |
| Sotalol | Sotalex | 160 | 0 | $\beta_1 + \beta_2$ | 0 | 2–3 × 80–2 × 320 |
| Pindolol | Visken | 5/15 | ++ | $\beta_1 + \beta_2$ | + | 3 × 5–2 × 15 |
| Oxprenolol | Trasicor | 80 | + | $\beta_1 + \beta_2$ | + | 3 × 40–3 × 80 |
| | T. ret. | 160 | | | | (Retard: 1 × 160) |
| Atenolol | Tenormin | 100 | 0 | $\beta_1$ | 0 | 1 × 50–200 |
| Metoprolol | Lopressor | 100 | 0 | $\beta_1$ | + | 2–3 × 50–100 |
| Acebutolol | Prent | 250 | + | $\beta_1$ | + | 2 × 250–500 |

*Intrinsic sympathicomimetic activity.

†Only some of these β-blockers are available in the U.S.

**Table 7.** Feasible Diuretic Therapy for Mild Hypertension*

| |
|---|
| Esidrix<br>(25 mg hydrochlorothiazide) 2–3 tablets daily |
| Hygroton<br>(50 mg chlorthalidone) 1 tablet daily |
| Moduretik<br>(50 mg hydrochlorothiazide + 5 mg amiloride) 1–2 tablets daily |
| Dytide-H<br>(25 mg hydrochlorothiazide + 50 mg triamterene) 1–2 tablets daily |
| Diucomb<br>(25 mg bemetizide + 50 mg triamterene) 1 tablet daily |
| Aldactone 100 or Osyrol 100<br>(100 mg spironolactone) 2–3 capsules daily |
| Aldactone 50—Saltucin<br>(50 mg spironolactone + 5 mg butizide) 2–3 tablets daily |

*Many of these combinations and their dosages are not yet available in the United States.

Although the necessity of treatment in mild hypertension has not yet been proved conclusively, one should not deny treatment to carefully selected high-risk patients with mild hypertension until suitable prospective studies have been completed. There is no doubt that such therapy can largely prevent the occurrence and progression of vascular and organ damage and prolong the life expectancy.

**Table 8.** Fixed Combinations of β-Receptor Blocking Drugs and Diuretics for Treatment of Mild Hypertension*

| | |
|---|---|
| Antra | Alprenolol 100 mg<br>Hydrochlorothiazide 10 mg |
| Moducrin | Timolol 10 mg<br>Hydrochlorothiazide 25 mg<br>Amiloride 2.5 mg |
| Torrat | Methypranol 20 mg<br>Butizide 2.5 mg |
| Trasitensin | Oxprenolol 80 mg<br>Chlorthalidone 10 mg |
| Viskaldix | Pindolol 10 mg<br>Clopamide 5 mg |

*Many of these combinations and their dosages are not yet available in the United States.

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# Systolic Hypertension in the Elderly: A Therapeutic Problem

30

A. V. Chobanian

Systolic hypertension in the elderly is a common clinical problem which represents a major therapeutic dilemma. The magnitude of the problem is increasing as the population of individuals over 50 years of age is expanding. Recent epidemiologic studies have suggested that systolic hypertension is an important risk factor for several major cardiovascular complications. However, the merits of treatment for the disorder remain obscure, and the optimum approach for lowering blood pressure has not been defined clearly. This paper will review some of the available information on this subject and will offer a personal approach to its management.

## Prevalence

Pure systolic hypertension is generally defined as a systolic blood pressure equal to or greater than 160 mm Hg and a diastolic pressure of less than 90 to 95 mm Hg. Various prevalence rates have been reported, depending on the population studied and the cut-off points used. Prior to age 50, the prevalence rate of pure systolic hypertension in the general population is less than 5%. However, there is a rapid increase in incidence subsequent to this period even though diastolic pressure tends to remain relatively stable. In the Framingham study group, the overall prevalence of systolic hypertension above age 70 was 27%, and 16% had pure systolic hypertension without diastolic elevation.[10] In studies of an elderly population at Seal Beach, California, approximately 14% had isolated systolic hypertension on initial evaluation, although the prevalence decreased markedly if subsequent determinations of blood pressure also were utilized.[3] High prevalence rates also have been reported in the United States National Health Examination Survey. In this survey, in white males and females from 65 to 74 years of age, 15% and 31%, respectively, had systolic blood pressures equal to or greater than 160 mm Hg and diastolic pressures less than 95 mm Hg. In blacks, the respective figures in males and females were 26% and 39%. Whatever the exact prevalence, there is no question that systolic hypertension is extremely common in older individuals.

## Vascular Changes with Aging

A variety of structural and biochemical changes occur in arteries as a result of aging. There is an age-related thickening of the intima and media which is associated with an increase in smooth-muscle cells, collagen, and elastin. Increased calcium deposition is also typical. The calcium tends to be distributed diffusely but is particularly associated with arterial elastin and glycosaminoglycans. Free and ester cholesterol and sphingolipids also increase in the intima as a result of age. Many of these changes have certain similarities to those occurring as a result of atherosclerosis. With atherosclerosis, there is a marked increase in intimal smooth-muscle cells and connective tissue constituents as well as of free and esterified cholesterol and sphingolipids. Arterial calcification is also common and tends to be focal in nature. The net effects of either aging or atherosclerosis on arterial function may be similar and additive in nature, and the end result is an arterial sys-

tem which has lost some of its elasticity or distensibility.

## Pathophysiology

With increasing age, there usually is a decrease in arterial compliance or capacitance,[1] which is defined as the unit change in volume of the artery per unit change in pressure. Arterial capacitance and the stroke volume of the heart are the major determinants of the arterial pulse pressure. Accordingly, as age increases, the systolic blood pressure will tend to be higher and the diastolic pressure lower (assuming that cardiac output, peripheral resistance, and mean arterial pressure are constant). When systolic hypertension is present in elderly patients, mean blood pressure is also elevated since the diastolic pressure is generally in the normal range and not reduced. Since cardiac output is not elevated in this group, the major contribution to the hypertension must be an increase in total peripheral resistance.

Contrary to some previous thinking, the blood pressure is not fixed in these patients but may exhibit much of the lability seen in normal subjects or in patients with diastolic hypertension. Thus, such factors as sleep, bed rest, and hospitalization tend to reduce the systolic pressure while other influences such as physical exertion or emotional excitement tend to raise the blood pressure. In addition, while the blood pressure response to antihypertensive drugs may not be as marked in this group as in other hypertensive subjects, effective lowering of blood pressure can be achieved with therapy. Unfortunately, normalization of mean blood pressure generally cannot be induced unless diastolic pressure is reduced to below the normal range. Such normalization may be hazardous since critical perfusion of vital organs may be impaired.

Other than for the changes in arterial capacitance with aging, little information is available concerning the mechanisms responsible for this form of hypertension. Plasma renin activity has been shown to decrease with age,[13] presumably as a result of decreased functional activity of the juxtaglomerular apparatus, but it is uncertain whether the systolic hypertensive group differs from the elderly population as a whole. Decreased baroreceptor sensitivity[4] and increase in plasma norepinephrine[12] have been reported in aging individuals. A decreased rate of degradation of circulating catecholamines and an increased effect of infused catecholamines on blood pressure of rats as a result of aging also have been suggested.[6,7] However, the relevance of these observations to the clinical situation is uncertain. Similarly, little if any information is available concerning such important characteristics as dietary sodium intake, fluid volume, and mineralocorticoid status in these patients.

## Associated Diseases

Systolic hypertension tends to parallel the degree of severity of atherosclerotic disease in the vasculature. Therefore, those diseases which are associated with enhanced atherogenesis tend to be more prevalent in elderly patients with pure systolic hypertension.

The prevalence of diabetes is particularly high in this population. In addition, many of the patients may have prior long-standing essential hypertension. Therapy with antihypertensive drugs may serve to normalize the diastolic blood pressure but, as a result of the diminished compliance in the arterial system, the systolic blood pressure might remain above the normal range in this group.

## Risks from Systolic Hypertension

The previously held view that systolic hypertension is a benign process has been put to rest by several independent investigations. In the Framingham study, after age 45 systolic blood pressure was actually more important than the diastolic blood pressure in influencing the morbidity and mortality from cardiovascular diseases.[9–11]

Elderly patients with isolated systolic hypertension have increased incidence rates for cardiovascular death, ischemic heart disease, congestive heart failure, strokes, and left ventricular enlargement.[3,5,9–11] Their risk appears to be particularly great when the systolic blood pressure exceeds 180 mm Hg. Unfortunately, no data are available concerning the effects of treatment in reducing these risks. The possibility certainly exists that elevated systolic pressure merely reflects the degree of vascular disease present and therefore might not be a causative factor in the later development of vascular complications. In addition, since these patients have a high prevalence of associated vascular disease, blood pressure lowering at times may prove to be poorly tolerated.[8]

## Clinical Evaluation

A schematic diagram summarizing the approach which should be followed is shown in Figure 1. The diagnosis depends on systolic blood pressures ex-

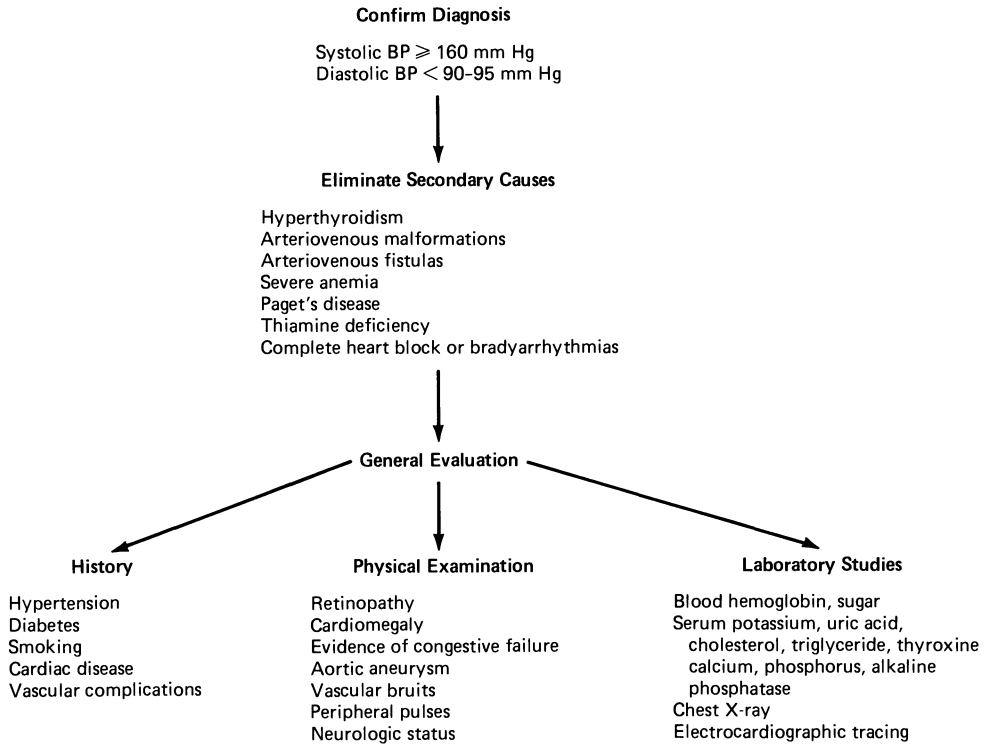


**Figure 1.** Evaluation of the elderly patient with systolic hypertension.

ceeding 160 mm Hg in the presence of a normal diastolic pressure (<90–95 mm Hg). Secondary causes which should be ruled out relate primarily to those conditions associated with an elevated cardiac output. Clinical states with marked bradycardia and a high stroke volume (e.g., complete heart block) also may have marked systolic hypertension.

The history or presence of significant vascular disease involving the heart, brain, and peripheral blood vessels should be evaluated in detail since the decision to treat, and the type of treatment utilized, may depend on this assessment. Some of these patients also may have an aortic aneurysm, which may at times be life-threatening unless surgically excised; therefore, a careful search for such aneurysms by physical examination also should be made.

The laboratory evaluation generally does not need to be excessive other than to help eliminate the secondary causes, assess the cardiovascular status, and follow those parameters which may be influenced by antihypertensive therapy. Hyperlipoproteinemia is an important known risk factor for atherosclerotic disease and may predispose elderly patients to systolic hypertension. However, its assessment and therapy may perhaps not be essential at an advanced age except as required for the detection of familial forms of hyperlipoproteinemia. The available data would suggest that hyperlipoproteinemia probably loses its importance as a cardiovascular risk factor in aged subjects.

## Indications and Objectives of Therapy

Because of the markedly increased incidence of cardiovascular complications and mortality when the systolic blood pressure exceeds 180 mm Hg, it would appear reasonable to attempt to lower the systolic pressure below this level. Indications for treatment would appear to be greater in patients who have not tolerated the hypertension well and who have evidence of end-organ damage related to the blood pressure elevation. Included in this category are patients with congestive heart failure or left ventricular enlargement, both of which can be induced or aggravated by the elevated systolic blood pressure, which is a major determinant of left ventricular afterload. Similarly, patients with prior cerebrovascular accidents are candidates for antihypertensive therapy, although particular care must be exercised to avoid sudden or marked blood pressure reductions. Patients with angina pectoris also may benefit considerably since the blood pressure reduction

**Table 1.** Relative Indications and Contraindications to Antihypertensive Therapy

| Indications | Contraindications |
|---|---|
| Systolic blood pressure >180 mm Hg | Systolic blood pressure ≤180 mm Hg |
| Hypertensive complications | No end-organ disease |
| Congestive failure | Transient ischemic attacks in brain |
| Cerebral hemorrhage | Peripheral vascular insufficiency |
| Renal failure | Poor response to step 1 and/or step 2 drugs |
| Angina pectoris | Side effects from mild antihypertensives |
| Good response to step 1 and/or step 2 drugs | |

could diminish cardiac work and myocardial oxygen demands. However, there would appear to be less potential benefit and greater risk of antihypertensive therapy in those patients with systolic hypertension who have certain other complications of atherosclerotic disease. For example, in patients with cerebrovascular disease exhibiting transient ischemic attacks, blood pressure lowering may diminish cerebral perfusion below critical levels and should generally be avoided unless marked systolic hypertension is present. Similarly, in patients with peripheral vascular disease, blood pressure reduction may aggravate the problem by diminishing tissue perfusion even further.

The relative indications and contraindications to therapy are summarized in Table 1. In general, the greater the indications, the more aggressive should be the therapy. However, in view of the uncertain state of current knowledge concerning the benefit/risk ratio of antihypertensive medications in this group, a relatively conservative therapeutic approach appears justified. Only the mild antihypertensive agents should be utilized in the vast majority of patients, and if ineffective at moderate doses, the therapy should be discontinued. It would seem most reasonable to reserve potent antihypertensive drugs for those individuals with either very severe systolic hypertension or with a history of such hypertensive complications as congestive heart failure or cerebral hemorrhage.

## Antihypertensive Therapy

Antihypertensive drug therapy is effective in elderly patients with isolated systolic hypertension as well as in those patients with both systolic and diastolic elevations. However, the blood pressure effects tend to be less dramatic than those observed in young individuals. Several experimental studies have suggested that vascular responsiveness to vasodilator stimuli may be diminished by aging. The responses to cyclic AMP and to beta-adrenergic agonists such as isoproterenol appear reduced in isolated arteries studied in vitro. In addition, the hypertensive effect of infusions of sodium nitrate in man has been shown to be decreased in elderly patients with systolic hypertension.

Little information is available concerning the optimal therapeutic approach, but certain general principles should be considered in the selection of medications. All the available agents are effective to some extent, but none are without hazard. In dealing with an elderly population of patients that can be expected to have significant atherosclerotic disease, any attempt to lower blood pressure must be carried out with caution, and abrupt changes such as those associated with orthostatic hypotension should be avoided. Fortunately, built-in protective mechanisms, such as the autoregulation of blood flow to the brain and the improvement in cardiac function when the blood pressure and left-ventricular afterload are reduced, help counteract the effects induced by severe lowering of blood pressure in many individuals. Nevertheless, such compensatory adjustments are not always adequate to prevent decreases in perfusion to critical sites.

Since the effects of therapy on cardiovascular outcome in this group of patients have not been delineated as yet, it would seem desirable to exclude very potent antihypertensive drugs or agents with potentially serious side effects. The dictum "physician, do no harm" is of particular relevance here. With these qualifications in mind, a step-care approach, which could represent a modification of that currently in force for the general hypertensive population, would appear appropriate (Fig. 2).

Diuretic agents may represent the best initial therapy in most of the patients. Careful attention should be given to the problem of hypokalemia and its effects in predisposing to cardiac arrhythmias, particularly since these patients often may have preexisting heart disease and may be receiving a digitalis glycoside. In addition, their dietary potassium intake may be relatively low. Furthermore, the adverse effects of the diuretic on blood sugar should also be considered since glucose tolerance decreases with age and the incidence of diabetes is high in this population. Potassium sparing diuretics (e.g., triamterene, spironolactone, amiloride) are frequently useful in these patients in combination with thiazides to minimize these problems.

As an addition to the diuretic regimen, or at times as an alternative to it, several agents which influence the sympathetic nervous system may be utilized.

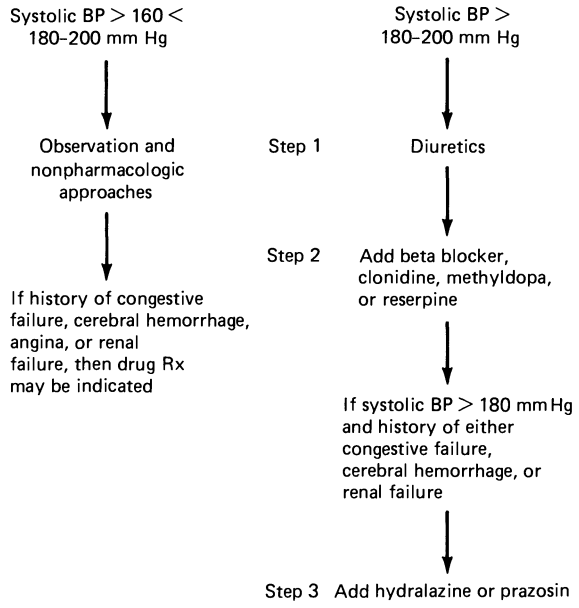


**Figure 2.** Proposed step-care approach to the treatment of systolic hypertension in the elderly.

These would include beta-adrenergic blockers, methyldopa, clonidine, and reserpine. Each of these drugs has certain limitations, and the choice of the agent should depend on the individual characteristics of a given patient. The clinical pharmacology and toxicity of these agents have been discussed previously and will not be repeated except for a few specific comments relating to this patient population. The *beta blockers* have the advantage of generally being well-tolerated with a low incidence of side effects. However, precipitation of congestive heart failure should be of some concern. Fortunately, in most individuals, if the beta blocker lowers blood pressure, the reduction in left-ventricular afterload that occurs is more than offset by its effects on cardiac contractility. Another complication that may be significant relates to the peripheral vasculature. Because of the peripheral vasoconstriction which may be induced by beta blockers, these drugs may precipitate or exaggerate the manifestations of peripheral vascular insufficiency. The broncho-constricting effects of beta blockers also could create problems, particularly since the incidence of chronic obstructive pulmonary disease is relatively high in this population.

*Methyldopa* has been used extensively in this group of patients and is often the second step drug of choice. It is usually well tolerated, but it can induce orthostatic hypotension, particularly if diuretic therapy or dietary sodium restriction has been employed concurrently. *Reserpine* has the advantage of a smooth effect, relative absence of orthostatic hypotension, a single daily dose, and relatively low cost. However, mental depression secondary to its use can be an important problem in the elderly population and the dose of reserpine should be kept low (e.g., 0.1 mg/day) to minimize this side effect. *Clonidine* also should be considered for these patients. It also is relatively well tolerated, but excessive sedation and dryness of the mouth may develop and limit somewhat its acceptance. The hypertension reported following abrupt withdrawal of clonidine could be of some concern but fortunately is a very uncommon problem, particularly if the dose of the drug is kept low.

Vasodilator drugs on theoretical grounds would have much to recommend them since a decrease in vascular compliance may be the major problem predisposing to the systolic hypertension. However, the potential toxicities of the available vasodilators serve to limit their use to the third step of therapy. *Hydralazine* is the most potent of the approved vasodilator compounds. It acts on arteriolar smooth muscle, producing a decrease in peripheral vascular resistance. A compensatory increase in heart rate and cardiac output may result which would serve to increase cardiac work and at times could induce or exacerbate angina pectoris and myocardial ischemia. Concurrent use of a beta blocker will generally offset much of this adverse response. Sodium retention may result, and diuretics also are usually required. The development of the lupus syndrome with hydralazine therapy is uncommon and tends to be dose-related. *Prazosin* blocks the alpha-1 adrenergic receptor and has the advantage of not causing sedation or depression. Its use in these patients is limited primarily because of the risk of postural hypotension, which can develop with prazosin as a result of its effect on blocking alpha-adrenergic activity.

*Guanethidine* and similar potent agents which can induce marked orthostatic hypotension are contraindicated in elderly patients with systolic hypertension.

Nonpharmacologic means of lowering blood pressure such as restricting dietary sodium intake or weight reduction also occasionally have merit. The value of such approaches may be particularly great in those individuals with only modest elevations in systolic blood pressure (less than 180–200 mm Hg) in whom we may want to avoid using antihypertensive drugs.

## Conclusion

Systolic hypertension is a relatively common disorder above age 55. Excessive cardiovascular mortality

and morbidity have been demonstrated in this group of patients, but the current state of knowledge is not sufficient to permit definitive recommendations concerning antihypertensive therapy. Neither the value of such treatment nor the optimal therapeutic programs have been determined as yet. The therapeutic dilemma confronting the physician is obvious and impossible to resolve completely. However, certain important principles can be considered and guidelines formulated which can assist in the difficult decision on treatment. It should be remembered, however, that the recommendations made in this chapter may well need to be revised in the future as further data become available.

A critical need exists for controlled clinical trials dealing with the effects of antihypertensive therapy in this population. One such trial has recently been initiated in the United States and another is nearing completion in Europe. Until the results of these studies become available, each physician will need to make his or her own decision regarding therapy.

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# Drug Interactions in Antihypertensive Drug Therapy

# 31

E. Weber

## Interactions between Antihypertensive Drugs

The synergism that usually results when two or more antihypertensive drugs are administered concurrently has effects in two directions: On the one hand, the phenomenon allows different antihypertensive drugs to be administered in a lower dose than during monotherapy, thereby reducing their toxicity. On the other hand, the concurrent administration of several antihypertensive drugs can easily lead to an excessive fall of blood pressure.

Moreover, some drugs exert one or more identical adverse side effects, such as sedation, dry mouth, and nasal congestion. When such drugs are administered together, their effects may be additive.

## Interactions between Antihypertensive Drugs and Drugs for Other Indications

All medications with a potential or obligatory hypotensive action may cause an excessive reduction of blood pressure if administered concurrently with antihypertensive drugs. The drugs associated most frequently with clinically significant side effects are the vasodilators; quinidine and procainamide (when given iv); certain psychotropic drugs such as phenothiazine, procarbazine, diazepam, and thioxanthene; narcotics; fenfluramine; furazolidone; the "loop diuretics" (ethacrynic acid, furosemide); and, finally, alcohol.[6,9]

On the other hand, drugs with a hypertensive action such as sympathomimetics or glycyrrhinic acid can, on chronic use, antagonize the effect of antihypertensive drugs. Moreover, the use of direct-acting sympathomimetics in patients taking guanethidine or reserpine can cause an increasing sensitization to these drugs after 1 or 2 weeks' treatment. This occurs because the otherwise strong (re)uptake into the storage vesicles of the postganglionic neuron which abolishes the drug action is inhibited.[6]

Indirect-acting sympathomimetics such as amphetamine and ephedrine given to patients receiving $\alpha$-methyldopa cause the release of the less potent vasopressor $\alpha$-methylnorepinephrine, instead of norepinephrine. Reserpine, like guanethidine, depletes norepinephrine from its storage vesicles and should therefore prevent the indirect sympathomimetics from taking effect. However, some clinical reports indicate that the pressor effect of amphetamine can lead to complications in patients taking guanethidine, apparently because the marked increase in norepinephrine sensitivity allows a response even to the minute quantities of norepinephrine released under these circumstances.[6] It has also been postulated that these phenomena may be the result of competition for uptake by the norepinephrine pump in the neuron[3] (see "Guanethidine" in chapter 32). Even the sympathomimetics present in cold remedies might be sufficient to produce this effect.[12] An increased proneness to cardiac arrhythmias is also present.

The tricyclic antidepressants represent a special case. They and certain other drugs competitively inhibit the norepinephrine pump in the postganglionic nerve fiber. Such substances abolish the action of guanethidine. Examples are desipramine,[11] imipramine,[7] amitriptyline,[10] as well as doxepin in doses

greater than 100 mg/day and chlorpromazine when used in the normal psychotherapeutic doses.[2] Owing to the competitive character of the inhibitory mechanism, it can be overcome by administering higher doses of guanethidine. If the psychotropic drugs are then withdrawn without reducing the high guanethidine dose, a dangerous fall of blood pressure may result.

Clonidine can also be inactivated by tricyclic antidepressants.[1] The mechanism of this is unclear.

In the case of $\alpha$-methyldopa, it is reported that its acute effect can be prevented by preliminary treatment with reserpine or imipramine.[5]

Monamine oxidase inhibitors prevent the wholesale degradation of norepinephrine in the postganglionic nerve fiber that ordinarily occurs during reserpine-induced norepinephrine release. This results in a strong vasopressor response when such drugs are administered concurrently with reserpine.[4]

Isoniazid reportedly strengthens the effect of antihypertensive drugs by inhibiting the nonspecific microsomal liver enzymes which destroy the drugs.[9]

All drugs which lead to potassium loss intensify the potassium deficiency produced by benzothiadiazines; examples are laxatives and glucocorticoids. The toxicity of cardioactive glycosides is increased. The action of concurrently administered *d*-tubocurarine and succinylcholine in benzothiadiazine-induced potassium deficiency is enhanced.

Salicylates administered in high doses can accumulate and thus lead to intoxication if their excretion is prevented by competitive inhibition from benzothiadiazines.[8]

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# Clinical Pharmacology of Antihypertensive Drug Therapy

# 32

E. Weber

Various causes underlie the family of symptoms called *hypertensive disease.* While certain secondary forms of hypertension are amenable to causal therapy, primary or essential hypertension is managed exclusively by symptomatic treatment with antihypertensive medications, to the extent that modifications of living habits (e.g., dietary salt restriction) cannot adequately lower the blood pressure. The hope of treating individual patients with specific drugs according to the etiology of the hypertension has not yet been realized.

The treatment of hypertension is geared mainly toward lowering the peripheral resistance. This goal can be achieved in various ways, most importantly by influencing the sodium balance, reducing the sympathetic tone, and inducing vasodilation in the periphery.

The drug or drug group of choice is determined more by its potential for exerting adverse effects than by its locus of action. It depends in large measure on the individual pathologic and morphologic status of the patient. This means that the spectrum of suitable antihypertensive drugs decreases with increasing age and morbidity. Given an adequate tolerance, the choice and dosage of the antihypertensive drug or drugs is determined solely by their ability to lower the blood pressure successfully.

From a clinical pharmacologic standpoint, antihypertensive drugs must satisfy a number of requirements:

1. The hypotensive action should be adaptable to individual patient needs during oral dosing.
2. The blood pressure should not fall too abruptly.
3. The action should be long-lasting and reproducible over a period of years.
4. The drug(s) should allow counterregulatory mechanisms to respond to acute demands.
5. The drug(s) should not alter the patient's mood.
6. Adverse effects, particularly serious ones, should be excluded.[68]

The experience of recent years has shown four groups of drugs to be of particular value in the therapy of hypertension:

a. Diuretics
b. $\beta$-Adrenergic receptor blocking drugs
c. Vasodilators
d. Sympathetic inhibiting drugs

Although it is widely agreed that an optimal antihypertensive therapy must be based on drugs of these classes, used either singly (i.e., diuretics or $\beta$-adrenergic blocking drugs) or in combination, their mechanism of action is by no means clear in all cases.

Nevertheless, a consensus has emerged with regard to the use of these drugs and the strategies to be employed. The following procedure has proved useful in finding the most satisfactory regimen:

1. Therapy begins with a diuretic or $\beta$-adrenergic blocking drug.
2. If adequate control is not achieved with diuretics or $\beta$-adrenergic blocking drugs alone, a combination is given which includes a diuretic. It is desirable to select a $\beta$-adrenergic blocking drug as the second component, owing to its mild effect on patient mood. If its use is contraindicated, however, a suitable drug from group (c) or (d) above must be prescribed.

3. If the combination of a diuretic and β-blocking drug proves to be inadequate, a vasodilator may be added. The reflex tachycardia produced by the vasodilator will be corrected at least in part by the β-blocking drug.
4. Should this combination fail to lower the blood pressure sufficiently, other drugs from group (c) or (d) above must be added.

The most significant advance in recent years was the discovery of the β-adrenergic blocking drugs, which opened the way for the development of vasodilators which directly relax the smooth muscles, thereby lowering the peripheral resistance without influencing the CNS or acting on the ganglia or postganglionic sympathetic fibers. Both classes of drug have little or no adverse effects on mood, nor do they impair the ability to perform mental tasks. As mentioned, the undesired reflex tachycardia can be controlled by the concurrent use of β-blocking drugs.

Although an ideal solution has not yet been found, the introduction of β-adrenergic blocking drugs has made it possible to achieve an effective reduction of blood pressure with few adverse effects in a very broad patient group. However, while there are at present a number of oral agents which can lower the blood pressure at least to some degree in practically any hypertensive individual, they do not allow the blood pressure to respond optimally to the demands of everyday life (e.g., standing or lying, rest or physical exertion, mental stress, pain). This problem remains to be solved.

## Diuretics

Diuretics with various chemical compositions and sites of action have proved effective as antihypertensive agents. Common to all diuretics is the property of increasing the excretion mainly of sodium, chloride, and bicarbonate ions and, secondarily, of water.

Two classes of diuretic are suitable for chronic antihypertensive therapy:

1. Diuretics of the benzothiadiazine type
2. Potassium-retaining diuretics

The "loop diuretics," furosemide and ethacrynic acid (so-called because of their site of action in Henle's loop), are unsuited for chronic antihypertensive therapy, because they produce a massive and abrupt excretion of electrolytes and water which evokes a strong counterregulatory response. Moreover, their brief duration of action requires dosing three to four times daily to achieve an antihypertensive effect comparable to that of the benzothiadiazines.[5]

### Diuretics of the Benzothiadiazine Type

The basic structure of the benzothiadiazines is the benzothiadiazine ring, in which the benzene ring is substituted at position 7 with a sulfonamide group and at position 6 with a chlorine atom (Fig. 1).

The pharmacodynamics of the various representatives of this group are so similar that they cannot serve as a selection criterion. Apparently these drugs inhibit the reabsorption of sodium, chloride, and to some extent bicarbonate ions in the distal tubule, thereby increasing their excretion in the urine. Potassium excretion, which is ordinarily determined mainly by secretion in the distal tubule, is increased by natriuretic drugs through an exchange of sodium for potassium in the distal tubule; the more sodium ions in this part of the tubule, the greater the exchange. Since benzothiadiazine therapy increases the quantity of sodium ions in that region, it becomes clear why a potassium deficit is particularly likely to develop in patients who take benzothiadiazines and do not restrict their salt intake. The antihypertensive effect of diuretics alone is slight.[14,38] A blood pressure reduction of no more than 15 to 20 mm Hg systolic and 10 to 15 mm Hg diastolic can be achieved. The mechanisms of this effect remain obscure. According to the findings of some authors, the initial decrease in extracellular fluid and plasma volume and the cardiac stroke volume abate after several days' treatment and are no longer discernible after a few weeks. Opinions also vary as to the behavior of the steady-state tissue concentrations of electrolytes (detailed discussion in ref. 36). The peripheral resistance increases somewhat initially but is decreased during chronic use. The antihypertensive effect of chronic diuretic therapy is attributed mainly to this fact.[37,100,153] A diminished response to vasoconstrictive stimuli from the catecholamines also appears to play a role.[58,61,108] This may be related to a reduced sodium concentration in the arterioles, perhaps because the sympathetic system has lost

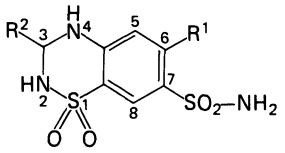


**Figure 1.** Basic structure of the benzothiadiazine derivatives.

some of its adaptive capacity under these conditions.[159]

***Undesired Effects.*** The various diuretics are also similar in terms of their undesired effects. They are remarkably nontoxic in the low doses ordinarily used in hypertension therapy. The most serious adverse effects are (1) hypokalemia, (2) hyperuricemia, and (3) reduced glucose tolerance and hyperglycemia. The most frequent adverse effect is hypokalemia associated with the main action of the drug. However, since subdiuretic doses are generally sufficient for the treatment of hypertension, the full-blown clinical picture of hypokalemia with neuromuscular, cardiac, intestinal, and renal symptoms is rare. The physician should be alert for signs of muscular weakness, particularly in the lower extremities, as well as for increased digitalis sensitivity, obstipation or ileus, and impaired renal function.

Up to 50% of patients treated with benzothiadiazine diuretics demonstrate an increase in uric acid to over 7 mg per 100 ml, probably owing to a competitive inhibition of proximal tubular secretion.[9,57] Uricosurics or allopurinol may become necessary.

The impairment of glucose tolerance during benzothiadiazine therapy sometimes necessitates a modification of hypoglycemic therapy in diabetics. It is questionable whether the reduced glucose tolerance that develops during the course of benzothiadiazine therapy or the appearance of manifest diabetes can be attributed to the diuretic therapy.[90] The benzothiadiazine-induced potassium deficit (increased glucose release from liver glycogen) and activation of adenylate cyclase with subsequent glycogenolysis by 3,5-cyclic AMP have been suggested as mechanisms.[72]

Less common events are an increase of serum amylase and acute pancreatitis, as well as allergic manifestations such as granulocytopenia, thrombocytopenia, and pancytopenia. Various types of exanthema, exfoliative dermatitis, vasculitis, and pneumonitis have also been described.

***Criteria for Drug Selection.*** The major differences among the benzothiadiazines relate to their duration of action, which thus forms the criterion for selecting the diuretic (Table 1).

**Table 1.** Survey of Selected Diuretics Currently Used in Antihypertensive Therapy*

| Generic Name | Brand Name | Onset of Action (h) | Duration of Action (h) | Mean Daily Dose (mg) |
|---|---|---|---|---|
| Diuretics of the Benzothiadiazine Type and Their Analogs | | | | |
| Chlorothiazide | Diuril | | 6–12 | 500 |
| Clopamide | Brinaldix | 1–2 | 12–24 | 10–20 |
| Cyclopenthiazide | Navidrex | 1–2 | 10–14 | 0.5 |
| Hydrochlorothiazide | Esidrix<br>Di-Clotride | 1–2 | 12–18 | 25–50 |
| Indapamide | Natrilix | | | 2.5 |
| Mefruside | Baycaron | 1–3 | 18–24 | 25 |
| Polythiazide | Renese | 1–2 | 18–24 | 1–2 |
| Quinethazone | Hydromox | 2 | 18–24 | 50 |
| Thiabutazide | Saltucin | 1–2 | 12–18 | 5–10 |
| Trichlomethiazide | Metahydrin | 1–2 | 10–14 | 2–4 |
| Xipamide | Aquaphor | 3–4 | 12–18 | 20–40 |
| Chlorthalidone | Hygroton | 2 | 24–36 | 25–50 |
| Potassium-Retaining Diuretics | | | | |
| Aldosterone-independent | | | | |
| Amiloride HCl | Arumil | 1–2 | 12–24 | |
| | Colestril | 1–2 | 12–24 | |
| Triamterene | Dyrenium | 1–2 | 12–24 | Pteridine derivative |
| Aldosterone-dependent | | | | |
| Spironolactone | Aldactone<br>Osyrol | 48–72 | 96 | 17–Spironolactone steroid |

*Some of these diuretics are not available in the United States.

***Pharmacokinetics.*** Intestinal absorption of the benzothiadiazine derivatives is generally good (70% to 80%), though the absorption of chlorothiazide is only 30% to 40%. The lipid solubility varies from drug to drug, and thus also the distribution area, which is usually greater than the extracellular space. Plasma protein binding is between 40% and 95%. As a rule, the benzothiadiazines are not metabolized but undergo glomerular filtration unchanged and are excreted by the kidney in varying degrees by active secretion in the proximal tubule.

### Potassium-Retaining Diuretics

The advantage of potassium-retaining diuretics can be utilized in antihypertensive therapy by combining them with the benzothiadiazines. This class of diuretic (survey in Table 1) acts synergistically to the benzothiadiazines in terms of sodium and water excretion and antagonistically in terms of potassium excretion.

The potassium-retaining diuretics can be classified into two groups, one of which acts independently of aldosterone, and the other only in the presence of aldosterone (see Table 1).

The site of action is the distal tubule. Triamterene and amiloride cause only a slight increase in sodium and chloride ion excretion. Important therapeutically is the inhibition of potassium secretion by triamterene and amiloride, as well as the competitive inhibition of the aldosterone receptors that mediate potassium excretion by spironolactone. Because aldosterone secretion declines with increasing salt intake, the effect of spironolactone is weakened or abolished by a salt-rich diet.

***Undesired Effects.*** The greatest danger in the use of these diuretics is hyperkalemia. They are contraindicated, therefore, in patients with impaired renal function. The principal undesired effects of triamterene and amiloride are associated with gastrointestinal intolerance. Calf muscle spasms and a feeling of weakness are also reported. Transitory visual disturbances have been described with amiloride.

In men, spironolactone can cause gynecomastia, loss of libido, and impotence. In women, virilization and amenorrhea can occur. The different pattern of adverse effects compared to the benzothiadiazines allows spironolactone to be used even in severe diabetes mellitus or in hyperuricemia.

***Pharmacokinetics.*** The drugs listed in Table 1 are absorbed from the bowel in varying degrees and are excreted at least in part by the kidney after they are largely metabolized.

## β-Adrenergic Receptor Blocking Drugs

β-Adrenergic receptor blocking drugs have been increasingly used since their introduction into antihypertensive therapy by Prichard.[128] Since then more than 30 different derivatives have become known, and others are being developed. So far, all the preparations tested clinically have proved to exert an antihypertensive action. Since they all block the β-receptors by competition with catecholamines, this would appear to be responsible for their action as antihypertensives. The remaining qualities vary somewhat from drug to drug (see below).

Since $\beta_2$-receptors mediate a dilatation of the resistance vessels and, according to measurements of α-receptors, occur only in small numbers in the vascular walls, the hypotensive effect of β-adrenergic receptor blocking drugs at first seems paradoxical. Indeed, the precise mechanism whereby these drugs exert their antihypertensive effect remains unexplained. Several hypotheses have been advanced, but compelling objections can be raised to each:

1. Lydtin et al. attributed the fall of blood pressure to a reduction of the cardiac stroke volume.[102] However, this hypothesis seems incompatible with the time discrepancy between the immediate reduction of stroke volume and the somewhat later onset of the blood pressure decrease.[60,154] Also, there is a good correlation between peripheral resistance and arterial pressure, but not between the latter and stroke volume.[121] Furthermore, all β-blocking drugs do not reduce the stroke volume.[54,120] Practolol has often even increased the stroke volume during chronic use.[120]
2. It has been postulated that the renal secretion of renin, which is at least partly controlled by adrenergic receptors, is inhibited by β-blocking drugs and that these drugs are most effective, therefore, in hypertensive patients who have high renin levels prior to treatment.[20] However, the results of subsequent studies have shown a poor correlation between the reduction of arterial pressure and the lowering of plasma renin,[4,15–17,114,161] as well as a discrepancy between the doses necessary for renin suppression and for lowering the blood pressure.[109] It must be noted, however, that neither the study population nor test protocol was fully comparable to that of Bühler et al.[20] Hollifield et al. concluded from the results of their own studies that at low doses propranolol affects the blood pressure by renin lowering, while in high doses propranolol has a renin-independent effect that may relate to its action in the CNS.[79]
3. Another hypothesis assumes a central locus of action for the β-blocking drugs, because the intra-

ventricular injection of propranolol produces a rapid fall of blood pressure in laboratory animals.[97] However, this conflicts with the fact that some β-blocking drugs, such as practolol, have difficulty traversing the blood-brain barrier, in contrast to other more lipophilic derivatives.

4. A peripheral adrenergic neuron blockade has also been suggested, similar to that produced by guanethidine.[42] However, this effect appears only in doses considerably higher than necessary to lower the blood pressure. It is also evoked by the (+)-propranolol isomer, which has no antihypertensive effect. Moreover, propranolol does not produce the hypotension during standing and physical exertion that is characteristic of the neuron-blocking agents.
5. Finally, it has been suggested that the β-blocking drugs act by resetting the baroreceptors via a central or peripheral mechanism. This is evidenced by the fact that the peripheral resistance returns to its initial level during continued therapy with β-blocking drugs.[129]

## Selection of β-Adrenergic Blocking Drugs

The intensity of the β-blockade varies somewhat from one derivative to another. But the therapeutic range of the known β-blocking drugs does not vary substantially, and so differences in drug potency can be compensated for by administering equipotent doses.

The β-blocking drugs differ not only quantitatively in their main action but also in their various qualities. These are:

1. The selectivity of their action on $\beta_1$- and $\beta_2$-receptors
2. Their sympathomimetic "intrinsic activity"
3. Their membrane-stabilizing effect

These features are reviewed, and the various drug potencies compared, in Table 2.

A distinction is made between $\beta_1$- and $\beta_2$-receptors, according to their function. The $\beta_1$-receptors control the force of contraction, stroke rate, and conduction velocity in the heart. The $\beta_2$-receptors are located in the smooth muscle of the bronchial tract, blood vessels, and uterus; when excited, they produce a decrease in tone. The β-mimetic–induced metabolic reactions such as lipolysis, glycogenolysis, and gluconeogenesis, as well as insulin and renin secretion, have not yet been associated with a specific receptor type. Some β-blocking drugs preferentially inhibit the $\beta_1$-receptors located in the heart and are therefore called *cardioselective*. These drugs are preferred in patients with bronchial asthma. However, the selectivity of the drugs is not absolute but is present only if suitable doses are given. The heart contains small numbers of $\beta_2$-receptors in addition to the $\beta_1$-receptors; the reverse is true for the bronchial muscles.[3] The dose-dependence of the selectivity implies that this selectivity is lost at higher doses and consequently is of limited therapeutic value.

On the other hand, there are β-blocking drugs with a demonstrable β-mimetic residual activity (*intrinsic activity,* Table 2). These are the drugs of choice when a strong cardiodepressive action and bronchoconstriction are to be avoided. Whether these pharmacodynamic differences among the β-blocking drugs are as significant as claimed remains unclear. From the physician's standpoint, however, any attempt to utilize possible differences in the interest of differential therapy is justified.

The membrane-stabilizing effect of the β-blocking drugs bears no relation to the β-receptor inhibiting effect and is apparently of no importance in terms of antihypertensive therapy.

***Undesired Effects.*** The use of β-blocking drugs is limited by their bronchoconstrictive and cardiodepressive action. They decrease the stroke rate of the heart, its contractility, its metabolism, and the coronary blood flow. As a result, even low doses can precipitate myocardial insufficiency in patients who require a high sympathetic tone to maintain adequate cardiac function.

It is difficult to say whether β-blocking drugs with sympathomimetic residual activity are more effective in arresting or preventing heart failure than β-blocking drugs which do not possess this activity. In the absence of more objective arguments against their use, the improved benefits of these drugs should not be withheld from older patients or those on the verge of cardiac decompensation. However, it must be understood that the protection offered by these drugs is only relative, as documented by the occurrence of cardiac failure even after such β-blocking drugs were administered.[52] According to findings in dogs, the effect on A-V conduction tends to be favorable.[62]

Similar considerations apply with regard to the bronchial constriction mediated by β-blocking drugs: The use of β-blocking drugs with β-mimetic residual activity or the use of cardioselective derivatives reduces the likelihood of precipitating an asthmatic attack compared with other β-blocking drugs.[11,33,81,145,147] Again, however, the protection they offer is merely relative, not absolute. Reportedly, it is possible to treat hypertensive patients with obstructive airway disease by the concurrent administration of β-blocking drugs and $\beta_2$-receptor agonists without losing the antihypertensive effect.[53]

Some authors report that "cold extremities" and

**Table 2.** Data on the Pharmacodynamics of Selected β-Adrenergic Receptor Blocking Drugs*

| Generic Name | Brand Name | β-Blocking Potency (Propranolol = 1) | Receptor Affinity | Sympathomimetic Residual Activity (Intrinsic Activity) | Membrane-Stabilizing Effect | Mean Daily Dose (mg) |
|---|---|---|---|---|---|---|
| Acebutolol | Prent | 0.3 | $\beta_1$ | + | + | 400 |
| Alprenolol | Aptin | 0.3 | $\beta_1 + \beta_2$ | + | + | 600 |
| Atenolol | Tenormin | 1 | $\beta_1$ | (+) | − | 150 |
| Bunitrolol | Stresson | 5 | $\beta_1$ | + | | 40 |
| Bupranolol | Betadrenol | 1.2 | $\beta_1 + \beta_2$ | ± | | 240 |
| Metoprolol | Beloc, Lopressor | 1 | $\beta_1$ | (+) | ? | 300 |
| Methypranol | Disorat | | | | | |
| Oxprenolol | Trasicor | 1 | $\beta_1 + \beta_2$ | + | + | 240 |
| Pindolol | Visken | 6 | $\beta_1 + \beta_2$ | ++ | + | 30 |
| Propranolol | Inderal | 1 | $\beta_1 + \beta_2$ | (+) | ++ | 240 |
| Sotalol | Sotalex | 0.3 | $\beta_1 + \beta_2$ | (+) | − | 480 |
| Timolol | Temserin | 6 | $\beta_1 + \beta_2$ | ± | − | 30 |
| Toliprolol | Doberol | 1 | $\beta_1 + \beta_2$ | + | | 200 |

*Some of these β-blockers are not available in the United States.

From Weidmann P, Fuss O, ref 157.

the rare Raynaud phenomenon are more likely to occur with noncardioselective β-blocking drugs or those which lack sympathetic residual activity.[104,162]

Various metabolic effects have been reported with β-blocking drugs. The most important in terms of antihypertensive therapy are hypoglycemic reactions. It is noteworthy that the drugs reduce the tachycardia that accompanies induced hypoglycemia but have no effect on hypoglycemic sweating.[99,113]

Effects on renal function depend upon the state of the kidneys, the blood pressure, and the type of β-blocking drug used. Patients with renal failure must be watched closely and the dosage adjusted if need be.

An immunologically based oculomucocutaneous syndrome has so far been observed only with practolol; it has been associated with a free aromatic amino group of one of its metabolites. Gastrointestinal symptoms appear to be uncommon.

CNS effects are observed with the lipophilic representatives of the β-blocking drugs. Occasionally patients report mental depression, blurring of vision, and hallucinations. Vivid dreams and nightmares are also reported, particularly with pindolol (result of sympathomimetic residual activity?).

***Pharmacokinetics.*** β-Blocking drugs are absorbed well when given orally. However, their bioavailability is sometimes poor owing to a "first-pass effect" in the liver, which causes the main portion of the drug to reach the systemic circulation in the form of inactive metabolite(s) (Table 3). This first-pass effect is a phenomenon in which the drug is absorbed by the intestinal mucosa but then enters the liver via the portal vein, where it is more or less intensively metabolized in its first pass through the liver. The drug effect may be weakened or nullified, depending on whether the metabolites are still pharmacologically active. With all β-blocking drugs that are metabolized to inactive products, the oral doses differ considerably from the doses administered iv.

The derivatives that undergo this first-pass removal in the liver show a greater individual variation in their effect than the others, because they are subject to both exogenous and genetically determined influences.

The biological half-life ranges from 2 to 13 h, depending on the drug. The drugs metabolized in the liver have shorter half-lives than those excreted by the kidney. The latter must usually be given in adjusted doses to patients with renal failure.

The half-life of the drug does not strictly correspond to the appropriate dose interval. Generally, the drugs may be given at intervals longer than their half-life.

A clear connection between the plasma levels of the β-blocking drugs and their antihypertensive effect has been established only for propranolol, pindolol, and sotalol.[71,96,115,152]

## Vasodilators

### Dihydralazine

Dihydralazine causes relaxation of the smooth muscles of the arterioles,[151] especially of the splanchnic region and kidneys, and to a lesser extent of the skin and skeletal muscles.[56] It may act through an increase of cyclic AMP.[6] The venous capacitance vessels are unaffected.[2] In the absence of an excessive blood pressure fall, the renal blood flow tends to be improved, and so renal function is unimpaired. However, all the arterial vasodilators cause sodium retention and decreased urine volumes. There is a reflex increase in the heart rate and cardiac output.[136] The antihypertensive effect is not very pronounced.

***Undesired Effects.*** Undesired effects are common with dihydralazine and result mainly from its hemodynamic actions. Palpitations, headache, flushing, dizziness, and sweating are reported. Angina pectoris attacks can be brought on in patients with coronary insufficiency. A dose-dependent lupus syndrome with the presence of nuclear antibodies can also occur; it is usually seen only at doses greater than 100 mg/day.[123]

***Pharmacokinetics.*** Dihydralazine is rapidly and almost completely absorbed. However, a first pass effect and interindividual differences in the rate of metabolic processes (e.g., acetylation and a suggested "deep pool") complicate the pharmacokinetics of the drug.

### Minoxidil

Minoxidil is a potent vasodilator from the piperidine-pyrimidine series with the same site of action as dihydralazine. It may be used when other antihypertensives have failed and is effective even in patients with malignant hypertension and renal failure. The (partially) reflex increase in cardiac output can reportedly be antagonized with a β-blocking drug, and the sodium and water retention with a saluretic. Minoxidil is reserved for severe hypertension that is refractory to other antihypertensive drugs.

**Table 3.** Data on the Pharmacokinetics of Selected β-Adrenergic Receptor Blocking Drugs*

| Generic Name | Brand Name | Lipophility | Plasma Half-life (h) | Bioavailability (%) | First-Pass Effect | Metabolism | Active Metabolite | Renal Elimination (%) |
|---|---|---|---|---|---|---|---|---|
| Acebutolol | Prent | | 2–4 | 60† | − | | + | ? |
| Alprenolol | Aptin | ++ | 2–5 | 20–50 | + | +++ | + | <3 |
| Atenolol | Tenormin | (+) | 6–7 | 50-30† | − | | − | 90 |
| Bunitrolol | Stresson | + | 6 | | | +++ | | |
| Bupranolol | Betadrenol | ++ | 1 | | | | | |
| Metoprolol | Beloc | + | 3–4 | 30–50 | + | +++ | − | <3 |
| | Lopressor | + | 3–4 | 30–50 | + | +++ | − | <3 |
| Methypranol | Disorat | | 5 | | | ++ | | |
| Oxprenolol | Trasicor | + | 2 | 75-90 | (+) | ++ | − | <3 |
| Pindolol | Visken | + | 3–4 | 90 | − | | − | 35 |
| Propranolol | Inderal | ++ | 2–6 | 20–50 | + | +++ | + | 3 |
| Sotalol | Sotalex | (+) | 6–13 | 90 | − | | − | 95 |
| Timolol | Temserin | + | 6 | | | ++ | | |
| Toliprolol | Doberol | + | 1 | | | +++ | | |

*Some of these β-blockers are not available in the United States.

†Absorption incomplete.

From Weidmann P, Fuss O, ref 157.

***Undesired Effects.*** There have been recent reports of persistent hypotensive states during the course of minoxidil therapy; it is still uncertain how this will affect its range of application.

The increased load on the heart resulting from the elevated cardiac output may contraindicate minoxidil in states of cardiac failure, either from the outset or during the course of therapy.

A troublesome side effect in women receiving minoxidil is excessive hair growth on the face and extremities.[28]

***Pharmacokinetics.*** Minoxidil is absorbed rapidly and well. Its half-life is 2 to 3 h.[65] Its pharmacologic effect persists longer than its brief half-life would suggest, probably owing to its accumulation in the vascular wall.[98] The drug is heavily metabolized; 90% is excreted in the urine after 48 h.

### Prazosin

Prazosin has proved to be the most potent of a series of antihypertensive aminoquinazoline derivatives.[141] It directly relaxes the arteriolar smooth muscles; this action is perhaps mediated by the phosphodiesterase-inhibiting properties of the drug with a consequent rise of the cyclic AMP level in the smooth-muscle cell.[77] It also displays an $\alpha$-receptor blocking effect which, unlike the classic $\alpha$-blocking drugs, reportedly acts uniquely and selectively on the postsynaptic $\alpha$-receptors.[22]

It is assumed that the antihypertensive effect of prazosin during chronic use is based primarily on vasodilatation. The selective postsynaptic $\alpha$-receptor blockade has been hypothetically associated with the finding that prazosin generally does not increase the heart rate or affect renin secretion.[66,91,137] Moreover, the cardiac output, renal blood flow, and glomerular filtration usually are not decreased.[91,101,105]

***Undesired Effects.*** One peculiarity is a sharp fall of blood pressure, accompanied by collapse, observed 30 to 90 min after the initial dose of prazosin in about 1% of all patients.[47] This is the result of overdose and has recently been associated with a reduced fluid volume due to hyponatremia.[110,150] These problems can be avoided by prescribing a low starting dose.[19] Other reported adverse effects include dizziness, palpitations, and edema (in 13.7%, 5.3%, and 4.1% of 934 patients),[125] as well as headache in 7.8% and nausea in 4.9% of patients.[21,51]

***Pharmacokinetics.*** The pharmacokinetics of prazosin are only partially known. Reportedly, prazosin is well absorbed after oral administration.[19,76] The peak serum level is attained in 2 to 3 h. The drug has a reported half-life of 1 to 2 h in man.[69] The fall of blood pressure does not parallel the serum level.[35] A marked accumulation of the drug in the vascular walls may account for its persistent effect.[77] Prazosin is strongly metabolized in the liver; only two of its metabolites appear to be active antihypertensively, according to studies in dogs. It is eliminated predominantly in the bile.[77,160] Elevated serum levels are reported in patients with renal failure.[19]

### Diazoxide and Sodium Nitroprusside

Diazoxide and sodium nitroprusside are powerful vasodilators which are used strictly for the management of hypertensive emergencies.

*Diazoxide,* though a benzothiadiazine derivative, exhibits a strong sodium- and water-retaining as well as diabetogenic action and is therefore unsuited for continued use. Owing to its strong protein-binding tendency, it must be administered iv in a large, rapid (15 to 20 s) bolus.[142] The blood pressure falls within a few minutes and remains lowered for 6 to 18 h or longer.

*Sodium nitroprusside* is the most potent antihypertensive drug in therapeutic use but must be administered by infusion owing to its extremely brief duration of action (1 to 2 min). It increases the heart rate but, unlike the other vasodilators, does not increase the cardiac output, probably because it relaxes the venous capacitance vessels as well.[155] Like nitroglycerin, the drug probably relieves the cardiac load by reducing both the preload and afterload. It is therefore suitable for use in hypertension, myocardial infarction, and left heart failure.[27,111]

*Undesired effects* are often manifestations of the blood pressure reduction. The final degradation product of sodium nitroprusside, thiocyanate, can be detected in the blood if infusion is continued for more than 3 days. Its plasma level should not exceed 12 mg per 100 ml.

## Sympathetic Inhibiting Drugs

The antihypertensive drugs most widely used before the era of the $\beta$-blocking agents were sympathetic inhibiting drugs, including clonidine, which was introduced later. The only exception was the vasodilator dihydralazine. Guanethidine is the only sym-

pathetic inhibiting drug which does not have a central locus of action. If the use of this drug is limited by orthostatic collapse, the use of drugs which act on the CNS, such as rauwolfia alkaloids, α-methyldopa, and clonidine, is limited by adverse effects relating to central nervous system dysfunction.

## Reserpine

The principal alkaloid of *Rauwolfia serpentina* is reserpine. It acts sympatholytically by interfering with the storage mechanism of norepinephrine (and its precursor dopamine) in the postganglionic sympathetic nerve fiber. It inhibits the active transport of the amine from the cytoplasm into the vesicles.[49,88] The norepinephrine which is unprotected by uptake into the storage vesicles is subject to degradation by cytoplasmic monamine oxidase. Besides norepinephrine, dopamine and serotonin are also depleted from their storage sites in the CNS.[10,80,126]

The depletion of norepinephrine in the periphery leads to a persistent decrease in vascular resistance even during long-term therapy.[138] The extent to which the antihypertensive effect is mediated by the depletion of noradrenergic neurons in the vasomotor center is uncertain (cf. ref. 106, for example). Additional effects related to sympathetic inhibition are sinus bradycardia and a partially associated decrease in cardiac output, which contributes to the antihypertensive effect.[30] The performance of the insufficient myocardium is further impaired. A connection with the reduced norepinephrine content of the heart in man is conceivable.[29]

***Undesired Effects.*** The prescribed doses should not exceed 0.5 mg/day during chronic therapy in order to avoid undesired effects. These effects relate to the depletion of adrenergic amines as well as serotonin in the CNS and periphery and are manifested in a predominance of parasympathetic influence in the heart and gastrointestinal tract. Reported effects include moderate to severe sedation, mental depression which may provoke suicide, parkinsonism, bradycardia and conduction disturbances, nasal congestion, exacerbation of peptic ulcers, diarrhea and, as a further sign of sympatholysis, disturbances of sexual function.

***Pharmacokinetics.*** Reserpine is absorbed from the bowel. It is metabolized to inactive products by hydrolysis and demethylation. Marked species differences have been found.[132]

The suspicion expressed by some groups of investigators regarding a connection between reserpine use and the development of breast cancer[7,73,82] has not been confirmed by subsequent analysis.[87,95,103,122]

## α-Methyldopa

For a long time it was thought that the release of α-methylnorepinephrine from the storage granules of the postganglionic sympathetic fiber in response to sympathetic stimulation[118] was the main antihypertensive mechanism of α-methyldopa, because this metabolic product of the drug was a less potent vasopressor than the physiologic substance norepinephrine. It is now believed that α-methyldopa stimulates α-adrenergic receptors in the brainstem, thus leading to an inhibition of sympathetic outflow.[74,75]

The antihypertensive effect results from a decrease in peripheral resistance which occurs even during chronic use. Apparently neither the heart rate nor cardiac output is significantly altered, although published findings are somewhat contradictory (see survey in ref. 138). Sympathetic reflexes during standing or exertion are largely preserved during α-methyldopa therapy. As with the other sympathetic inhibitors, there is an increase in plasma volume which must be counteracted with a saluretic.[46]

***Undesired Effects.*** The undesired effects resemble those of reserpine and clonidine: sedation, dry mouth, nasal congestion, extrapyramidal disturbances, depression, and impotence. About 20% of patients show a positive Coombs' test. A much less common effect is hemolytic anemia[23] which, like allergic phenomena, forces discontinuation of the drug. The latter phenomena may consist of drug fever or, less frequently, hepatic disease resembling hepatitis.[48,64] Granulocytopenia and thrombocytopenia are rare.

***Pharmacokinetics.*** Absorption shows strong individual variations, ranging from 9% to 75%,[93,146] and 80% to 90% of the drug is excreted partially unchanged by the kidney within 48 h.[146] Therefore, accumulation can occur in patients with renal failure.[119] Onset of action is 2 to 3 h. The duration of action is usually 5 to 10 h, but may persist up to 24 h. Doses above 2 g exert no additional antihypertensive effect.

## Clonidine

The antihypertensive effect of clonidine is based on a stimulation of postsynaptic α-adrenergic re-

ceptors of the vasomotor center of the medulla oblongata.[13,139] It is thus analogous to the effect of α-methyldopa. This site of action of the imidazoline derivative clonidine is related to its derivation from the family of sympathomimetics, as which it was originally developed.[67]

Intravenous administration produces a two-phase effect: A short-term blood pressure increase lasting several minutes (and occasionally longer), followed by a fall of blood pressure lasting about 4 h.[34] The heart rate and cardiac output decrease, especially at higher doses, probably owing to a centrally controlled dilatation of the venous capacitance vessels with a resultant decrease in cardiac afterload.[116] The peripheral resistance is not changed significantly. In view of the simultaneous fall of blood pressure and decrease in stroke volume, the latter was interpreted as a diminished reactivity of the reflex control mechanisms.

Except for the initial blood pressure increase, oral administration leads to basically the same changes seen after intravenous administration. Schneider found a decreased peripheral resistance during chronic clonidine therapy.[140] The mechanism of the long-term action of the drug is unclear, however, Clonidine does not abolish the homeostatic responses, and so the danger of orthostatic collapse or collapse induced by physical exertion is relatively slight (see refs. 116 and 149, for example).

It has been suggested that the decreased reactivity of vessels to vasoactive stimuli observed in cats after chronic clonidine use[94] is one cause of its antihypertensive effect and may explain the favorable effects of the drug in migraine reported by some authors. This hypothesis is not unchallenged, however.

It has not been determined whether the decreased catecholamine levels measured in the blood and urine during clonidine therapy, as well as the lowered plasma renin levels,[78] should be attributed exclusively to the decrease in sympathetic tone.

***Undesired Effects.*** The most important are (usually transitory) sedation and dry mouth, which are centrally evoked;[130] these are occasionally combined with parotid pain, varying degrees of bradycardia, and impotence (see survey in ref. 8). The sodium retention that usually develops after 2 to 3 weeks partially antagonizes the antihypertensive effect of clonidine and necessitates concurrent diuretic therapy.[40]

The marked pallor of many patients treated with clonidine is caused by α-adrenergic effects on the cutaneous vessels.

The sudden cessation of clonidine therapy is potentially hazardous, since it can cause a rebound effect with a rapid rise of blood pressure, agitation, nausea, sweating, and sleeplessness.[70] The countermeasure is reinstitution of clonidine.

***Pharmacokinetics.*** In view of the high efficacy of clonidine and its consequent very low therapeutic doses, only recently has a gas-chromatographic–mass-spectrometric technique been developed for assaying the drug in man.[45] From 70.6% to 81.5% of the drug is absorbed from the gastrointestinal tract.[41] The serum levels correlate with the pharmacodynamic effects within certain concentration ranges. The peak serum level is attained 1 h after oral administration; the half-life of the β-phase is 5.2 to 13 h for the same route. Up to about half the iv or orally administered dose is excreted unchanged by the kidney.[44]

## Labetalol

Labetalol is a sympatholytic drug which competitively blocks both α- and β-adrenergic receptors in animals and man. The effect on the β-receptors is clearly predominant.[32,50] According to Boakes et al.,[12] it is four times more potent than the α-receptor inhibiting effect. The β-receptor blocking effect is nonselective and can be demonstrated in both the blood vessels and bronchi.[50] The drug possesses no intrinsic activity.[32,50,133] The combination of α- and β-receptor blocking properties leads to a diminished reflex response of the blood pressure decrease that occurs after iv injection of 1.5 mg/kg or the oral administration of 200 to 400 mg. The antihypertensive effect is immediate, in contrast to the action of classic β-blocking drugs.[134] The heart rate[59,86] and cardiac output[86,89] are largely unchanged.

During chronic labetalol therapy the blood pressure is lowered primarily by a decrease in peripheral resistance.

A final assessment of this new type of antihypertensive drug is not yet possible.

***Undesired Effects.*** Orthostatic dizziness may occur, especially at high doses and at the start of therapy.[39,84] Nasal congestion, disturbing dreams, ejaculatory disturbances and, at high doses, epigastric pain are also described. Transient headache, nausea, lethargy, and fatigue have also been reported.[63]

***Pharmacokinetics.*** From the pharmacodynamic effects of labetalol, Richards et al. concluded that it is well absorbed from the gastrointestinal tract.[133] Tritium labeling showed peak serum levels 1 to 2 h after oral administration in two subjects. The level of unchanged drug was low, indicating a marked

first-pass effect. Protein binding in human plasma is about 50%. The drug has a half-life of about 4 h and is excreted mainly by the kidney. About one-fourth of the radioactivity was eliminated in the feces within 96 h.[63]

## Guanethidine

Guanethidine is one of the strongest antihypertensive drugs known. The quality of its action is purely symptomatic.[55] It acts at the postganglionic sympathetic fiber, where it accumulates in the norepinephrine storage vesicles. The relatively polar guanethidine molecule cannot cross the blood-brain barrier. Despite these favorable properties, guanethidine is reserved for the treatment of severely hypertensive patients who respond poorly to other measures, owing to the marked orthostatic hypotension it produces.

The pharmacodynamic actions of guanethidine are complex. The following have been demonstrated:

1. Depletion of norepinephrine from its storage site[24,26]
2. (Partial) replacement of norepinephrine with guanethidine, a nonvasoconstrictor,[18,112] which is then released instead of norepinephrine during sympathetic stimulation[143]
3. Inhibition of the reuptake of norepinephrine[76]
4. Inhibition of norepinephrine release[76,124]
5. Inhibition of neuromuscular transmission (only at very high doses[43,92]

It is generally thought that guanethidine acts essentially by serving as a substrate for the norepinephrine pump, thus accumulating in the postganglionic adrenergic nerve fiber.[112] However, it is possible that the antihypertensive effect of guanethidine is based more importantly on the inhibition of the transmission of nerve impulses at the neuronal membrane.[143] Like denervation at the sympathetic postganglionic fiber, the administration of guanethidine causes strong sensitization to the vasoconstricting effect of exogenous norepinephrine.[1,127]

Taken orally, guanethidine initially reduces the cardiac output and usually the heart rate as well.[31,135] Regarding its effect on peripheral resistance, findings vary according to the pathophysiologic status of the patient; the peripheral resistance is decreased or unchanged.[25,31] Pronounced venous pooling of blood in the lower extremities decreases the stroke volume and thus leads to severe orthostatic hypertension, since guanethidine abolishes the reflex increase of vascular resistance in the periphery and/or splanchnic region. During chronic guanethidine therapy, the stroke volume again approaches the initial value, with an accompanying decrease in peripheral resistance and heart rate.[25,156]

Guanethidine causes sodium and water retention,[148] which must be countered with diuretics. Otherwise, resistance develops to the antihypertensive effect of guanethidine. The plasma volume is expanded.[117] Owing to the inhibition of venoconstricting reflexes, the venous capacitance is increased. It is postulated that fluid enters the venous system from the extracellular space as a result of the reduced capillary pressure caused by diminished postcapillary resistance.[158]

***Undesired Effects.*** The most troublesome effects of guanethidine involve orthostatic complaints, including collapse. All states that are accompanied by water loss or vasodilation, such as physical exertion, alcohol consumption, or heat exposure, aggravate this tendency, since the reflex increase in peripheral resistance is abolished by guanethidine.[8] Severe diarrhea is not uncommon and cannot be attributed to the adrenergic neuron blockade. Disturbances of sexual function consist in delayed or retrograde ejaculation.[55] The (muscular) "weakness" reported by some patients may be the result of inhibited neuromuscular transmission.[8]

***Pharmacokinetics.*** About half the drug is absorbed when administered in powder form.[131] However, its bioavailability is reduced by a first-pass effect whose extent is still unknown.[107] The slow phase of its plasma half-life is about 5 days.[144]

The drug is excreted almost exclusively by the kidney and about half is excreted unchanged. High renal clearance values are indicative of its tubular secretion.[85,107]

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# Therapeutic Aspects of Hypertension

# 33

J. Rosenthal

Results were recently published of the hypertension detection and follow-up program in the United States based on population studies performed on 10,000 men and women between 30 and 70 years, who were grouped according to whether they received medication or other forms of treatment. In the group with diastolic values between 90 and 104 mm Hg, mortality after 5 years was 20% lower in the drug-treated group. Further analysis showed a reduction in mortality of 22% in the group with diastolic values between 90 and 94 mm Hg, of 23% for those between 95 and 99 mm Hg, and of 14% for those between 100 and 104 mm Hg.[1]

## Reasons for Treating Hypertension

Of all the patients who present with hypertension, particular efforts should be directed toward lowering blood pressure in those patients with a diastolic pressure of over 95 mm Hg, in those in whom organ involvement is already evident, and in those for whom there are additional risk factors. The reasons for selecting these particular criteria are the following:

1. Experiments in animals and studies in man have demonstrated that the vascular system can be protected from the consequences of hypertension by lowering the arterial blood pressure.
2. Morbidity and mortality have been shown to be correlated directly with the degree of hypertension and to improve after treatment with antihypertensive drugs.
3. Epidemiologic studies have shown that the arterial blood pressure tends to rise most in those in whom it is already slightly elevated.

Numerous investigations in animals have demonstrated that the vascular system is damaged by arterial hypertension of various types. Just as hypertension accelerates the course of artherosclerosis in man, it has been shown that hypertensive animals fed on a high-cholesterol diet have a greater chance of developing atherosclerosis than their normotensive counterparts fed on the same diet. The vascular lesions and the further development of atherosclerosis could be reduced by lowering the blood pressure with antihypertensive agents. The model of so-called spontaneous hypertension in rats displays a greater similarity to essential hypertension in man than any other experimental model. High blood pressure in these animals can be controlled with antihypertensive drugs which can prevent the development of hypertension and its pathologic consequences if given early enough. These results demonstrate that even when hypertension is genetically predetermined, early treatment with antihypertensive agents can hinder the progression of the disease.

The three clinical conditions under which the extent of vascular damage and the degree of hypertension are particularly well correlated are unilateral renovascular hypertension, coarctation of the aorta, and pulmonary hypertension. These conditions are characterized by varying levels of blood pressure in the different vascular beds. In the kidney with narrowed arteries blood pressure is lower than normal, whereas in the contralateral kidney it is raised. Atherosclerosis does not occur in the stenosed kidney but develops only in the contralateral kidney, so much so that sometimes the contralateral kidney

has to be removed in addition to correcting the stenosis in order to control the hypertension. The vessels that are proximal to an aortic stenosis and subjected to high pressures become atherosclerotic and accumulate mucopolysaccharides, sodium, and water, whereas the vessels distal to the coarctation do not undergo such changes. In the pulmonary artery, where blood pressure is usually low, there is a low incidence of atherosclerosis, but if pressure is raised because of a mitral stenosis or other forms of congenital heart disease, the arteries and arterioles of the pulmonary bed often become arteriosclerotic. These examples demonstrate that it is the magnitude of the blood pressure in the vascular bed, and not any other factor, which is responsible for vascular damage—tissues with a low pressure are protected, whereas those with a high pressure develop pathologic alterations.

Long-term studies performed over approximately two decades have indicated that high blood pressure is most probably self-perpetuating and that the higher the blood pressure, the more extensive the vascular damage. Only a few patients who had been successfully treated for hypertension but who discontinued treatment remained normotensive without treatment, and the higher the pretreatment blood pressures, the more rapidly the patients became hypertensive.[2]

Much of the skepticism concerning the necessity of controlling high blood pressure with antihypertensive drugs can be attributed to a lack of long-term studies and also the absence of controlled prospective investigations. The value of antihypertensive therapy in malignant hypertension was relatively easy to demonstrate because of the short duration of the disease and its almost inevitable fatal outcome in untreated patients. The evidence that treatment of nonmalignant essential hypertension with antihypertensive agents was indeed beneficial took longer to establish.

The decisive Veterans Administration study in 1963 involved 143 men with diastolic blood pressures between 115 and 129 mm Hg. A difference in morbidity and mortality between 70 patients receiving placebos and 73 patients treated with diuretics, reserpine, and peripheral vasodilators was apparent after 18 months. In a subsequent study in 380 men with diastolic pressures between 90 and 114 mm Hg, a period of up to 5 years was required to show a statistically significant improvement after therapy. A total of 19 patients in the placebo group but only 8 in the treatment group died from high blood pressure complications; serious diseases occurred only in the placebo group, and complications were apparent in 29% of the placebo group, compared to 12% of the treated group.[3]

The statistical analyses made by the life insurance companies have provided a better assessment of the risks of high blood pressure. After considering various factors, such as the criteria for acceptance in the study, it was found that the risk of developing serious cardiovascular complications during a 5-year period dropped after treatment with antihypertensive agents from 55% to 18%. The benefit of treatment became apparent early in the study and increased in accordance with how well the hypertension was controlled.[4] A further analysis showed that the reduction in morbidity was highly significant for men with a diastolic blood pressure between 105 and 114 mm Hg. Unfortunately, this investigation was discontinued as soon as the benefit of treatment was established for the whole group, and so the possible favorable effects of treatment for the lower pressure group were not demonstrated. However, it does appear that even a modest reduction in blood pressure can lower mortality. Patients in whom the diastolic blood pressure remained over 90 mm Hg during treatment showed a reduction in morbidity to 50% of that occurring without therapy. Furthermore, patients whose diastolic blood pressure was lowered to 80 mm Hg or less during treatment showed an even more pronounced drop in morbidity.[5] This study has, however, been subjected to criticism because of the high degree of patient selection.

Nevertheless, a subsequent 10-year study in the United States has produced similar results.[6] A total of 389 patients between 21 and 55 years, with a mean blood pressure of 148/90 mm Hg and with no indication of organ involvement, were included in the investigation. Treatment with diuretics and reserpine was effective against the complications of hypertension in over 50% of the subjects. The protective effect was most evident in the ECG and radiographs of the heart and in the alarming increase in diastolic blood pressure in 12% of the untreated subjects to values of over 130 mm Hg.

There is as yet only circumstantial evidence that the treatment of mild hypertension is beneficial or protects the patient from coronary heart disease. Nevertheless, mild hypertension, which is the most commonly occurring type of high blood pressure, is associated with increased morbidity and mortality. An analysis of the Framingham study highlights the dangers.[7] In this study 42% of the premature deaths occurred in subjects with a diastolic blood pressure between 90 and 100 mm Hg. Data from the life insurance tables show that a man of 43 years with a blood pressure of 145/90 mm Hg has a 65% increased risk of mortality. A reduction of blood pressure to 135/80 mm Hg lowers this risk to 30% over the next 2 years and to 15% over the next 5 years.

Despite the lack of definitive proof that treatment of mild hypertension can reduce the incidence of coronary heart disease, the progression of all other hypertensive complications was found to be significantly slowed upon correction of mild hypertension in each of the investigations.

Particularly impressive are the results of studies which show that antihypertensive therapy does reduce the incidence of stroke. No protection could be found, however, in patients who had already suffered one stroke and who had a mean blood pressure of 167/100 mm Hg over a 3-year period despite antihypertensive therapy so that blood pressure was not lowered to 140/90 mm Hg in more than 40% of the patients.[5] In another investigation involving hypertensive patients, it was shown that the incidence of recurrent strokes was reduced only when blood pressure was lowered to normal values.[9]

The effect of antihypertensive therapy on renal function is not very dramatic. Early studies have shown that there was a protection of renal function during treatment in patients with a diastolic pressure above 130 mm Hg but that there was no clear improvement in renal function in a small group of patients with diastolic pressures under 130 mm Hg.[10] Similar conclusions were drawn when it was found that there was only a modest and insignificant improvement in renal function during therapy and that, although the incidence of proteinuria was reduced, there was no improvement in glomerular filtration rate or renal plasma flow.[5]

Although the lowering of arterial blood pressure leads to a reduction in most of the complications of hypertension, it does not lower the incidence of coronary heart disease. In various studies it was shown that treatment of hypertension offered no protection from myocardial infarction and the number of patients who died from coronary heart disease actually increased.[10] This could be considered to be a numerical artifact, resulting from the improved survival rate in diseases more closely related to blood pressure, such as stroke, heart failure, and renal failure. However, it has been shown that some patients do not acquire coronary heart disease subsequent to being treated for hypertension but already have ischemic heart disease at the beginning of therapy. All in all, the mortality from coronary disease has fallen over the last decade, but the role that better control of blood pressure may play in the reduction of mortality is not yet known. However, it does seem that patients treated with beta blockers for their hypertension do suffer from myocardial infarction less frequently and that lowering blood pressure does reduce the incidence of angina pectoris.[11] Newer results published recently, though, have demonstrated that treatment with $\beta$-adrenergic blocking agents can indeed favorably influence coronary heart disease.[8,120]

## General Directives for Antihypertensive Therapy

There is still insufficient conclusive evidence, in spite of recently published results,[1] that therapy is beneficial to the patient whose diastolic blood pressure is between 90 and 104 mm Hg, and so treatment should be performed according to the discretion of the physician even though newer data appear to reverse this opinion. It still remains to be proven that stepped-care treatment is decidedly different from randomized treatment.[121] The physician may choose to treat mild hypertension without the use of medication and may recommend salt restriction, weight reduction, and biofeedback training. If there are already signs of organ involvement or if additional risk factors are present, such as the patient being male, under 45 years, a smoker, having a systolic pressure of over 165 mm Hg, and having hyperlipidemia or diabetes mellitus, the use of medication may be indicated. The use of medication will undoubtedly benefit the patient with a diastolic blood pressure of 105 mm Hg and over and should be prescribed in all such cases. Those circumstances for which therapy is required immediately and those for which treatment with medication is a possibility are listed in Table 1.

If it has already been decided to treat the patient, some basic principles should be followed to increase the effectiveness and reliability of treatment. Therapy is life-long and should not be interrupted arbitrarily in a patient whose blood pressure is well controlled. The patient should be informed of the importance of continued treatment, despite the absence of symptoms. Written instructions and audiovisual aids, such as those supplied by the American Heart Association and by the various pharmaceutical firms, should be used as supportive material in patient education. All directions should be given to patients in writing, so that they know the name of each of the drugs they take.

The objective of therapy is to maintain blood pressure between 100/70 mm Hg and 140/90 mm Hg when lying and standing. Higher values are acceptable in patients with cerebrovascular disease, angina pectoris, renal insufficiency, or generalized atherosclerosis. Blood pressure should be measured with the patient supine, following 5 min rest, and 2 min after reverting to a relaxed, standing position. A fall in blood pressure upon rising can occur in nontreated patients and should be taken into consider-

**Table 1.** Guidelines for the Treatment of Hypertension

I. Treatment essential
  a. Hypertensive crisis
  b. Accelerated malignant hypertension
  c. Clear organ involvement
    1. Heart
      a. Cardiac insufficiency
      b. Enlargement of the heart
      c. ECG indications of cardiac overwork
    2. Aortic aneurysm
    3. Cerebrovascular disease
    4. Renal damage
    5. Retinal involvement (Keith-Wagner II or more)

II. Treatment necessary
  a. Women with blood pressures over 165/100 mm Hg
  b. Men with blood pressures of 140/95 mm Hg and above
  c. Men and women under stress, with cardiovascular disease and blood pressures of 140/95 mm Hg and over

III. Treatment optional
  a. Men and women with labile blood pressures
  b. Hypertensive patients with other diseases whose prognosis is worse than that of the hypertension
  c. Patients with extensive neurologic damage resulting from terminal arteriovascular disease

ation when deciding upon the treatment procedure. Moderate fluctuations in blood pressure should not disturb the physician, as long as they do not exceed a diastolic variation of $\pm 10$ mm Hg in the lying position. The physician must be assured of the cooperation of the patient, so that he or she can prescribe as few drugs as possible at the minimal dosage. The therapeutic regimen should be as simple as possible, and additional drugs should be included only if the blood pressure is not well controlled. With few exceptions, it is not generally necessary to use more than three types of medication taken as two doses a day.

Patients should be checked at least every 3 months and should bring all their medications with them. In those patients who are to be treated with diuretics and salt restriction, which has an associated 10% to 40% incidence of hypokalemia, plasma potassium should be checked before the start of therapy, to exclude the existence of a primary aldosteronism.

Patients should be warned that all therapy which successfully lowers blood pressure can produce temporary phases of weakness and fatigue, which usually disappear after a few months. The autoregulation of cerebral blood flow changes in hypertensive patients, so that there is a reduction in perfusion when the blood pressure is lowered to values well tolerated by normal patients. Blood pressure should be lowered slowly and carefully, in 5 to 10-mm Hg steps, particularly in patients with cerebrovascular disease, who have suffered an ischemic insult, who show excessive morbidity, or who are older (see also Chap. 30).

Patients receiving drugs with a ganglion-blocking action, prazosin, or angiotensin converting enzyme inhibitors together with a diuretic, should be warned of dizzy spells upon assuming an upright position. They should always arise slowly in the morning and may benefit from sleeping with their head raised a little.

## Additional Treatment without Medication

Sudden and drastic alterations in the patient's way of life can be stressful in themselves, and so any additional therapeutic maneuvers should be introduced gradually. A restriction in salt intake to 4 to 6 g/day should be attempted in all patients, but in patients with renal insufficiency or congestive heart failure a more severe salt restriction may be necessary.

Overweight patients should be put on a low-calorie diet, and the consumption of saturated fats and cholesterol should be reduced in all hypertensive patients. Nicotine consumption should be limited. Tranquilizers and sedatives do not generally reduce blood pressure but are useful for combating stress. Patients should be encouraged to relax, avoid stress, and undertake any form of isotonic exercise.

The most serious side effect of treatment with diuretics is an increased potassium loss which may de-

**Table 2.** Effects of Hypokalemia

1. Metabolic alkalosis
2. Renal damage
   a. Structural
      (1) Vacuolization of tubular epithelium—rare
      (2) Interstitial nephritis—rare
   b. Functional
      (1) Loss of concentration power—rare
      (2) Reduced bicarbonate excretion—rare
      (3) Sodium retention with consequent retention of extracellular fluid volume—not so rare
3. Cardiac damage
   a. Structural: Myocardial necrosis—rare
   b. Functional
      (1) ECG changes (high-peaked or inverted T waves, prolongation of the PR interval, complete heart block, atrial asystole, deterioration of ventricular complexes)—frequent
      (2) Arrhythmias—frequent
      (3) Oversenstivity to digitalis—frequent
4. Vascular damage
   a. Deficient vasodilation after exercise and exposure to heat—rare
   b. Increase of renin and angiotensin—rare
   c. Decreased renal perfusion and reactivity to angiotensin II—rare
5. Gastrointestinal manifestations: Reduced motility—not so rare
6. Metabolic changes
   a. Carbohydrates: Reduced glucose tolerance, reduced secretion of insulin and growth hormone—rare
   b. Proteins: Reduced nitrogen utilization, reduced growth—rare
   c. Fats: Increased serum cholesterol and triglycerides—rare
7. Neuromuscular changes
   a. Structural: Rhabdomyolysis, myoglobinuria—rare
   b. Functional: Weakness up to paralysis, cramps, pain—rare

velop into hypokalemia. Approximately 1% of total body potassium is to be found in plasma, the greater part is to be found in the cell. Some investigators have found a correlation between plasma and intracellular potassium concentrations, whereas other investigators have found little correlation. The majority of isotopic determinations of total body potassium in hypertensive patients taking diuretics have failed to show a reduction even though in most there was a decrease in plasma potassium. Some of the dangers of hypokalemia are listed in Table 2.

For the typical hypertensive patient with only mild hypokalemia, muscle weakness, polyuria, and a tendency to cardiac arrhythmia become evident. For patients who, in addition to diuretics, also take digitalis preparations, there is a potentiation of the toxicity of this medication. With more pronounced hypokalemia, there can be structural alterations in the kidney, in the heart, and in the skeletal muscle. During strenuous exercise, the potassium-depleted muscles may develop extensive rhabdomyolyses, since inadequate vasodilation results in hypoperfusion. Animal experiments have shown that in potassium-depleted dogs there is a significant increase in body sodium, extracellular volume, renin, and cardiac output, together with a decrease in total peripheral resistance. These changes are accompanied by an increase in the urinary output of prostaglandins, and could be reversed by administering the prostaglandin synthetase inhibitor, indomethacin.[12] Diuretic-induced hypokalemia does not generally lead to such drastic alterations in body function, but the fluid retention and resultant increase in plasma angiotensin can offset the blood-pressure–lowering effect of the diuretics, and patients with long-standing hypokalemia are more susceptible to ventricular arrhythmia. Of 70 patients who were resuscitated following ventricular fibrillation, plasma potassium values were 3.2 mmol/liter, a value which is distinctly lower than that found in patients admitted for acute cardiac infarction.[13]

There are different ways to relieve potassium deficiency. Additional potassium can be obtained by consuming larger amounts of orange juice, bananas, or dried fruit if caloric intake is no problem. Potassium supplements should be in the form of chloride,

since other anions do not correct the alkalosis or the intracellular potassium deficiency. Potassium chloride may be given as a substitute for table salt. It not only is well tolerated by the patient but also reduces dietary salt intake. Occasionally it may cause intestinal ulceration or even hemorrhage. Should the incidence of intestinal complications prevent oral potassium substitution, potassium-sparing diuretics should be given in conjunction with the thiazides. These include amiloride, triamterene, and the aldosterone antagonist, spironolactone. In patients who also have a magnesium deficiency, the hypokalemia may be refractory during potassium replacement. Magnesium deficiency can occur during diuretic treatment, in particular in patients with secondary aldosteronism, in those who are undernourished, or in those who are alcoholics.

Since the introduction of diuretics, the reliance on a low-salt diet to control blood pressure has become increasingly infrequent. A retrospective study of 5000 physicians has shown that only 6% of their patients were treated by salt restriction.[14] Since little attention is now paid to dietary salt consumption, which may be as high as 15 to 20 g/day, it is hardly surprising that the antihypertensive effect of diuretic therapy is masked in the face of this massive salt intake. Dahl[15] has indicated the reasons why sodium restriction is not employed more often to lower blood pressure: most patients have been reared since childhood on a relatively salt-rich diet and for them salt restriction makes their food tasteless and unappetizing. Furthermore, most patients are discouraged by sodium-free diets because the preparation of the food is so complicated. Finally, most people are unaware that milk, cheese, and most prepared foods have a high sodium content.

A moderate reduction in salt consumption lowers blood pressure by lowering plasma volume, thereby potentiating the effect of the diuretics. In numerous studies it has been shown that a reduction in salt intake to 4 to 6 g/day has a definite blood-pressure–lowering effect and does so without discomfort or side effects.[16–21] To avoid the difficulties associated with preparing special diets, hypertensive patients can restrict their salt intake by simply not salting their food and by avoiding milk, milk products, and all prepared foods, except canned fruit and juices. Patients should be made aware that a lot of salt is added to convenience foods to enhance the shelf-life of the product and make it more appetizing; fresh asparagus contains 2 mg of sodium per 100 g but in cans it contains 236 mg per 100 g.

Substitutes for table salt containing almost no sodium may be used to flavor food, and salt-free antacid preparation should be used. However, care should be exercised when prescribing preparations in which sodium has been exchanged for potassium because of the danger of hyperkalemia, particularly in patients with renal insufficiency who are also taking potassium-sparing diuretics. Also, in patients with renal disease, in particular in those with analgesic nephropathies, there may be excessive salt loss from the kidney, and so excessive salt restriction may worsen renal function and, by activating renin release, aggravate the hypertension.

Physicians often try to make their patients lose weight, but this attempt is seldom successful. Overweight patients with high blood pressure should be persuaded to stick to a sensible diet, but only rarely is it possible to lower blood pressure through weight reduction. Recently, however, a reduction in blood pressure of 20/26 mm Hg has been reported in 81 overweight patients on a low-calorie diet who lost an average of 9.5 kg each over a 2-month period. Although this was achieved without additional salt restriction, it should not be forgotten that a diet low in calories is also low in salt, and so the effect of weight reduction will be enhanced by the reduced salt intake.[22]

Isotonic or dynamic exercises, such as running or swimming, raise systolic but not diastolic blood pressure and increase stroke volume and heart rate. The increase in mean arterial pressure is greater in patients with high blood pressure, but after a period of adaptation arterial pressure and heart rate increase less during exercise. In a relatively small group of untrained hypertensive patients, blood pressure was found to be reduced after a period of training by 14/10 mm Hg on average.[23] It has also been reported that severe exercise not only influences blood pressure but also reduces the incidence of lethal heart attacks.[24]

In contrast, with isometric or static exercise, such as lifting or pulling, both diastolic and systolic blood pressure are raised. In untreated hypertensive patients blood pressure may rise to alarming values and cannot easily be influenced by beta blockers. Consequently, patients should avoid isometric exercises and be warned against using those pieces of equipment on the market which are claimed to improve cardiovascular function and which encourage isometric exercise.

## Compliance

Patients with hypertension have a unique problem which arises from the characteristics of their disease; most of them are absolutely unaware of the nature of their disease, its causes, its possible consequences, and the necessity of treating it. Since the

disease proceeds without symptoms, there is no impetus to seek advice or treatment or to continue therapy once it has been initiated. Many patients discover their hypertension only when they are in their late thirties or early forties, at a time when a loss of strength and vitality starts to become threatening. Diagnosis of high blood pressure often provokes a strong denial reaction. Furthermore, the diagnosis is socially threatening. It requires a change in life-style and may incorporate the fear of a loss of employment or a reduction in sexual potency, not to mention the difficulties regarding life insurance. Although it is possible in theory to find adequate therapy for each individual patient, only about one-third of the hypertonic patients receive adequate treatment.

The reasons for inadequate treatment of high blood pressure are many and involve the patient, the physician, and the medication itself. However, without the cooperation of the patient it is simply not possible to lower blood pressure. Thus, the physician should be aware of the psychological and sociological problems which may persuade patients not to actively participate in the treatment of their complaint. First, patients believe that their disease is of little consequence, because they experience no symptoms. Second, they are little interested in their state of health, forget to take their tablets, do not believe they are effective, and cannot be bothered with the whole business. Some patients adopt this attitude deliberately. Third, they may react to sickness aggressively and treat it as an enemy. Finally, as a result of poor education they may be unable to understand or retain the instructions they are given or may simply be forgetful. Whatever the particular problem, every effort should be made to motivate patients to participate in the treatment of their disease.

## Specific Drug Therapy

The number of substances available for reducing blood pressure has increased enormously in the last 15 years. Not all of these are freely available. Some are still undergoing clinical testing and have not yet been released for general use. Others, such as practolol and ticrynafen have been withdrawn from the market because of serious and irreversible side effects.

The blood pressure response to increasing doses of most of the antihypertensive agents is biphasic in nature. During the first phase, the therapeutic effect of the medication increases as the dose is raised. Then a point is reached beyond which an increase in dose produces no further effect. This characteristic requires careful dose regulation on the part of the physician. A particularly steep dose-response curve is shown by guanethidine; a moderately steep curve is characteristic of clonidine, hydralazine, and propranolol; and a flat curve is typical for thiazide diuretics and reserpine.

In addition to the single-substance preparations, a number of combination preparations are available which usually consist of a diuretic together with a vasodilatory substance. A number of investigations have shown that the continuance of the blood-pressure–lowering action of various types of drugs, including adrenergic blockers and vasodilators, depends upon the maintenance of a reduced vascular volume. The practice of combining thiazides with other antihypertensive substances helps to keep plasma volume contracted in the face of the sodium retention that other types of blood-pressure–lowering medication invariably produce. Because of the change in the characteristics of the pressure-natriuresis curve in essential hypertension, a reduction in blood pressure quickly leads to fluid retention. Also, if cardiac function is barely sufficient, the administration of adrenergic blockers without diuretics, which will lead to fluid retention, may result in congestive heart failure.

### Diuretics

At the present time there are three types of diuretic agents on the market. Newer diuretics, which are still being clinically tested, promise to be at least as effective in treating hypertension as the older ones, with a much lower degree of side effects. The currently available diuretics can be classified as thiazides, loop-diuretics, or potassium-sparing diuretics. These substances have differing sites of action in the nephron and different mechanisms inducing diuresis and natriuresis. This explains both their differing potencies and the variation in urinary electrolyte excretion which they produce (Table 3).

All diuretics reduce plasma volume and thus activate renin release and cause a mild form of secondary aldosteronism. The increase in renin and angiotensin levels induces a mild vasoconstriction, which offsets the blood-pressure–lowering effect. Although the work of Laragh[25] considers the possible vasculotoxic effect of increased renin, there is no conclusive evidence for this phenomenon at the present time, and numerous investigations, which have unquestionably demonstrated the benefit of antihypertensive therapy, have been performed on patients taking diuretics.[26]

The daily use of diuretics in patients with an un-

**Table 3.** Commonly Used Diuretics

| Generic Name | Product Name | Average Daily Oral Dose (mg) | Duration of Action (h) |
|---|---|---|---|
| | *Thiazides* | | |
| Chlorothiazide | Diuril | 500–1000 | 6–12 |
| Hydrochlorothiazide | Esidrix | 25–200 | 12–18 |
| Benzthiazide | Aquatag | 25–200 | 12–18 |
| Hydroflumethiazide | Saluron | 25–50 | 18–24 |
| Bendroflumethiazide | Naturetin | 5–20 | ~18 |
| Methyclothiazide | Enduron | 2.5–10 | ~24 |
| Trichlormethiazide | Metahydrin | 2–4 | ~24 |
| Polythiazide | Renese | 1–4 | 24–48 |
| Cyclothiazide | Anhydron | 1–2 | 18–24 |
| | *Related Sulfonamides* | | |
| Chlorthalidone | Hygroton | 25–100 | 24–72 |
| Quinethazone | Hydromox | 50–200 | 18–24 |
| Metolazone | Zaraxolyn | 2.5–5 | 24 |
| | *Loop Diuretics* | | |
| Furosemide | Lasix | 40–120 | 6–8 |
| Ethacrynic acid | Edecrin | 50–400 | 12 |
| Piretanid (HOE 118)* | Arelix | 6–18 | 6 |
| | *Potassium-Sparing Diuretics* | | |
| Spironolactone | Aldactone, Osyrol | 25–100 | 24–96 |
| Triamterene | Dyrenium | 100–300 | 12 |
| Amiloride | Midamor | 5–10 | 12–18 |

*This newly developed drug is not commercially available yet.

restricted salt intake can make the patient the potential target for the major side effect of diuretic therapy, hypokalemia. Most diuretics restrict salt reabsorption proximal to the distal segment, where potassium is exchanged for sodium, so that more sodium and water are delivered to this distal site. The increased flow rate in the distal tubule leads to an increase in potassium secretion and therefore an increase in urinary potassium losses. On a high-salt diet even more salt and water are delivered to the distal segment and further potassium losses result. By reducing sodium intake only modestly to about 4 to 6 g/day, the increase in distal salt and water delivery is less severe and the potassium losses are less pronounced.

### Thiazides and related substances

Thiazides work by inhibiting the sodium and chloride reabsorption in the cortical diluting segment of the ascending limb of the loop of Henle, but a small portion of their action can be attributed to an action on the proximal tubule. Plasma and extracellular volume are reduced, and cardiac output falls. When given chronically, plasma volume often returns to normal but total peripheral resistance then falls.[27] The reduction in peripheral resistance is most probably attributable to a diminished vascular response to pressor substances.[28] Older studies have suggested that the reduced vascular response may be due to a reduction in the sodium and water content of the vascular wall itself, but other investigators have been unable to confirm this after chronic administration of thiazides.[29]

After 3 or 4 weeks of thiazide therapy, blood pressure falls between 8/4 and 9/11 mm Hg. In another study, 45% of the patients with mild hypertension taking thiazides alone experienced a fall in blood pressure of at least 20 mm Hg or had a blood pressure of 140/90 mm Hg or less. Thiazides can also be taken for much longer periods of time. In 80% of the cases with mild hypertension, thiazides alone reduced blood pressure from an average value of 203/121 to 162/97 mm Hg over a treatment period of 12 years. Furthermore, a comparison between treatment with either thiazides or beta blockers showed that, even at modest doses, the diuretics are more effective in lowering blood pressure.[30] However, thiazides are generally prescribed in combination with

other forms of medication, permitting better control of blood pressure and allowing the dosage of thiazides to be reduced.

It has proved possible, by modifying the original benzothiazide structure, to synthesize longer-acting thiazides with improved potency. However, these new derivatives are not much help to the patient who still has to take 1 to 2 tablets a day, regardless of whether they contain 2 mg of trichloromethiazide as opposed to 50 mg of hydrochlorothiazide. The long-lasting action of chlorthalidone and metolazone has enabled a reduction in the dose to 1 tablet every second day, but most physicians still prescribe 1 or 2 tablets a day to ensure regular dosage.

The major side effect of thiazide treatment is hypokalemia. The incidence of hypokalemia is variable from report to report and ranges between 0% and 40%. In one study serum potassium values of under 3.5 mmol/liter were found in approximately 10% of the patients taking thiazides chronically;[31] in another, 3.5 mmol/liter was the average value found. This variability may be attributable to the differing consumptions of sodium and potassium, to the varying degrees of secondary aldosteronism resulting from the diuretics, to the use of laxatives or other medication which induces potassium loss, or to the extracellular-intracellular potassium shifts which accompany acidosis, none of which were controlled in these studies. Patients who consume a lot of sodium will, in general, lose more potassium than those with a modest salt intake; furthermore, patients with a low potassium intake, in particular older patients, tend to develop hypokalemia more readily. The amount of potassium which is needed to compensate for thiazide-induced hypokalemia is about 40 to 60 mmol/day, and care should be taken, particularly in older patients, that oversubstitution and hyperkalemia do not result. It is important for the physician to realize that hypokalemia in a hypertensive patient need not indicate primary aldosteronism, particularly if it becomes apparent only during or after prolonged treatment with thiazides. However, primary aldosteronism must be suspected if the hypokalemia cannot be explained by thiazides, other diuretics, or other obvious causes.

High plasma values of uric acid are found in up to 30% of untreated hypertensive patients, and thiazide therapy increases this incidence by more than a factor of 2. Some patients develop gout. Since thiazides reduce the excretion of uric acid from the kidney by reducing plasma volume and therefore lowering glomerular filtration rate (GFR) and renal blood flow (RBF) and also uric acid secretion into the renal tubules, the fear has been voiced that a gradually increasing urate deposition in the kidney may lead to a further reduction in renal function. Despite the continuous use of thiazides over a 15-year period, there is no evidence that they contribute to renal damage. Furthermore, it has been shown in numerous patients with gout, who have been observed over extensive periods of time, that hyperuricemia is not the only factor which is detrimental to renal function. Consequently, most investigators have come to the conclusion that a thiazide-induced hyperuricemia need not be treated unless the plasma values are so high that the renal excretion of uric acid exceeds 700 mg/day. In such patients, urate synthesis can be reduced by allopurinol. In thiazide-induced uricemia with lower levels of uric acid in the urine—and that is the case for most patients—the urinary excretion of uric acid can be increased with probenecid.

A reduction of glucose tolerance and difficulty in controlling diabetes have been observed in patients taking thiazides. In a prospective study on 137 patients with high blood pressure and a normal glucose tolerance, treatment for 1 year with different diuretics caused no change in the average levels of blood glucose, insulin, or free fatty acids, and only three patients developed a manifest diabetes.[32] Further observations on 51 patients showed a significant worsening of glucose tolerance following 6 years of treatment with diuretics.[33] The mechanism behind this thiazide-induced hyperglycemia is unknown, but some authors have postulated a correlation to hypercalcemia. Nevertheless, despite the reported changes in glucose tolerance, hyperglycemia is seldom a problem during thiazide treatment.

Thiazides have many actions on calcium homeostasis and they can, occasionally, induce hypercalcemia in patients who had previously shown normal calcium levels.[34] Hypercalcemia is more often encountered in patients with preexisting hyperparathyroidism or with vitamin-D–treated hypoparathyroidism. Thiazides suppress calcium excretion in the urine. They also produce an increase in total and ionic calcium, apparently by increasing calcium release from the bones, which is greatest in patients who already have increased bone resorption, such as those suffering from hypoparathyroidism or who are receiving vitamin D treatment. The acute hypercalcemic action of the thiazides is dependent upon the presence of circulating parathyroid hormone,[35] but the blood levels of parathormone are not clearly altered, even though a parathormone hyperplasia has been demonstrated.[36] Thus it appears that the action of the thiazides on calcium metabolism is to potentiate the renal action of parathyroid horomone, which leads to a calcium retention and a partial suppression of parathormone secretion (see also Chap. 12).[37]

The recently emphasized increase in serum cho-

lesterol and triglycerides in patients taking diuretics may reflect the decrease in insulin secretion which occurs during hypokalemia. An increase in serum cholesterol to 12 mg per 100 $ml^{-1}$ and of triglycerides to 36 g per 100 $ml^{-1}$ has been found in 32 patients who were treated for 1 year with chlorthalidone, even though they had also been given a lipid-reducing, low-calorie diet. The long-term observations on hundreds of patients undergoing diuretic treatment reported in the Framingham study failed to show an increase in serum cholesterol, which was reduced to 6 mg per 100 $ml^{-1}$, and no mention was made of the triglyceride levels. Since other studies have confirmed that triglyceride levels in plasma do increase during diuretic treatment, this parameter should be checked at yearly intervals during therapy. The additional risk of cardiovascular disease as a result of the raised serum lipid concentrations could offset the benefit of the reduction in blood pressure.[38,39]

### Loop diuretics

As their name implies, the site of action of the loop diuretics is in the loop of Henle. These diuretics are potent inhibitors of the solute reabsorption in the ascending limb of Henle's loop which leads to the dilution of the tubular fluid and the establishment of a medullary solute gradient for urinary concentration. Of the many variants of loop diuretics, furosemide and ethacrynic acid are the commonest.

Furosemide is a highly potent diuretic which, given intravenously, has proved itself to be exceptionally useful in the treatment of acute hypertensive crises. Oral administration is used only to control volume-dependent hypertension which, in general, accompanies renal insufficiency, and to control moderate to severe hypertension. For this purpose, a special furosemide preparation is particularly suitable which, because of its retarded absorption, is much longer-acting. Treatment with thiazides is seldom effective in lowering blood pressure if glomerular filtration is less than 25 ml/min, so for patients with reduced renal function, in whom plasma creatinine is 2 mg per 100 ml or more, furosemide is often used. The increase in urinary output was found to be the same in furosemide- or thiazide-treated patients, but the cumulative incidence of hypokalemia was only 8% in the furosemide-treated group, compared to 62% for the thiazide-treated group.[40] When furosemide is given in conjunction with anticonvulsants, the diuresis is reduced; if given with chloral hydrate, unpleasant side effects can occur. Ethacrynic acid, although structurally quite different from furosemide, shows approximately the same potency. The same side effects occur during treatment with ethacrynic acid as occur with furosemide. Although a decrease in hearing ability has been reported for both drugs, a permanent hearing impairment has been reported only with ethacrynic acid.

### Potassium-sparing diuretics

The similarity in structure between spironolactone and the mineralocorticoid hormones allows this substance to displace the mineralocorticoid from its intracellular receptor site, when applied in relatively large concentrations, and so to act as a competitive inhibitor.[41] This drug is most commonly employed in the therapy of essential hypertension in cases of nephrosis and cirrhosis (ascites). At a dosage of 50 to 100 mg/day, as given in the combination preparations with hydrochlorothiazide and furosemide, the side effects of feminization in males and amenorrhea in women occur less frequently. At a dosage of 100 mg/day it is more effective than 60 mmol of KCl per day as a compensation for thiazide-induced potassium losses. Caution is required when some degree of renal insufficiency is present, because the reduced ability to excrete potassium can lead to hyperkalemia. There has been a disquieting report of an increase in frequency of breast cancer during spironolactone therapy. These findings have been investigated further and seem not to apply to the commonly employed doses.[42] This drug can, independent of its action as an aldosterone antagonist, reduce blood pressure in patients who do not have excessive levels of aldosterone. The diuresis can be inhibited by aspirin.

Triamterene has a smaller intrinsic antihypertensive action than spironolactone, and its potassium-sparing action is produced by a mechanism which does not involve any hormonal side effects. Inasmuch as triamterene is given in conjunction with thiazides, its action is comparable to that produced by spironolactone alone or spironolactone given in conjunction with thiazides. Amiloride is a potent potassium-sparing diuretic which has an action similar to that of triamterene. At a dosage of 5 mg/day its action is less effective than 25 mg of spironolactone given two times daily.

### Newer diuretics

There are a variety of newer diuretics which deserve mention, such as indapamide, which is structurally similar to the thiazides but does not induce potassium loss, bumetanide, which is structurally similar to furosemide but functions differently, and mefruside which is a structural mixture between the thiazides and furosemide and has an action similar to that of the thiazides. Two other diuretics, ticrynafen and indamon, are derivatives of the acetic acid molecule. Both increase urine output by reducing the

tubular reabsorption of urate. Preliminary investigations with ticrynafen showed that its diuretic and antihypertensive action was comparable to that of the thiazides and that it significantly reduced plasma uric acid levels. However, ticrynafen had to be withdrawn from the market because of side effects. Chemically unrelated to the presently existing diuretics is etozolin, which has shown minimal toxicity in animal experiments. Etozolin has its site of action in the ascending limb of the loop of Henle and should, therefore, be considered as belonging to the group of loop diuretics.

Also of interest is muzolimine, a pyrazolone derivative, which is still in the development stage. This diuretic is a high-ceiling diuretic with a long-lasting action, which has been shown to have an antihypertensive action in dogs, spontaneously hypertensive rats, and rats with renal hypertension.[43,44] The major advantages of this diuretic compared to others have become apparent from clinical observations, in which it has been determined that there is no rebound phenomenon after oral administration and that the drug is effective in patients with severe renal insufficiency. An intense and long-lasting diuresis and blood-pressure–reducing action were demonstrated, even in patients with severely reduced renal function and values of glomerular filtrate as low as 3 ml/min, and the drug was shown to be well tolerated. The daily dose appropriate for cases of edema of cardiac, renal, or hepatic origin is 30 mg, whereas the dose indicated for renal insufficiency may reach 240 mg daily.

## Adrenergic Blockers

It is necessary to briefly describe the major features of the adrenergic nervous system in order to understand the mode of action of the adrenergic blockers. Upon stimulation, the adrenergic nerve releases its transmitter substance from the nerve ending which diffuses across the synapse and stimulates the postsynaptic alpha or beta receptors of the effector organ. For this to occur, norepinephrine, which is synthesized from tyrosine and stored in the granules of the nerve ending, must be available in the depot granules of the nerve ending. Recently, the presence of alpha and beta receptors has been demonstrated on the nerve cells themselves. Stimulation of these presynaptic alpha receptors has been found to suppress the release of norepinephrine from the nerve ending, whereas stimulation of the presynaptic beta receptors enhances the release of norepinephrine at the synapse.

Thus, there are three modes of action with which adrenergic blocking agents can act upon this system to reduce blood pressure. They may act upon the neurons to restrict the release of norepinephrine from the nerve ending (neuronal blockers). They may act to block the alpha or beta receptors at the effector organ (peripheral receptor blockers). Finally, they may have their site of action on the more central presynaptic receptors and, by either stimulating these alpha receptors or blocking the beta receptors, inhibit the release of norepinephrine from the nerve ending. The action of both the alpha and beta blocking substances on blood pressure may reflect their influence not only on the postsynaptic receptors of vascular and cardiac muscle but also on the presynaptic alpha and beta receptors. The currently available substances, their mode, and site of action are listed in Table 4.

Adrenergic blockers are very potent forms of medication with which to combat hypertension but can produce unpleasant and occasionally serious side effects. Used at the correct dosage, they are both effective and safe. A number of authors suggest that adrenergic blockers should be used first in treating hypertension. This does not seem to be appropriate, however, since approximately 50% of all hypertensive patients show a definite reduction in blood pressure after treatment with diuretics and a modest reduction in salt intake.

It is only if therapy with diuretics does not lower blood pressure to acceptable levels that additional therapy with adrenergic blockers should be employed. This combination therapy, which produces few side effects, even with overdosage, is a safe, simple, and inexpensive form of treatment which has

**Table 4.** Adrenergic Blockers Used in the Treatment of Hypertension

- I. Peripheral-acting
  - A. Neuronal blockers
    - 1. Reserpine
    - 2. Guanethidine
  - B. Receptor blockers
    - 1. Alpha blockers
      - a. Postsynaptic blockers with presynaptic action
        - (1) Phenoxybenzamine (Dibenzyline)
        - (2) Phentolamine (Regitin)
      - b. Postsynaptic blockers: Prazosin (Minipress)
    - 2. Combined alpha and beta blockers: Labetolol
    - 3. Beta blockers:* Propranolol and others
- II. Central-acting
  - A. Alpha-receptor stimulators
    - 1. Methyldopa
    - 2. Clonidine
  - B. Beta-receptor blockers:* Propranolol and others

*Beta blockers probably have at least dual mechanisms of action

been recommended by various authors.[45] Beta blockers, the most favored alternative to diuretics, succeed in lowering blood pressure only in approximately half the patients with hypertension and have the extra disadvantage of their not inconsiderable side effects. These drugs work best in conjunction with diuretics. When given without diuretics, the beta blocker propranolol caused a paradoxical increase in blood pressure in 11% of hypertensive patients, of whom most of those with essential hypertension displayed low renin levels.[46]

## Peripheral-acting adrenergic blockers

### *Neuronal Blockers*

*Reserpine.* Reserpine is one of the many alkaloids which originate from the roots of *Rauwolfia serpentina.* It possesses many of the desirable pharmacologic properties of the various members of the group and can be considered as the prototype of the family of alkaloids found in this Indian plant. Reserpine prevents the transport of norepinephrine into the depot granules, so that less of the neurotransmitter is available for release, once the nerve has been stimulated. The consequence is a reduction in sympathetic tone and a lowering of total peripheral resistance. The release of catecholamines from the brain is also decreased. This could explain the action of this drug as a sedative and as a depressant and also its action on the heart to reduce cardiac output. Although this latter influence on heart muscle could be problematic in the treatment of patients with heart failure, difficulties seldom occur, but an occasional incidence of bradycardia may result.

Reserpine is reabsorbed without difficulty from the gastrointestinal tract and is rapidly deposited in fat-containing tissues. Its pharmacologic action develops slowly and continues for a long time, even after it has been excreted, so that a single daily dose is sufficient to produce the desired effect.

When given alone at a dosage of 0.5 mg/day, reserpine has only a modest antihypertensive action, and blood pressure is reduced only by 3/5 mm Hg. In combination with a thiazide the decrease in blood pressure is more pronounced and reaches 14/11 mm Hg. The effectiveness of reserpine in treating mild to moderate hypertension is attested to in its worldwide use for this purpose. A single daily dose of 0.25 to 0.50 mg produces the antihypertensive effect.[47]

The possibility of treating mild hypertension with a single daily dose of reserpine and a long-acting diuretic offers a great advantage. In a double-blind study it was shown that in patients receiving a single daily dose of reserpine of 0.25 mg, together with a thiazide derivative, blood pressure was better controlled and there were fewer side effects than in patients receiving $\alpha$-methyldopa or bethanidine, a sympathetic blocker similar to guanethidine.

Mild side effects are rhinitis and an increase in the secretion of gastric juice, which is of importance only if treatment for ulcers is being undertaken at the same time. The major side effect of importance is a depression of the central nervous system. This can be mild but in some instances may be so severe that the patients become suicidal. These problems arise rarely at a daily dose of 0.25 mg but more frequently at a dosage of 0.5 mg/day. In patients with a history of endogenous depression this form of medication should be avoided. All patients should be warned to discontinue treatment if they start to feel depressed or if they awake in the early morning and are unable to fall asleep again.

*Guanethidine.* Guanethidine and its derivatives are taken up by an active transport mechanism into the adrenergic nervous system. This is the same system which transports extracellular norepinephrine across the nerve membrane and back into the cell. This pumping mechanism can be inhibited with ephedrine, amphetamine, and tricyclic antidepressives (e.g., imipramine, amitriptyline), a fact which explains the poor action of guanethidine in patients taking these forms of medication. Once guanethidine has entered the adrenergic nervous system, it blocks the release of norepinephrine. Its mode of action is to induce the release of norepinephrine from the depot granules, thus reducing the intracellular reserves of the neurotransmitter and the amount that can be released upon stimulation of the nerve. Guanethidine also causes the myocardial catecholamine stores to be depleted. However, it cannot cross the blood-brain barrier, and so the catecholamines in the central nervous system are released from the depot granules only to a minor extent.

Many physicians prescribe guanethidine for patients with only moderate hypertension, since it always lowers blood pressure, need be taken only once daily, and the relationship between the fall in blood pressure and the dosage is very favorable. Other physicians prefer to use it only for cases of severe hypertension, since its pharmacologic action can be accompanied by severe orthostatic problems. Guanethidine induces a reduction in vascular tone and a modest lowering of total peripheral resistance. The decrease in the myocardial catecholamine reserves is probably the reason for the reduction in heart rate, in stroke volume, and in cardiac output, which is primarily responsible for the hypotensive action. The reduction in blood pressure is much more prominent in the standing than in the lying position, since the normal vasoconstrictive response to stand-

ing is suppressed by the drug so that the physician should be prepared for an orthostatic response.

Guanethidine is a dangerous drug, because the therapeutic dosage is often exceeded and the patients then suffer from an acute hypotensive crisis. Its combination with other antihypertensive drugs and other types of medication should be undertaken with great caution, because patients are often already taking antidepressant drugs. However, since guanethidine also induces fluid retention, it should always be given in conjunction with a diuretic.

Absorption from the gastrointestinal tract is poor and varies between only 3% and 27%. Oral doses of guanethidine are accumulated slowly and are active for many days. This is the reason that the full antihypertensive action develops only after a few days and the drug need be administered only once daily.

The dose of guanethidine which is required to reduce blood pressure during standing to acceptable levels varies between 25 and 75 mg/day. The initial dose should never exceed 25 mg and supplements of 10 to 12.5 mg every 3 to 5 days are sufficient. Higher doses are not to be recommended at the beginning of treatment. Some patients fail to react even to larger doses of guanethidine, presumably because the low amounts of remaining norepinephrine available in the nerve endings are sufficient to maintain blood pressure at high values. The administration of additional phenoxybenzamine can be beneficial in these cases and can lead to the desired lowering of blood pressure.

The side effects of guanethidine are a direct consequence of the pharmacologic action of the drug. There is a tendency to orthostatic hypotension, which must be avoided at all costs in patients with cerebral vascular disease. Physical work may also result in hypotension and lead to symptoms of reduced cerebral or myocardial blood flow. There is some degree of fluid retention, which can be prevented by simultaneous administration of diuretics but which must be circumvented in patients with cardiac insufficiency. Some patients develop diarrhea.

Men may experience impotence and difficulty with ejaculation. The occurrence of psychiatric disturbances is also a possibility as a result of reduced cerebral blood flow, following a too precipitate fall in systemic blood pressure. However, guanethidine has no sedative or depressant action on the brain, for it is unable to cross the blood-brain barrier.

## Receptor blockers

***Alpha Blockers.*** Alpha blockers are substances that are capable of blocking the alpha postsynaptic receptors at the effector organ. Although alpha blockers are useful in the therapy of pheochromocytoma, they have proved to be of little value for the treatment of essential hypertension. However, when prescribed together with other substances or when given as combination preparations with beta blockers, the alpha blockers do seem to be effective in the treatment of hypertension. Up until the introduction of prazosin there was no alpha blocker available that was suitable for the treatment of essential hypertension. Alpha blockers such as phenoxybenzamine or phentolamine not only block the postsynaptic receptors at the effector organ but also have some action on the central, presynaptic alpha receptors. Prazosin, however, seems to block only postsynaptically, thus leaving the central alpha receptors free to suppress the release of norepinephrine.

*Prazosin.* Prazosin is a quinazolin derivative that is chemically quite different from the other hypertensive agents. Prazosin, although originally introduced as a vasodilator, is an alpha-receptor blocker[48] which acts specifically on the postsynaptic receptors. This specificity for the peripheral receptors may explain why this drug does not produce tachycardia. Its hemodynamic action in man leads to a fall in total peripheral resistance and no increase in cardiac output, renal blood flow, or glomerular filtration rate, and only under particular circumstances[122] does it result in a decrease in plasma renin activity during an increase in plasma volume. After longer periods of administration, plasma renin levels fall. Prazosin seems also to have an influence on the visceral vasculature, and an increase in visceral blood flow may account for the tendency to hypotension often encountered in the initial phase of therapy with this drug.

Prazosin has shown itself to be a fairly potent antihypertensive agent in patients with raised blood pressure. In various investigations this drug has been shown to be equivalent in its action to that of methyldopa, not only in its antihypertensive action but also with regard to its side effects. A dose of 1 mg of prazosin appears to be equally as potent as 25 mg of dihydralazine, and many investigators show a preference for prazosin for this reason.

Prazosin can be effectively combined with beta blockers to lower blood pressure, which then results from a dual action in lowering peripheral resistance and decreasing cardiac output. Prazosin is also useful for treating moderate hypertension and for patients with chronic renal failure. It is rapidly absorbed, reaches peak concentrations in blood after only 2 h, and has a plasma half-life of 2 to 3 h. The drug is strongly bound to plasma proteins, undergoes metabolism in the body, and is excreted predominantly in the bile and feces. In order to avoid

severe hypotension and possible collapse, the first dose should definitely not exceed 1 mg and preferably should be confined to 0.25 to 0.5 mg taken at bedtime. At an initial dose of 2 mg, 16% of 74 patients examined showed a definite hypotensive reaction; with 0.5 mg only 5% of patients developed mild symptoms of dizziness. For maintenance, not more than 12 mg/day taken in three doses should be given.

In addition to an initial hypotension during which patients have a tendency to collapse within the first 30 to 90 min, there may be a persisting hypotension with accompanying dizzy spells, faintness, and loss of consciousness. However, even excessive dosage cannot result in any further complications as long as the patient is in a reclining position. Other side effects, in 934 patients who were observed for an average period of 4.7 months, were edema in 5%, anticholinergic effects in 16%, lethargy in 14%, and symptoms originating from the central nervous system (headache, tiredness, nervousness, dizziness) in 26%.

***Combined Alpha and Beta Blockers.*** Some authors have recommended a combination therapy, with alpha and beta blockers given together. In the initial experiments, in which phenoxybenzamine was given in conjunction with propranolol, there were a massive orthostatic reaction, fluid retention, and severe depression. Other authors reported that this combination of drugs was both safe and effective in combating hypertension. The combination of phentolamine with oxyprenolol has led to better control of blood pressure and has reduced the incidence of side effects to insignificance.

*Labetolol.* Labetolol is a particularly effective combination preparation of alpha and beta blockers which works when given orally and when given intravenously to lower blood pressure during a catecholamine-induced hypertensive crisis. The hemodynamic alterations it produces are almost ideal; it induces a fall in blood pressure primarily through a reduction in total peripheral resistance, and also a modest decrease in cardiac output.

***Beta Blockers.*** Beta blockers are very effective in the treatment of hypertension, and, once certain high-risk patients have been excluded from therapy, they are generally free from disturbing side effects. At the present time this category of drugs, except for the diuretics, is the most frequently used for treating hypertension. A great advantage of using beta blockers lies in the slow onset of their hypotensive action. In contrast to the adrenergic neuronal blockers, such as guanethidine, propranolol reduces the blood pressure in the lying position and, therefore, does not lead to orthostatic reactions upon standing up or performing exercise. This type of medication is particularly useful in patients who, as a result of their occupation, their age, or the presence of an ischemic vascular disease, are particularly prone to orthostatic hypotensive crises. Of all the antihypertensive agents available, the beta blockers show the least tendency to induce fluid retention and resultant loss of hypertensive activity, probably because they lower plasma renin levels. Consequently, for those patients in whom treatment with diuretics is contraindicated such as those with gout, diabetes mellitus, or hypersensitivity, treatment with beta-blocking substances is probably the safest therapy. However, there are isolated reports regarding fluid retention after beta blockers,[49] a dangerous state for the patient which offsets the antihypertensive action.

There are a great number of beta blockers available. This category of substances can be divided into those of the first generation and those of the second generation. First-generation beta blockers act upon the beta-1 receptors in the myocardium and upon the beta-2 receptors in the smooth muscle of the bronchioles and peripheral vasculature, whereas those of the second generation block mainly the beta-1 receptors and are therefore referred to as cardioselective. The second-generation beta blockers show a 50 times greater affinity for the myocardial beta-1 receptors than for the beta-2 receptors, and so these substances have an antihypertensive action without inducing bronchospasm or peripheral vasoconstriction. Although the cardioselective beta blockers are becoming increasingly popular, their antihypertensive potency is almost identical with the equivalent doses of first-generation beta blockers. In addition to their differing selectivity, the first- and second-generation beta blockers have different degrees of intrinsic sympathomimetic action. From the practical point of view, these differences do not seem to be of any importance with regard to controlling blood pressure. However, this is not true of acebutolol, which possesses both cardioselective and sympathomimetic actions that may be of importance in differential therapeutic considerations (oral and parenteral administration).[50]

The intrinsic sympathomimetic action of most of the other beta blockers is weak in comparison to their antagonistic action, but those drugs with a considerable agonistic action, such as pindolol, definitely do induce a less pronounced fall in heart rate and cardiac output than the others. The difference in membrane-stabilizing function of the various beta blockers is without clinical relevance, since about 1000-fold higher doses are required to pro-

**Table 5.** Pharmacologic Properties of Some Beta Blockers**

| Generic Name | Product Name | Daily Dose (mg) | Potency (propranolol = 1)* | Cardio-selectivity† | ISA‡ | MSA§ |
|---|---|---|---|---|---|---|
| Metoprolol | Lopressor | 50–200 | 1 | + | 0 | 0 |
| Nadolol | Corgard | 80–320 | 1 | 0 | 0 | 0 |
| Pindolol | Visken | 10–30 | 6–8 | 0 | +++ | + |
| Propranolol | Inderal | 80–320 | 1 | 0 | 0 | ++ |
| Penbutolol | Betapressin | 40–80 | 4 | 0 | + | 0 |

*Potency: Propranolol as reference substance is given the value 1.
†Cardioselectivity means preference to $\beta_1$-receptors.
‡ISA = intrinsic sympathicomimetic activity.
§MSA = membrane-stabilizing activity.
**For a more complete list of internationally available beta blockers see also Chaps. 29 and 32.

duce this effect than are generally used in the treatment of hypertension. A list of the different beta blockers and their major features is given in Table 5.

Most beta blockers are closely related structurally to the beta agonist, isoproterenol, and competitively block the peripheral beta receptors of the heart or smooth muscle. The mode of action of beta blockers in lowering blood pressure is attributable to several different actions. There may be a blockade of myocardial beta receptors, which, by reducing heart rate and contractility, decreases cardiac output by about 18%. This effect upon the heart is probably the most important for the antihypertensive action of beta blockers, but a reduction in cardiac output will occur even if blood pressure is not reduced. If the vascular beta receptors are blocked, the vasodilatory component, which is normally caused by circulating epinephrine, is removed so that there is an increase in vascular tone, owing to the unopposed action of the alpha receptors. This initial increase in vessel resistance slowly reverts, and total peripheral resistance returns to values which are normal or slightly below. This effect is possibly crucial for the success of chronic therapy with beta blockers.[51]

There may be a blockage of central beta receptors, most probably in the floor of the fourth ventricle, which leads to bradycardia and vasodepression. Finally, there is a blockage of the renal beta receptors which inhibits the release of renin in response to various stimuli.[52] The renin-suppressing ability of the various beta blockers is quite variable, and the role of renin suppression in lowering blood pressure is disputed. It is the experience of most investigators that the antihypertensive action of the various beta blockers does not correlate with the degree of renin suppression they induce. The clearest correlation between the antihypertensive and renin-suppressing action of beta blockers was obtained by Bühler.[53] Only patients with normal and increased levels of plasma renin initially showed a decrease in arterial blood pressure, and the degree to which the blood pressure fell was closely correlated to the extent to which renin release was suppressed. These findings were confirmed for propranolol, acebutolol, atenolol, oxyprenolol, and alprenolol by the same authors. However, similar results were not obtained by a variety of other investigators who were searching for the same phenomena. In addition, there are several experimental findings which are not consistent with the role of renin suppression in lowering blood pressure. First, renin release is suppressed almost instantly after the administration of many beta blockers, before the antihypertensive action becomes apparent. Second, some beta blockers, such as pindolol, do not suppress renin release at all, and the dose of propranolol needed to maximally suppress renin release is much lower than that required to lower blood pressure. Third, the hemodynamic consequences of suppressed renin secretion should be a decrease in peripheral resistance, whereas beta blockers cause an initial increase in peripheral resistance. Although the experimental results seem to indicate that renin suppression is not necessary for beta blockers to lower blood pressure, one argument still remains: that patients with higher renin values need only small doses of propranolol (160 mg/day) to decrease blood pressure, whereas patients with lower renin values need much higher doses to achieve the same effect (320 mg/day).[123]

In addition to these mechanisms of action, there may be other means by which beta blockers lower blood pressure. Lewis considers the major action of these drugs to be the suppression of efferent impulses to the central nervous system originating in the heart, which leads to a decrease in the sympathetic activity of the heart.[54] Amer proposes that the differing actions of beta blockers are due to a loss of receptor sensitivity after exposure to large quantities of catecholamines.[55] This would also reduce the reactivity of other vasodilators, such as the prostaglandins and histamines; the vasoconstrictive

component would then predominate and blood pressure rise. The beta blockers are then postulated to protect the vascular beta receptors from the catecholamine-induced loss of sensitivity, so that sensitivity is slowly regained, the vasodilatory influence on the vasculature is increased, and blood pressure falls. This theory is attractive conceptually, but the desensitization of the beta receptors by the catecholamines does not take into account the influence of the prostaglandins, and so the major argument is not supported by any experimental evidence.[56]

Finally, beta blockers also interact with central nervous receptors via serotonin, one of the most important central nervous transmitter substances. A long-term therapy with different beta blockers slowly induces a decrease in the activity of the enzymes tyrosine hydroxylase and dopamine beta-hydroxylase, in particular in sympathetic ganglia.[57] To what extent this is clinically relevant cannot be determined at the present time. Following a 3-month period of therapy with the cardioselective beta blocker metoprolol, the basal and stimulated catecholamine values were found to be normal.[58,59] Nevertheless, a reduction in the activity of the sympathetic and central nervous system could play a critical role in the mechanism of action of the beta blockers.

The majority of the side effects associated with beta blockers are attributable to the mode of action of the drugs. These are listed in Table 6 and include bradycardia and cardiac insufficiency, bronchospasm, poor peripheral circulation, and disturbances of the central nervous system. The cardioselective beta blockers, such as acebutolol, atenolol, and metoprolol, have fewer pulmonary side effects than the beta blockers of the first generation. The poor circulation in the periphery is probably the result of alpha-adrenergic vasoconstriction and arises with all beta blockers, both cardioselective and noncardioselective. Patients with cardiac, pulmonary, metabolic, or other diseases which entail the participation of an adrenergic nervous component in the maintenance of normal homeostasis are particularly susceptible to serious side effects with beta blockers.

**Table 6.** Side Effects of Beta Blockers

| |
|---|
| Cardiac insufficiency |
| Bradycardia and hypotension |
| Circulatory disturbances (coldness of the extremities, intermittent claudication, Raynaud's syndrome) |
| Bronchospasm |
| Gastrointestinal disorders (diarrhea) |
| Hypoglycemia |
| Skin irritation |
| Central nervous system disturbances (drams, hallucinations, disturbed sleep) |
| Purpura (thrombocytopenic and nonthrombocytopenic) |

One of the most important side effects that become apparent with beta blockers was completely unexpected, that of the progressive oculomucocutaneous syndrome which developed after administration of practolol. This syndrome is characterized by a skin rash, lesions in the eye, sclerotic peritonitis, and pericarditis. This serious side effect was first noted after the cumulative experience obtained after treatment over a period of 1 million patient-years. At that time practolol was the most commonly prescribed beta blocker in England.[59] This potentially life-threatening side effect is a specific feature of practolol and not of all beta blockers, since this substance is different from all the others in that it contains an acetonilide group, to which some patients develop an immunologic reaction. This syndrome has not been observed with propranolol, after 15 years of use, or with any other beta blocker.

*Propranolol.* Propranolol is still by far the best-investigated beta blocker. Its antihypertensive action was described first by Prichard and Gillam.[60] Of the many investigations which followed, those of Zacharias et al.[69] are worthy of mention, because the findings are representative and the study was conducted on 480 patients observed over a period of 10 years. The average blood pressure values in a group of 221 patients taking an average daily dose of 510 mg of propranolol fell from 192/113 to 143/88 mm Hg after a mean treatment period of 62 months (these high doses are no longer considered necessary). Of these 221 patients who were taking propranolol in combination with diuretics, in 86% the diastolic blood pressure fell to under 100 mm Hg. A further 103 patients required additional medication, and in 79% of them blood pressure was adequately controlled. Working on the premise that this type of medication is not given to patients with obstructive lung disease or cardiac insufficiency and that treatment is started by giving small doses, propranolol is generally a safe drug, which is well tolerated over a long period of time and which does not lose its effectiveness after long-term administration.

However, there have been such serious side effects that treatment had to be discontinued in 10% of patients and a reduction in dosage had to be undertaken in 14.4% of patients. The most important side effects were tiredness, bronchial spasm, coldness of the extremities, digestive disorders, and sleeplessness. Only 3 of 390 patients reported a decrease in libido. Despite the decrease in cardiac output, congestive heart failure occurs only seldom, since

left ventricular work is reduced by a simultaneous fall in systemic arterial pressure.

Some authors recommend giving beta blockers alone, in order to simplify the treatment procedure and to avoid the side effects which diuretics can produce. However, only about one-half of the patients with high blood pressure, who were receiving up to 480 mg of propranolol per day, showed an adequate blood pressure response, and only rarely did patients taking lower doses have diastolic blood pressure values of under 95 mm Hg. The poor response of the older hypertensive patients to beta blockers has been suggested to reflect the low levels of renin commonly found in this group. It is also possible that in older patients the number of beta receptors decreases.[62]

The drug is useful for the treatment of angina pectoris and may provide some protection from this disease and from recurrent cardiac infarction. Such a protective action has also been claimed for other beta blockers.[63,64] Propranolol can, in patients who have just experienced a myocardial infarction, also reduce the symptoms of ischemic injury to the myocardium.[65] However, patients who are receiving continuous treatment with propranolol and who have survived one heart attack are more liable to develop heart failure,[66] and the sudden discontinuance of propranolol treatment in patients with coronary disease can help trigger a heart attack.[67]

Propranolol is, in all probability, completely reabsorbed from the gastrointestinal tract and reaches a peak concentration in plasma after approximately 90 min. However, about 50% to 70% of the dose is extracted and metabolized in its first passage through the liver (first-pass effect), and so the plasma concentrations which result from multiple oral doses may differ extensively.[68] Propranolol and its metabolites are able to inhibit the action of beta agonists for a period of over 24 h, but their excretion proceeds for a longer period of time. The extension of the duration of action which occurs during chronic administration is explainable by a saturation of the hepatic binding site and of the systemic clearance.[69] For mild and moderate hypertension the initial dose should consist of 10 to 40 mg two or three times daily and should be gradually increased over a period of 2 to 3 weeks. For severe hypertension the dosage can be raised more rapidly. The maximal daily dose should not exceed 360 mg, but most patients respond well to doses between 160 and 240 mg. Less frequent doses may also be adequate, since it has been shown that two doses a day are just as effective as four a day, and even that one dose a day is just as effective as two. The metabolism of this form of medication is little affected by renal insufficiency, and, consequently, it can be used freely in patients with renal damage. Its action in pregnancy has been investigated little, but isolated cases of deformity have been described.[70] The drug is secreted in the milk, and so nursing mothers should not take propranolol.

Most of the complications associated with propranolol are shared by all the beta blockers, such as reduction of cardiac output, bradycardia, and bronchospasm. This drug should therefore be prescribed with caution for patients with congestive heart failure, atrioventricular conduction block, or bronchial asthma. Hypoglycemia can lead to dangerous reactions in patients with diabetes mellitus being treated with insulin, possibly as a result of interference with the normal mechanisms that serve to compensate for a rapid fall in blood sugar. Poor peripheral circulation is the most common symptom, whose incidence has been given as 10%.

Unspecific and rarely occurring side effects include disturbances of the central nervous system and the gastrointestinal tract and purpura. Skin rashes have also been described on occasion and, even more rarely, eye complaints.[71]

In some patients treated with propranolol there is a paradoxical increase in blood pressure, which is most probably explained by fluid retention. In 188 patients treated by Drayer et al.,[46] 11% developed an increase in blood pressure of more than 7%. In contrast to the patients who experienced a fall in blood pressure, these patients showed a significant gain in weight, on average by 2.7 kg. Their tendency to gain weight and the resultant increase in blood pressure was associated with an initially low plasma renin, which was not suppressed further during treatment. Patients with normal renin levels who receive propranolol compensate this tendency to fluid retention by a decrease in renin and, therefore, also aldosterone levels, but patients with low initial renin values no longer have this possibility to restrict their fluid retention. If propranolol is to be given alone, one should recall that approximately 30% of hypertensive patients have low renin values. It is therefore advisable to give diuretics initially. In patients treated in this way, fluid retention is much less of a problem, the development of paradoxical hypertension occurs only seldom, and the antihypertensive action of the beta blockers is enhanced. Since a sudden interruption in treatment with propranolol may promote heart attacks, possibly by an increase in the number of beta receptors[73] and an overly strong reaction to endogenous catecholamine release, when this drug is to be discontinued, doses should be tailed off over a period of several days. During emergencies, in particular during surgical intervention,

propranolol should be continued and the anesthetist should be informed that the patient is taking this drug.

*Pindolol.* Pindolol is a beta blocker with an intrinsic sympathomimetic action, which is capable of lowering blood pressure in a large number of cases. A single daily dose of 15 mg was able to reduce blood pressure in 64% of treated patients to within a normal range. The success rate can be raised to 94% in a comparable group of patients if the beta blocker is combined with a diuretic.[74,75]

*Bupranolol.* Bupranolol was synthesized in 1962 and belongs to the group of beta blockers which acts both in the beta-1 and beta-2 receptors, has no sympathomimetic action of its own, and has an additional membrane-stabilizing action. Of all the beta blockers currently available for use, bupranolol shows the highest degree of receptor affinity. Together with some other beta-receptor blockers, such as propranolol, alprenolol, metroprolol, and sotalol, bupranolol is subjected to the first-pass effect in the liver. The metabolites which result, hydroxybupranolol and carboxybupranolol, have been shown to be pharmacologically active. Bupranolol strongly supresses lipolytic activity, inhibits thrombocyte aggregation, and stimulates deaggregation in vitro.

The use of bupranolol is indicated for patients with coronary heart disease, psychosomatic circulatory disturbances, and tachycardial arrhythmia. Ever since Prichard and Gillam demonstrated the blood-pressure–lowering effect of beta-receptor blockers,[60] bupranolol has been used in high doses (over 400 mg/day) to treat hypertension. In numerous studies performed on hypertensive patients who were hospitalized or treated on an outpatient basis, it was shown that the blood-pressure–lowering action develops slowly over a period of 4 to 6 weeks, and so difficulties in adapting to the reduced blood pressure level do not arise. The decrease in blood pressure is equally low when standing or lying. Consequently, orthostatic disturbances do not arise, and existing orthostatic problems may often be improved.[76,77]

***Other Beta Blockers.*** A large number of beta blockers have not yet been discussed; their actions and dosages vary, but they differ little in their effectiveness in reducing blood pressure. Propranolol is most certainly a valued and well-tested substance, but the newer cardioselective beta blockers and the combination of alpha and beta blockers offer more promise for the future.[78] Furthermore, more recent reports have come to the conclusion that a differential therapy with beta blockers has moved into the realm of possibility,[79] particularly with regard to patients with bronchial spasm, who fare better on pindolol than on practolol. The reason for this seems to lie in the diverging behavior of the plasma catecholamines caused by these beta blockers.[80,81] The individual biochemical and hemodynamic characteristics of both beta blockers[82,83] may be linked with the differing alpha-adrenergic reflex activity. Another distinction betweeen noncardioselective and cardioselective beta blockers is related to their different metabolic effects which apparently influence myocardial oxygen consumption thus rendering the former more favorable[124]

## Central adrenergic blocking substances

***Methyldopa.*** Alpha-methyldopa, a close relative of its natural precursor, norepinephrine-dopa, interferes with the biosynthetic pathway in the nerve endings. The alpha-methylnorepinephrine produced there displaces norepinephrine from its stores in both the adrenergic nerve endings and the central nervous system. When this drug was introduced, its site of action was believed to be at the peripheral endings of the adrenergic nerves, where it occupied the receptor site, without inducing arteriolar constriction. More recent investigations, however, increasingly support the assumption that its site of action is more centrally situated.[84]

The enzyme, dopa decarboxylase, is responsible for the transformation of methyldopa to methyldopamine. If the activity of this enzyme is suppressed, the formation of the false transmitter, alpha-methylnorepinephrine,is blocked. If the enzymatic transformation is blocked in the entire organism, there is no reduction in blood flow after methyldopa, but, if the conversion is blocked only outside the brain, there is a reduction in blood pressure. The addition of methyldopa to the cerebrospinal fluid leads to a fall in blood pressure, which can be reversed by the addition to the cerebrospinal fluid of the alpha-receptor blocker, phentolamine. The presence of intact, central adrenergic nerves in the lower brainstem is necessary to induce a hypotensive action with alpha-methyldopa. Methyldopa also possesses a series of characteristics similar to those of clonidine.

The hypotensive action of alpha-methyldopa results from a decrease in total peripheral resistance with a variable but usually insignificant action on stroke volume and heart rate. However, in patients with congestive heart failure who are to a certain extent dependent upon adrenergic stimulation of the heart, methyldopa may further reduce the cardiac

index and stroke volume. Resistance in the renal vasculature is more strongly reduced than in the other vascular beds, and so glomerular filtration rate and renal blood flow are generally increased, or at least maintained, despite the reduction in blood pressure. Blood pressure is lowered to a greater extent in the lying than in the standing position. As a result of the sympathetic nervous blockage by methyldopa, which is considerably less than that of, for instance, guanethidine, orthostatic hypotensive reactions are generally rare. Methyldopa very often induces fluid retention so that its antihypertensive action is diminished.[85] When a diuretic is administered simultaneously, plasma volume may remain slightly elevated, but the decrease in blood pressure is then greater, probably as a result of a further reduction in adrenergic nervous activity leading to a reduction in venous tone, an increase in venous capacity, and a reduction in the venous return to the heart.[86]

For most patients, treatment should be commenced with 250 mg once or twice daily before raising the dose to a maximum of 1 to 2 g (in rare cases to 3 g) daily, given in two or three doses. However, it has been shown that a single dose taken at night is just as effective as the same amount spread over three doses daily. For patients with renal failure the dose should be reduced by one-half and care should be taken to ensure that blood pressure does not drop excessively. This drug can be combined with beta blockers with no problems, thus producing an even stronger antihypertensive action. Blood pressure is generally maximally reduced 4 h after oral administration of alpha-methyldopa, and this blood-pressure–lowering effect can persist for up to 24 h. The effectiveness of alpha-methyldopa in lowering blood pressure has been assessed differently by different investigators. Some authors consider it to be less effective than, for instance, reserpine; others consider it to be just as effective as guanethidine, but statistics from the World Health Organization indicate that it is prescribed more frequently than other drugs for hypertension.

Hypertensive patients with renal insufficiency are particularly responsive to alpha-methyldopa, which is the reason this drug is especially recommended for these patients.[87] Because this substance is excreted in the urine, it was supposed that the reason for its greater effectiveness in patients with renal failure was attributable to a retention of the drug in the systemic circulation because of reduced excretion. However, measurements of the plasma concentrations of unconjugated alpha-methyldopa in normal patients and those with renal insufficiency failed to show any difference between the two, so that the reason for the increased responsiveness during impaired renal function is not yet clear.[88] Alpha-methyldopa can reduce the secretion of renin from the kidney, which explains its particularly favorable action in patients with a high level of plasma renin. However, if renin release is held constant by experimental means, blood pressure still falls, so that a reduction in plasma renin activity may not be decisive in the blood pressure lowering action of methyldopa. Since alpha-methyldopa seldom induces orthostatic reactions and also does not lead to an increase in cardiac output, this drug is particularly recommended for patients with various coronary, cerebral, or vascular complications.[89]

During the first weeks of treatment with alpha-methyldopa there may be some sleepiness, particularly if the daily dose exceeds 500 mg. In addition to the expected orthostosis and fluid retention, there are two other important side effects of alpha-methyldopa. First, there may be an increase in body temperature, accompanied by a disturbance in liver function. The disturbed liver function usually disappears when the drug is discontinued, but there are at least 83 reported cases of serious hepatotoxicity.[90] This medication is therefore probably not suitable for patients who have an existing liver disease. Second, blood shows a positive reaction to the direct Coombs' test in about 20% of the patients, but hemolytic anemia was found only in less than 1% of the patients.[91] Even though some investigators are of the opinion that all patients receiving this treatment should be checked for this complication following at least 6 months of therapy, other authors do not support this view.

Additional side effects are dryness of the mouth, impotence or impaired erection, a diminution of mental alertness, and even dementia during concurrent administration of haloperidol. There may be galactorrhea with an accompanying increase in prolactin release, myocarditis and, on rare occasions, even hypertension as a result of an interaction with phenothiazide or sympathomimetic amines, or as a rebound phenomenon, when the drug is suddenly discontinued. Less frequently, skin allergy reactions may develop. Some additional biochemical parameters may be altered by treatment with methyldopa, such as the red color in the aqueous and butanol phase of the modified Watson-Schwarz test for the determination of porphyrobilinogen.[92] This parameter is used to check the amount of the drug that the patient is receiving. An increase in plasma creatinine and a decrease in vanillic mandelic acid present in urine have also been reported on rare occasions. With regard to alpha-methyldopa and parkinsonism, it should be mentioned that the drug can induce symptoms similar to parkinsonism, possibly through an inhibition of the enzyme decarboxylase, which is necessary for the conversion of dopa to do-

pamine. But patients who are also receiving levodopa treatment may show a better control of blood pressure and an improvement in their parkinsonism.

***Clonidine.*** In many respects clonidine is similar to alpha-methyldopa, but it also shows a number of important distinctions. Although this drug is prescribed frequently, its various side effects probably explain why it is not used even more often. Clonidine is an imidazol derivative. Since it is not a metabolite of any naturally occurring substance, it is easier to follow in the central nervous system and its action is almost certainly confined exclusively to the central nervous system.[93] Clonidine is easily absorbed, the absorption after oral administration varying between 26% and 74%, thus explaining the wide range of the recommended doses, and maximal values are reached in plasma after 1 h. The plasma half-life lies between 6 and 13. Less than 10% of the total dose is incorporated as a false transmitter, the remaining 90% being excreted in the urine as unidentified metabolites.

Clonidine works by stimulating the central alpha-adrenergic alpha-1 and alpha-2 receptors, which reduce the rate in the sympathetic nervous system and thereby lower sympathetic tone. Its action is prevented when the central adrenergic neurons in the brain are destroyed or when alpha-receptor blockers, such as phentolamine, are injected centrally.[94,95] In patients with a severed spinal cord, blood pressure does not fall after administration of clonidine, which demonstrates the dependence of its antihypertensive action upon the intactness of descending, bulbospinal neurons.[96]

The hemodynamic actions of clonidine include a decrease in basal heart rate and cardiac output, with an almost normal response upon increased demand. There is a decrease in peripheral resistance, renal blood flow is maintained, and renin secretion is suppressed.[125] Renin suppression is not essential to the action of clonidine but can be useful for inducing an immediate drop in blood pressure in patients with high renin levels.[97] Since the reduction in sympathetic activity results from a central action of the drug and does not involve any neurotransmission, beta blockade, or direct arteriolar vasodilation, there is almost no incidence of orthostatic reactions. Clonidine itself leads, as do almost all antihypertensive adrenergic blockers, to fluid retention, and so the administration of a diuretic is recommended.[98] When diuretics are given simultaneously, 80% of patients experience a significant hypotensive response, which can be maintained almost indefinitely. Even severe forms of hypertension can be kept under control with this drug.[99]

When clonidine is given orally, blood pressure starts to fall within 30 min and the full effect is apparent after 2 to 4 h. The duration of action lies between 12 and 24 h. The initial dose should be about 0.1 mg twice daily and the maximal dose lies at 2.4 mg/day. The major part or even all of this dose can be taken at night before going to bed, in order to make use of the sedating effect. The antihypertensive action of 0.15 mg of clonidine is comparable to that of 250 mg of alpha-methyldopa. When clonidine is given intramuscularly, its action starts within 5 min, reaches a maximum after 75 min, and continues for approximately 5 h. When given intravenously, there is an almost immediate fall in blood pressure, which may persist for up to 24 h. If injected too quickly, there may be a short-lived hypertensive reaction, caused by an initial peripheral stimulation of the alpha receptors. This can be prevented by giving phentolamine beforehand.

The most important and commonest side effects of clonidine are tiredness and dryness of the mouth due to a reduction in saliva production. These also result from a central action. The dryness of the mouth can be improved by giving 2 drops of pilocarpine (1 g per 100 ml) in water three times daily. These symptoms generally start to disappear after a few months, and most patients are not bothered by these side effects 6 months after beginning the therapy. Clonidine does not induce the same hepatic and hematologic alterations as often accompany treatment with alpha-methyldopa. Impotence is a less frequent problem.

If the drug is suddenly discontinued, blood pressure can rise to its initial value within 24 h, possibly because of the short half-life of this substance in plasma. Only seldom is there a rebound or withdrawal syndrome, which is accompanied by headaches, tremor, overexcitability, and restlessness. Even rarer is the occurrence of blood pressure values in excess of those measured before the onset of therapy. Occasionally, 48 to 60 h after discontinuation of clonidine, a rebound phenomenon may be observed. This phenomenon can be unpleasant for patients who forget to take their tablets and dangerous for patients who are about to be subjected to anesthesia or surgery. The intravenous or intramuscular administration of clonidine is indicated in these cases.

The rebound phenomenon, although more frequent after clonidine, seems to occur also with all other antihypertensive, adrenergic blockers and possibly reflects a rapid return of the catecholamine secretion, which was suppressed during therapy. This syndrome can be treated by renewed administration of clonidine or by giving a combination of alpha and beta blockers. The combination preparation, labetolol, is particularly useful for this purpose.[100] A newly developed substance in this group,

guanfacine, may prove to have fewer side effects.[101] Of the many clonidine derivatives, tiamenidin (Hoe 440) deserves mention, for it is claimed to have much less sedative action. A further development in clonidine derivatives for the treatment of hypertension is the substance B-HT 933, which has been produced from the antitussive compound.[102]

In some patients a fall in blood pressure does not occur with clonidine. This is possibly due to a stimulation of the peripheral alpha-adrenergic receptors, which leads to a vasoconstriction. In a similar manner, a hefty overdose of clonidine also leads to an increase in blood pressure. Possibly the antagonism between clonidine and the beta blocker sotalol results from a similar phenomenon.[103] The antihypertensive effect of clonidine may also be absent during concomitant administration of tricyclic antidepressives and tranquilizers. In contrast to alpha-methyldopa and reserpine, clonidine does not lead to an increase in serum prolactin levels.

## Vasodilators

When the action of a diuretic and a peripheral or central adrenergic blocker is not sufficient to lower blood pressure, the third stage in therapy is the use of a vasodilator.

The vasodilators presently available and those still being clinically tested are quite variable in their strength, duration of action, and degree of influence on the arteries, veins, and heart.[104] The mode of action of all these substances rests upon their interference with the movement of calcium into the smooth-muscle cells, which is responsible for the initiation and maintenance of smooth-muscle contraction. The action potential in the muscle membrane initiates the release of calcium from the intracellular vesicles into the sarcoplasm, where it activates the actinomyosin ATPase and induces muscle contraction. When less calcium is released into the sarcoplasm, the strength of contraction is diminished.[105]

Peripheral vasodilation is a highly appropriate way to treat hypertension, since the primary defect is usually an increase in peripheral vascular tone.[106] Until recently the application of vasodilators was limited by the simultaneous activation of compensatory, cardiostimulating, sympathetic reflexes which resulted. In addition, there was an increase in renin release, which promoted fluid retention. By giving adrenergic blockers and diuretics at the same time, vasodilators could be given in higher doses with fewer side effects and greater potency. At present, the combination of a vasodilator with an adrenergic blocker and a diuretic is the most favored treatment for a moderate or severe hypertension.

### Hydralazine/dihydralazine

Of the various phthalazine derivatives with a hypotensive action, dihydralazine* is the most often used. This drug acts predominantly by relaxing the smooth-muscle cells in the walls of the peripheral arterioles, therefore mainly the resistance and not the capacitance vessels. This induces a reduction in peripheral resistance and a lowering of blood pressure.[107] The action of this drug is not the same in all vascular beds; blood flow is increased in the splanchnic, coronary, cerebral, and renal vessels, whereas it remains unaltered in skeletal muscle and skin vessels.[51] Concurrent with the dilatation of the peripheral vessels, there is an increase in heart rate, stroke volume, cardiac output, and myocardial oxygen consumption. Most of these reactions reflect a receptor-induced reflex increase in sympathetic activity, although a direct action of the central nervous system may also be involved.[108] Despite the fact that a certain tolerance of these symptoms develops over a period of time, they can restrict the use of dihydralazine alone and even in combination with diuretics.

Dihydralazine is absorbed well from the gastrointestinal tract and reaches maximal concentration in plasma after about 1 h. The half-life in plasma is about 2 to 3 h, but its action may persist for 24 h, and it may, possibly, remain in the walls of the smooth-muscle cells for even longer.[109] A portion of the dosage is acetylated before excretion. It has been shown that in patients who develop a lupus-type toxicity to the drug, the rate of acetylation is lower, and so they are exposed to the drug longer.[110] In patients with a reduction in renal function, the plasma half-life is most often prolonged, probably as a result of a reduced renal clearance and a decrease in metabolic turnover. The metabolites themselves are probably responsible for the prolonged hypotensive action.

Irrespective of whether given alone or in combination with other medication, 25 mg of dihydralazine should be given twice daily, although some authors recommend giving three or four doses a day; the difference in antihypertensive effect is small. The maximal dose should not exceed 75 mg/day, for at higher doses a lupus-type syndrome of a hypertensive sort or of an induced or activated systemic lupus erythematosus can develop in up to 10% of patients.[109] Even though this complaint is reversible upon withdrawal of medication, it is to be recommended that patients with a slow rate of acetylation be given doses of only 25 or even 12.5 mg/day. The mean reduction in blood pressure achieved by 25 mg of dihydralazine a day given together with a thiazide diuretic is very modest. If, however, 0.25 mg of re-

*In the United States only hydralazine is available.

serpine is given twice daily in addition, the hypotensive effect of the three substances is enhanced. Furthermore, the unpleasant cardiac side effects of dihydralazine can be neutralized by the adrenergic blocking action of reserpine.

Recently, the beta-adrenergic blocker propranolol has been combined with dihydralazine for the treatment of moderately severe hypertension. The results have shown that patients whose blood pressure could not be well controlled with diuretics, with methyldopa, or with guanethidine showed a greater decrease in blood pressure on an average dose of 160 mg of propranolol and 25 mg of dihydralazine than with any of the other substances. The mean fall in blood pressure was 44/31 mm Hg, whereby the diastolic pressure fell to less than 90 mm Hg in 17 of the 23 patients.[111] Another reason for combining adrenergic blockers with peripheral vasodilators is that dihydralazine produces an increase in plasma renin levels, possibly through a reflex stimulation of the sympathetic nervous system, which could offset its blood-pressure–lowering action, while the adrenergic blockers suppress renin secretion. A further reason to prescribe vasodilators in conjunction with propanolol is that, when vasodilators are given alone, reflex tachycardia with increased myocardial activity may often result. The concurrent administration of a beta blocker prevents this undesirable side effect of increasing cardiac output, which not only is unpleasant for the patient but also reduces the antihypertensive action of the vasodilator.

In most of the patients receiving dihydralazine alone, there is a temporary period of headaches and sweating spells, resulting from a reflex stimulation of the heart. More serious, however, are the already-mentioned toxic reactions. Studies, extending over a 20-year period, have shown that 12% to 15% of the patients developed signs of toxic reactions (serum sickness). Since these symptoms invariably disappeared after the treatment was stopped, the very rarely occurring late toxicity is found only in patients who inactivate the drug slowly. The remission of these symptoms occurs more frequently in severe hypertensives, and survival in patients who develop toxicity to the drug may be increased.[112] Other side effects include anorexia, queasiness, vomiting, diarrhea and, rarely, paresthesia, tremor, and muscular cramps. The medication should be given with caution to patients with coronary heart disease and should be avoided in patients with a dissected aortic aneurysm or a recent cerebral hemorrhage, since it produces an increase in cardiac output and cerebral blood flow. Great care should be exercised when prescribing dihydralazine together with parenteral diazoxide since this combination of drugs can lead to a considerable hypotension.

### Minoxidil

Extensive experience with this drug has shown that it is a very potent and long-acting vasodilator. When given alone, this substance induces considerable side effects (sodium retention with weight gain, tachycardia, hirsutism), and so the combination with a diuretic and a beta blocker is always indicated. Minoxidil has not yet been released for general use.[113]

### Nitroprusside and diazoxide

These drugs are used during hypertensive crises as a means of lowering blood pressure actuely.

### Converting Enzyme Inhibitors

A more recent approach to the treatment of hypertension has resulted from the possibility of influencing the concentration of circulating and possibly tissue-bound angiotensin II, one of the most important vasoconstrictory agents. With the aid of orally administered converting enzyme inhibitors, which block the conversion of angiotensin I to angiotensin II, it has been possible in many cases of severe hypertension (both renin-dependent and renin-independent forms) to lower blood pressure considerably. The well-known converting enzyme inhibitor captopril (Capoten®) has a strong antihypertensive action which is largely attributable to a decrease in peripheral resistance. Captopril is given in doses of 25 to 450 mg/day alone or, if it fails to produce the desired effect, in conjunction with a diuretic. Orthostatic side effects may result. Further side effects are mostly reversible and include skin rashes, loss of taste, proteinuria (possibly with nephritis-like symptoms), and bone marrow depression. Other converting enzyme inhibitors (i.e., MK 421), still in the developmental stage, are expected to produce fewer side effects.[114,115]

### Calcium Antagonists

A promising development is the increasing availability of calcium antagonists (verapamil, nifedipine, diltiazem) which can be employed for treatment of mild to moderate hypertension and also in hypertensive emergencies.[126]

## Selection of Antihypertensive Medication and Initiation of Treatment

With the drugs currently available it is possible to control blood pressure adequately in almost every patient, provided they are used correctly and the

**Table 7.** Commonly Used Antihypertensive Agents For Long-Term Oral Therapy

| Generic Name | Product Name* | Daily Dose (mg) | No. of Doses per Day | Important Clinical and Biochemical Parameters Which Must Be Checked |
|---|---|---|---|---|
| Hydrochlorothiazide | Esidrix | 50–100 | 1–2 | Potassium, calcium, urea, glucose |
| Chlorthalidone | Hygroton | 25–100 | 1 | Potassium, calcium, urea, glucose |
| Furosemide | Lasix | 40–200 | 1 | Potassium, calcium, urea, glucose |
| Etozolin† | Elkapin | 200–400 | 1–2 | Potassium, calcium, urea, glucose |
| Spironolacotone | Aldactone, Osyrol | 25–400 | 2–3 | Hyperkalemia, gynecomastia |
| Triamterene | Dyrenium | 100–200 | 1–2 | Hyperkalemia |
| Amiloride† | Arumil | 5–10 | 1–2 | Hyperkalemia |
| Reserpine | Serpasil | 0.10–0.25 | 1 | Depression, rhinitis sicca |
| Guanethidine | Ismelin | 10–20 | 1 | Orthostasis, impotence, diarrhea |
| Alpha-methyldopa | Aldomet | 500–3000 | 1–3 | Sedation, liver and blood disturbances |
| Clonidine | Catapres | 0.1–0.3 | 1–2 | Dryness of the mouth, sedation, rebound phenomenon |
| Prazosin | Minipress | 1–20 | 2–3 | Syncope, headache, sedation, dizziness |
| Propranolol | Inderal | 40–640 | 2–3 | Myocardial depression, bradycardia, bronchial asthma, peripheral vasospasm |
| Hydralazine | Apresoline | 75–200 | 2–3 | Tachycardia, headache, lupus erythematosus |

*The product name given here is only one of a number of possible choices.
†Currently not available in the United States.
‡Propranolol listed as prototype of the available beta blockers. (See also Table 5.)

patient is cooperative. A list of the more commonly employed antihypertensive agents, their commercial names, and dosages is given in Table 7. It is obviously very difficult to give a simple method for treating all hypertensive patients. Treatment should be selected according to the severity of the hypertension, the patient's age, race, psychological state, and willingness to take medication. By considering the pharmacologic characteristics of the various types of medication, it is possible both to control the hypertension and to take into account the needs and wishes of the patient. General guidelines for the choice of medication for the different categories of patients with essential hypertension are given in Table 8.

There are numerous preparations combining two or more types of medication. Although many physicians have hesitated to prescribe such combination preparations because the content of the individual components is fixed, experience with these preparations has justified their use. Despite the existence of some combination preparations which are not useful, most are tailored to the needs of the patient

larly true for the combination of diuretics with beta-receptor blockers.[75] Furthermore, the availability of such fixed pharmaceutical preparations has been the subject of a series of conferences[116] with the sole objective of increasing patient cooperation by simplifying the treatment procedures.[117] The criteria which must be fulfilled by the combination prepa- and can be used without misgiving. This is particu- most important requirement is the confirmation that the individual components are active pharmacologically, as has been shown for the two-preparation combinations (e.g., Nortensin) and for the three-preparation combinations (e.g., Briserin[119]).

Some patients have accompanying symptoms or diseases which influence the choice of medication. A list of complaints which commonly accompany the hypertensive disease and for which some types of medication are contraindicated is given in Table 9.

**Table 8.** Choice of Antihypertensive Medication

1. Standard therapy for most patients with diastolic blood pressure under 120 mm Hg and no organ involvement
   a. Diuretic therapy: Thiazide or similar diuretics for 1–4 weeks; for hypokalemia use potassium-sparing diuretic or potassium substitution; with diabetes mellitus which threatens to get out of control, discontinue diuretic therapy
   b. Diuretic and beta blocker
   c. Diuretic and prazosin
   d. Diuretic and alpha-methyldopa
   e. Diuretic and clonidine
   f. Diuretic and reserpine (0.25 mg once daily)
   g. Diuretic with reserpine and dihydralazine (25–75 mg daily, given as 1–3 doses)
   h. Diuretic and angiotensin converting enzyme inhibitor
   i. Diuretic and calcium antagonist
2. Therapy for diastolic blood pressure over 120 mm Hg without organ involvement
   a. Diuretic and beta blocker
   b. Diuretic with beta blocker and dihydralazine or prazosin
   c. Diuretic with beta blocker and clonidine or guanfacine
   d. Diuretic and guanethidine
   e. Diuretic and converting enzyme inhibitor (irrespective of systolic or diastolic blood pressure)
3. Therapy for organ involvement
   a. Cerebrovascular involvement
      (1) Diuretic and reserpine
      (2) Diuretic and alpha-methyldopa
      (3) Diuretic and beta blocker
   b. Coronary heart disease
      (1) Diuretic with cardioselective beta blocker/calcium antagonist*
      (2) Diuretic with alpha-methyldopa and clonidine
   c. Renal insufficiency
      (1) Diuretic
      (2) Diuretic with dihydralazine and beta blocker
      (3) Diuretic and alpha-methyldopa
4. Therapy for geriatric systolic hypertension
   a. Diuretic
   b. Diuretic and prazosin
   c. Diuretic and reserpine
   d. Diuretic and alpha-methyldopa or clonidine
   e. Diuretic and beta blocker

*Beware of combining beta blockers with the calcium antagonist verapamil.

Once it has been decided which form of therapy is to be used and treatment is to be started, the following factors should be taken into account:

1. Patients should be informed that the treatment may induce specific and general side effects, particularly during the first month of significant blood pressure reduction.

**Table 9.** Accompanying Diseases Which Influence the Choice of Antihypertensive Therapy

| Accompanying Disease or Symptom | Antihypertensive Drugs Which Are Contraindicated |
|---|---|
| Asthma | Beta blockers of the first generation |
| Tendency to orthostatic reaction | Guanethidine, prazosin, converting enzyme inhibitor |
| Cerebrovascular disease | Guanethidine, dihydralazine |
| Collagen disease | Dihydralazine* |
| Cardiac insufficiency | Beta blockers |
| Coronary heart disease | Guanethidine, dihydralazine |
| Diabetes mellitus | Diuretics, beta blockers |
| Gout | Diuretics |
| Hyperkalemia | Spironolactone, triamterene, almiloride |
| Hypokalemia | Thiazides, furosemide |
| Liver disease | Alpha-methyldopa |
| Psychological depression | Reserpine, guanethidine, alpha-methyldopa |
| Migraine | Dihydralazine* |
| Gastric and duodenal ulcers | Reserpine |
| Renal insufficiency | Spironolactone |

*In the U.S. only Hydralazine is available.

2. Unpleasant side effects should, as far as possible, lead to a change of medication. It is well known that even under the most favorable circumstances patients tend to discontinue taking their medication. Therefore, it is unrealistic to suppose that they will continue treatment when side effects arise and they do not feel well.
3. Different types of medication should be introduced in succession, in order to be able to assess the effectiveness of the drugs and pinpoint these responsible for side effects.

**Table 10.** Predisposing Factors and Dangers of a Hypertensive Emergency

Predisposing factors
1. Malignant hypertension
2. Encephalopathy
3. Acute or chronic glomerulonephritis
4. Pheochromocytoma
5. Discontinuing clonidine therapy

Dangers of a hypertensive crisis
1. Central nervous system complications (cerebral hemorrhage)
2. Acute left heart failure with pulmonary edema
3. Acute dissected aortic aneurysm
4. Postoperative bleeding following cardiac vascular surgery.

**Table 11.** Therapy in Hypertensive Emergencies

| Generic Name | Product Name | Dose | | Time Course of Action | | | | Site of Action |
|---|---|---|---|---|---|---|---|---|
| | | iv (mg) | im (mg) | Interval (h) | Onset (min) | Peak (min) | Duration (min) | |
| 1. Clonidine | Catapresan | 0.15–0.30 (injected slowly or infused) | 0.15–0.30 | 3–4 | 10–20 | 120–180 | 60–240 | Central |
| 2. Hydralazine† | Apresoline | 12.5–25 | 10–15 | 1–2 | 10–30 | 20–40 | 180–480 | Direct arteriolar dilation |
| 3. Diazoxide† | Hyperstat | 100–600 (5 mg/kg; bolus) | | 4–5 | 3–5 | 120–180 | 5–10 | Direct arteriolar dilation |
| 4. Phentolamine | Regitine | 5–10 | 10–20 | | 1–3 | 3–5 | 2–4 | Arteriolar dilation through alpha-receptor blockage, direct action |
| 5. Nitroprusside‡ | Nipride | 0.03–0.05 mg/min | | | 0.5–1.0 | 1–2 | | Direct dilation of arterioles and veins |
| 6. Hemodialysis | | | | | | | | |

*Abbreviations and symbols: HR = heart rate; CO = cardiac output; TPR = total peripheral vascular resistance; Contr = contractility; ↓, decreased; ↑, increased; —, unchanged.
†Advisable to add furosemide.
‡Only by iv drip and only for hospitalized patients.
Note: Calcium antagonists (i.e., nifedipine, diltiazem) are reportedly extremely effective in treating hypertensive emergencies. Further data to confirm these early observations are necessary.

| Hemodynamic Profile* | | | | | | | |
|---|---|---|---|---|---|---|---|
| HR | CO | TPR | Contr | Relevant Side Effects | Antidote | Indications | Care Required or Contraindications |
| ↓ | ↓ | — | (↓) | Sedation, short-term rise in blood pressure, rebound phenomenon on discontinuance | Tolazoline (Priscoline) | Every hypertensive crisis | Congestive heart failure (because of initial rise in blood pressure) |
| ↑ | ↑ | ↓ | ↑ | Tachycardia, aggravation of angina pectoris, headache, erythema, queasiness, fluid retention | | Malignant hypertension, acute hypertensive encephalopathy, postoperatively, acute left heart failure | Acute left heart failure, aortic dissection, diabetes mellitus, postoperative bleeding |
| ↑ | ↑ | ↓ | ↑ | Hyperglycemia, queasiness, vomiting, tachycardia, chest pains, fluid retention, extrapyramidal symptoms, orthostasis | Norepinephrine, angiotensin | Malignant hypertension, acute hypertensive encephalopathy, postoperatively, acute left heart failure | Cerebral hemorrhage, coronary insufficiency, aortic dissection, diabetes mellitus, postoperative bleeding |
| ↑ | ↑ | ↓ | — | Tachycardia, sickness, severe hypotension | Beta blockers | Hypertensive crisis of pheochromocytoma, MAO inhibition, clonidine withdrawal | Severe hypertension with volume deficiency |
| ↑ | ↓ | ↓ | — | Thiocyanate intoxication, muscular pains, vomiting, excitability | Sodium thiosulfate | Acute hypertensive encephalopathy, hypertensive crisis with MAO inhibition, acute left heart failure, cerebral hemorrhage, postoperatively | Rare hypotensive reactions may occur |

4. With a mild or moderate hypertension, treatment should be started by giving a diuretic first, before progressing to other medication.
5. With severe hypertension, treatment should be initiated by prescribing a diuretic plus a second form of medication.
6. When an adequate fall in blood pressure is obtained, an attempt should be made to maintain the patient on the lowest possible dose and to slowly reduce the amount of medication taken.
7. Some of the reasons for poor control of blood pressure are the interference of other types of medication (e.g., oral contraceptives), an unfavorable or incorrect sequence of taking the different drugs, or fluid retention as a result of inadequate treatment with diuretics or excessive salt consumption.
8. In some patients blood pressure is lower at home than in the physician's office. This can result from the anxiety associated with the examination (anticipation hypertension). If, on the basis of these falsely high values, the dose of antihypertensive drug is increased too drastically, orthostatic reactions may result. Blood pressure should, therefore, be measured as frequently as possible, preferably by a nurse at home, by the patient himself or by a member of the family.

## Hypertensive Emergency and Its Treatment

Malignant hypertension and hypertensive crisis with encephalopathy are two distinct pathophysiologic entities. Malignant hypertension is characterized by a continually raised blood pressure with diastolic values between 120 and 130 mm Hg, characteristic retinal changes (fundus hypertonicus III–IV), indications of a rapidly progressing reduction in renal function, and a decline in the general state of health, if effective therapy is not given in time. There is always an increase in the activity of the renin-angiotensin-aldosterone system, there is hypokalemia, and often hyponatremia, possibly as a result of the decrease in cardiac output.

A hypertensive crisis, however, is characterized by a suddenly occurring steep rise in both diastolic and systolic blood pressure and symptoms originating from the central nervous system in the form of a high-pressure encephalopathy, resulting from cerebral edema. There is a consistent occurrence of tachycardia, sweating, headache, dizziness, ringing of the ears, aphasia, disturbed vision, confusion, paresis, partial loss of consciousness, cramps, angina pectoris, and breathlessness. This emergency situation with an acute rise in blood pressure may result from an essential, mostly malignant hypertension, or from any of the forms of secondary hypertension, such as pheochromocytoma, toxemia of pregnancy, acute renal infection, and acute renal failure. More rarely, the blood pressure crisis may develop from intoxication with thallium, lead, carbon monoxide, or nicotine or after severe psychological stress. These hypertensive crises can occur under a variety of different clinical circumstances. They rarely develop in patients whose blood pressure has been normalized and who have acute glomerulonephritis, eclampsia, collagenous disease, or concussion. More frequently they develop as a complication of the accelerated or untreated phase of badly controlled chronic hypertension of differing etiologies. The major characteristics are a necrotic arteriolitis, arteriolar spasm and organ damage, such as heart failure, renal failure, encephalopathy, or neuroretinitis. An abrupt increase in blood pressure may also result from pheochromocytoma or the release of catecholamines from the tissues by drugs or various foods in patients treated with monamine oxidase inhibitors.

A number of other situations can also be counted as hypertensive crises, not as much according to the extent to which blood pressure is raised but rather according to the complications which may arise as a result of even a moderate increase in blood pressure. These include dissected aortic aneurysm, cerebral bleeding, and acute cardiac failure. A summary of the situations under which a hypertensive emergency situation may arise and the dangers associated with it is given in Table 10.

Although it is possible, in theory, to bring most cases of hypertensive crisis under control by oral administration of medication, it may take weeks or even months to obtain the right dose and combination of antihypertensive agents which lower blood pressure adequately. Sudden and dramatic increases in blood pressure require an immediate lowering in order to avoid serious and possibly lethal consequences. Two concepts form the basis of controlling a hypertensive crisis.

First, the immediate and intensive therapy of the crisis has absolute priority over time-consuming diagnostic procedures. Because of the rapid rate of progression of vascular disease, the reversibility of vascular damage depends entirely upon the speed with which an effective therapy is achieved.

Second, those antihypertensive agents should be used whose blood-pressure–lowering, hemodynamic, and metabolic effects are immediately apparent, in order to overcome the crisis situation quickly, and differential therapeutic considerations should be

utilized to decide which drugs are most useful in each individual situation. The pharmacologic and therapeutic properties of the presently available drugs and the indications and contraindications for their use and their hemodynamic actions are listed in Table 11.

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# Resistant Hypertension

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## Definition

The problem of resistant hypertension is peculiar in that its magnitude depends in great part on its definition. If the term is taken to mean severe hypertension resistant to modern antihypertensive therapy, the problem is restricted to relatively small numbers of patients. However, if the term refers to patients whose blood pressure is not normalized by treatment, then resistant hypertension is a common and probably growing problem. The paradox of a seeming increase in resistant hypertension despite the greater number of effective drugs can be explained by many factors, including the increase in the total number of patients undergoing treatment and the greater sensitivity to the need for optimal blood pressure control. Given the importance of hypertension as a risk factor for heart failure, myocardial infarction, and strokes, the broader definition of "resistance to treatment" seems the more appropriate.

Clinical experience has demonstrated that in the vast majority of cases so-called resistance to antihypertensive drug therapy is more apparent than real. Truly resistant hypertension is defined as blood pressure that cannot be adequately controlled with a suitable triple-therapy regimen (Table 1), provided that the medications are taken as prescribed. This refractory condition is less common than is poor blood pressure control due to poor compliance or to inadequately planned antihypertensive therapy. Resistance to treatment can, therefore, be classified as either "true" when blood pressure remains high despite adequate treatment or "false" when poor control is due to misjudgments or misunderstandings from patient or physician. Given the wide range of pressor influences that may affect a patient's response to medication, differentiating true from false resistance could be difficult, but in most cases the distinction can be made without recourse to elaborate diagnostic procedures, by screening out the major causes of pseudoresistant hypertension (Table 2). The more common (and commonly overlooked) of these are noncompliance and excess salt intake on the part of the patient and inadequate dosage or choice of medication or combination on the part of the physician.

Many of the diagnostic and therapeutic problems of so-called "resistant hypertension" are similar to those encountered in the first approach to and follow-up of patients with the more usual forms of hypertension. The same care and general principles apply in measuring blood pressure, in assessing the meaning of an elevated reading, and in deciding the need for special investigations as well as in discussing long-term therapy with anxious or unconvinced patients. The main differences stem from the emphasis on some factors, possibly from the greater yield from investigations, and from the particular problems in approaching a patient who has heard similar arguments before. In contrast with the basic approach to patients with newly discovered hypertension and stepped-care therapy for them, the approach to patients with "resistant hypertension" has not yet been charted in detail. This is possibly because it is a "second generation" problem in hypertension—if detection, follow-up, and proof of efficacy of treatment are considered "first generation" questions. Although some general principles have been developed, much still needs to be elucidated in order to deal with the scientific, human, and practical problems of resistant hypertension.

**Table 1.** Minimal Regimens* that Should Be Tried Before Labeling a Patient's Hypertension Resistant

| |
|---|
| Regimen 1 |
| 1. Oral diuretic (equivalent to 1.0 g of chlorothiazide, 100 mg of hydrochlorothiazide, 10 mg of bendroflumethiazide or metolazone, or 100 mg of chlorthalidone)† |
| 2. Sympathetic depressant (propranolol, 320 mg, or methyldopa, 2.0 g) |
| 3. Vasodilator (hydralazine, 300 mg) |
| Regimen 2 |
| 1. Oral diuretic as above |
| 2. Sympathetic depressant as above |
| 3. Guanethidine, 100 mg |

*Values refer to daily doses.
†Furosemide in doses of at least 160 mg daily must be used when renal failure is present (creatinine clearance < 25 ml/min).
From Gifford and Tarazi, ref. 4.

Resistance in hypertension could be classified as primary or secondary. "Primary resistance" is applied to those conditions in which hypertension was never well controlled from the time it was diagnosed. Cases in which, after an initial good response, blood pressure rose again despite continuation of therapy fall under "secondary resistance". This subdivision might help orient the diagnostic approach, but many of the same factors could lead to either primary or secondary resistance.

**Table 2.** Resistant Hypertension

| |
|---|
| 1. Lack of compliance with therapy |
| 2. Drug effectiveness reduced by |
| a. Doses too small |
| b. Infrequent administration |
| c. Interfering factor |
| (1) Excess salt |
| (2) Drug Interaction |
| 3. Office hypertension |
| 4. Specific pressor mechanism interfering with "standard" treatment |
| a. Related to primary disease, for example, pheochromocytoma, volume-dependent hypertension |
| b. Compensatory reaction to antihypertensive agent |
| (1) Secondary aldosteronism of diuretics |
| (2) Fluid retention of sympathetic inhibitors |
| (3) Hyperkinetic circulation, high PRA, and fluid retention of vasodilators |
| c. Complication of long-standing hypertension |
| (1) Atherosclerotic renal arterial disease |
| (2) Adrenal hyperplasia |
| (3) Advancing nephrosclerosis |

From Tarazi, ref 9.

## Causes of Poor Blood Pressure Control

### Problems in Blood Pressure Determinations

I. H. Page has repeatedly emphasized the many errors that can be made during the simple clinical maneuver of recording a blood pressure[7]—the fact that it is a simple, frequently repeated, seemingly easy procedure does *not* reduce but may indeed enhance the chances of error. Brilliant pharmacology or astute psychology can do little if the basic determination for diagnosis is erroneous. Normotensive subjects can be wrongly labeled hypertensive, and hypertensive patients called resistant to treatment, on the basis of poor blood pressure records. Using a wrong-sized cuff for an obese person may produce falsely elevated readings. The same result has been observed in arteriosclerotic patients whose arteries are so heavily calcified that they resist compression by the cuff.

More frequent and difficult to deal with is the problem of "office hypertension." This problem of patients who show abnormal pressor responses to office examinations is more widespread and more complicated than is generally supposed. The diagnosis in patients already labeled resistant to treatment is often missed, sometimes by experienced internists, because it may present no obvious alerting signs and because of the difficulty in challenging an established diagnosis of hypertension. Studies at the Cleveland Clinic showed that the office blood pressure readings of some patients were consistently higher—sometimes by as much as 30 or 40 mm Hg—than home readings. Although office hypertension has been generally associated with anxiety, physical evidence of emotional stress may not be apparent. A rapid pulse rate is not always present, and the patient may exhibit none of the stereotypic signs of anxiety. It could also be that marked increases of blood pressure in adolescents during a test were not necessarily associated with a high cardiac output. In our experience, beta-adrenergic blockade had no significant effect on office hypertension, although it effectively prevents stress-related tachycardia.

Final diagnosis will depend on the demonstration of significant, reproducible differences in blood pressure levels between reliable home and office readings. Occasionally, continuous intra-arterial recordings for 12 to 24 h might be needed. However, the more important clinical step is to consider this possibility in patients "not responding to treatment." A marked disparity between arterial blood pressure and target-organ effects may provide a good clue. If a patient who is seen month after month, year after year, persists in having very high pressure levels but normal heart, eye grounds, and

renal function, then a diagnosis of office hypertension should be strongly suspected. The simplest approach, then, would be to have the patient or a relative measure the blood pressure regularly at home.

### Compliance with Therapy

The problem of noncompliance, though widely discussed in the literature on hypertension, is often minimized under the pressures of daily practice. Superficial questioning or routine admonitions are not adequate to evaluate it, and noncompliance no doubt accounts for many instances of "false resistance." Failure to obey a prescribed regimen may be due to many factors, not all of which are necessarily attributable to mistakes, carelessness, or psychological problems of the patient. These certainly occur, and some subjects have a natural aversion to pill taking. However, the fault in many cases lies in a needlessly complex schedule of treatment, in imprecise or hurried instructions, or in lack of information and sympathetic discussions about the nature of hypertension and the constraints of its treatment.

Frequent changes in medication are rarely compatible with maintained optimal blood pressure control. Symptoms can develop from any pill—even placebos.[1] It is tempting to ascribe any discomfort or sexual failing to drugs, and to switch, discontinue, or reduce doses to ineffective levels. On the other hand, noncompliance is not solved by stern or threatening lectures. Success in dealing with this problem depends largely on the physician's ability to develop a warm, supportive relationship—one in which the patient feels comfortable enough to ask questions and express anxieties. The first and all-important step in building such a relationship is to allow adequate time for full discussion of the patient's concerns. This relationship is more important, in my opinion, in assessing and securing compliance than pill counting or biochemical tests, useful as the latter are in investigational studies. Determination of blood levels or of urinary excretion rates is now possible for many drugs; this may help in problem cases to differentiate poor absorption or abnormally rapid elimination from noncompliance.

Although not usually included under this heading, regulation of *salt intake* is best considered here because it is involved in many of the problems of compliance with therapeutic regimens. Curtailment of dietary salt, once a cornerstone of antihypertensive therapy, has been decreasingly stressed by most physicians because of the effectiveness of diuretics in maintaining a negative salt and water balance. In the process, however, an important aspect was overlooked, namely, that large amounts of ingested salt (above 15g/day) can override the antihypertensive effectiveness of diuretics and interfere with the hypotensive effects of most other agents. Taking a dietary history could be very helpful but may still be inconclusive because many patients are unaware of the magnitude of their sodium intake since a good part of it is not tasted as salt but comes from preserved food or commercially prepared drinks. The most accurate diagnostic index is a determination of the 24-h urinary sodium excretion; if greater than 150 mEq, it suggests excess salt intake. For effective dietary control, general rules and ordinary advice may not be sufficient; consultation with a dietitian and practical guidelines may make all the difference in good blood pressure control.

## Pathophysiologic Mechanisms

Resistance to treatment can arise from many pathophysiologic mechanisms that interfere with effectiveness of antihypertensive drugs or alter the course of the disease. These can be conveniently subdivided under three headings:

1. Specific pressor mechanisms as a cause of resistance to treatment
2. Reaction to the use of antihypertensive measures
3. New factors developing during the evolution of hypertension

Secondary hypertension was widely held at one time to be resistant to medical therapy. It has become clear, however, that this is not always true; renovascular hypertension can be controlled by antihypertensive therapy, and primary aldosteronism will respond to adequate diuretic therapy if hypokalemia can be prevented. However, poor blood pressure response to conventional therapy, while not diagnostic of a secondary cause, might increase the possibility of finding one.

### Specific Pressor Mechanisms

Even within the heterogeneous group of essential hypertension, an unrecognized specific mechanism might interfere with blood pressure response to therapy. Thus, investigations from various centers have outlined a subset of essential hypertension characterized by expanded blood and extracellular fluid volume associated with low plasma renin activity. Experience at the Cleveland Clinic has shown that adequate volume depletion must be achieved for optimal blood pressure control in those patients

with hypervolemic essential hypertension. The mere intake of a diuretic does not necessarily mean that enough salt and water depletion has been achieved; superimposition of second- and third-line drugs on an inadequate diuretic regimen will not control blood pressure in such patients. The identification of volume-dependent types of hypertension will lead to correct therapy; the latter consists of diuretics in adequate doses and combinations, and in monitoring or quantifying their effects on blood or extracellular fluid (ECF) volume.

The concept of identifying the dominant pressor mechanism in order to direct a rational choice of therapy may not prove practical in newly discovered hypertensions. Stepped-care therapy has proved very useful in this first approach; the situation might be different in patients whose blood pressure proves to be resistant to standard measures. The number of patients involved is smaller and their problems probably more severe. Moreover, there is also the need to establish whether the drugs used were achieving their purpose. By the time a truly resistant hypertension is being evaluated, the regimen should already contain drugs intended to combat most of the known hypertensive mechanisms [hemodynamic, volume, humoral (renin-angiotensin), and neurologic] plus some direct vasodilators. Investigations should aim at revealing which drug or drugs are failing to do what they are expected to do. In this context, it is important to differentiate whether a hypertension persisted *because* a drug failed to reduce renin activity, volume expansion, or a high peripheral resistance or *despite* effective control of these mechanisms.

## Counteracting Mechanisms Evoked by Antihypertensive Therapy

Of the many concepts that evolved from the extensive work in hypertension, few have proved as durable or productive as the mosaic theory of Page.[6] Hypertension is multifactorial not only in its development but also in its response to therapy. Each antihypertensive measure sparks a series of counteractions that modify or thwart its effectiveness. In fact, use of three agents in combination—a diuretic, a sympathetic blocker, and a vasodilator in severe hypertension—is based on the observation that the hypotensive effect of any drug or group of drugs cannot be maintained unless one also controls the compensatory responses that they trigger. Virtually all antihypertensive agents induce these compensatory mechanisms which tend to restore arterial pressure to its high pretreatment levels. Diuretics given to reduce extracellular fluid volume also stimulate the renin-angiotensin system, resulting in secondary aldosteronism which tends to *expand* fluid volume by increasing the reabsorption of salt and water in the proximal tubules. All sympathetic inhibitors reduce vasoconstriction, but (with the exception of beta-adrenergic blockers) they also promote sodium and water retention, which may reduce or nullify their hypotensive effect. Unless complemented by diuretic therapy, the initial hypotensive response to neural blockade will be superseded by a gradual rise in blood pressure. Vasodilators lower blood pressure by reducing total peripheral resistance, but they also produce compensatory increases in cardiac output, heart rate, and blood volume that again tend to elevate blood pressure. This complex intertwining of actions and counteractions is the basis of many cases of "false secondary resistance" to antihypertensive drugs—"false" in opposition to a true developed drug resistance which apparently does not occur.

Although the mechanisms of these responses to antihypertensive agents seem clear, the reasons why they should occur are not at all clear. First, they do not develop to the same extent in all patients; second and more importantly, the consequences of arterial pressure reduction by medication stand in sharp contrast with those produced by cure of a secondary hypertension. Dustan et al. pointed out that when blood pressure and peripheral resistance fall following relief of renal arterial stenosis, no compensation apparently occurs to block the decrease of arterial pressure.[2] Antihypertensive drugs evidently do not abolish the basic mechanism of a hypertension—and compensatory reactions develop to their hypotensive effect. It is very important to define the mechanisms of these reactions because of their practical implications. On the basis of the drug used, one can expect, guard against, or purposefully correct unwanted responses.

## New Factors Developing during the Evolution of Hypertension

Hypertension is not a static disease, nor is its therapy a short-term course of treatment. During its long evolution, secondary alterations can develop which may accentuate the rise in pressure or alter its responsiveness to therapy. Atherosclerotic narrowing of a renal artery, with resultant renovascular hypertension, can induce malignant transformation of a long-standing essential hypertension. Prolonged renin stimulation can promote adrenal hyperplasia with marked secondary aldosteronism that might conceivably become autonomous. Progressive loss of renal function and reduction of the glomerular filtration rate in patients with chronic hypertension

may reduce the efficacy of thiazides and necessitate the use of loop diuretics to control pressure.

It is important in such cases to recognize that, although the patient is still the same, hypertension is no longer the disease that was treated years ago—it has developed new mechanisms that sustain the elevated arterial pressure and increase its resistance to therapy. Secondary hypertension of this type (i.e., secondary to the complications of chronic hypertension) should be strongly suspected in a patient who, after years of medication, suddenly becomes resistant to therapy.

## Drug Interactions

Interactions of drugs are sometimes responsible for resistance to antihypertensive drug therapy. Since many hypertensive patients are also receiving medications for other systemic disorders, the risk of antagonistic drug interactions must always be considered (Table 3). This applies particularly to patients under treatment for such common and often concurrent diseases as arthritis, depression, obesity, emphysema, and thrombophlebitis. The effectiveness of furosemide, for example, can be reduced by indomethacin and by anticoagulants. It has also been recently noted that indomethacin may attenuate the hypotensive effect of thiazides; more studies are needed to determine whether inhibition of prostaglandin synthesis may interfere with the antihypertensive effects of all diuretics. The antihypertensive action of guanethidine, bethanidine, and probably methyldopa can be reversed by tricyclic antidepressants, amphetamines, methylphenidate, ephedrine, and the monamine oxidase inhibitors. The tricyclic antidepressants may also reduce the hypotensive effects of clonidine,[11] and several reports have suggested that these psychotropic agents may be antagonists to the potassium-sparing diuretic, spironolactone. Isolated studies have also suggested that the addition of propranolol to methyldopa may sometimes produce a paradoxical hypertensive reaction. Such episodes, though not impossible, have been rare in my experience, and many physicians have used this pharmacologic combination successfully. There is, however, another potential danger in a combination of propranolol with a centrally acting antihypertensive such as clonidine; persistent beta blockade in such cases may exaggerate the rebound hypertension sometimes associated with the abrupt termination of clonidine therapy.

More important, possibly because less suspect or easier to overlook, are antagonisms involving frequently used drugs. Thus ordinary doses of aspirin can block the diuretic effects of spironolactone. Oral contraceptives and estrogenic substances can produce hypertension de novo or exacerbate preexisting hypertension and sometimes make it resistant to

**Table 3.** Interactions that Can Blunt or Abolish the Effectiveness of Antihypertensive Drugs

| Antihypertensive Drug | Effectiveness Blunted By |
|---|---|
| 1. Diuretics | |
| a. As a class | Excessive salt intake |
| b. Specific drugs | |
| (1) Thiazides | Indomethacin |
| (2) Furosemide | Indomethacin |
| | Oral anticoagulants |
| (3) Spironolactone | Salicylates |
| 2. Neural blockers | |
| a. Guanethidine | Tricyclic antidepressants |
| | Amphetamines, methylphenidate, and ephedrine |
| | MAO inhibitors |
| | Chlorpromazine |
| b. Methyldopa and clonidine | Tricyclic antidepressants* |
| | Propranolol† |
| 3. Converting enzyme inhibitor | |
| a. Captopril | Indomethacin |
| | (?) Aspirin |

*Based mainly on animal studies.

†The action of propranolol is different in this context for methyldopa and clonidine. As regards the latter, it is *not* a direct antagonism but rather an exaggeration of the rebound hypertension that can follow sudden withdrawal of clonidine. As regards methyldopa, a paroxysmal rise of blood pressure was reported following intravenous propranolol in patients taking methyldopa.

therapy. To rule out potential interactions, a complete inventory of all drugs taken by the patient—including nonprescription items—is essential. Attention to so-called minor or household medications is especially important because some of them can significantly alter the effectiveness of antihypertensive agents. Orally administered nasal decongestants contain indirect sympathomimetic amines (ephedrine, pseudoephedrine, phenylpropanolamine) that can increase arterial pressure in patients taking guanethidine, reserpine, or methyldopa. Although this interference is usually mild, the effect of their interaction with a sympathetic blocker may be sufficiently marked to confuse the course of treatment.

## Management

Adequate management begins by a thorough clinical review of the patient's history and clinical status. Diagnosis in resistant hypertension cannot be a snap judgment; to establish one apparent cause of resistance to therapy does not rule out the possible participation of other less evident factors. Treatment begins by establishing clear, sympathetic, and dependable lines of communication with the patient. A careful review of the clinical history, dietary habits, and *all* pills or medications taken by the patient is essential, as is an assessment of the patient's understanding of the disease and of the goals of therapy.

Once the physician has established that the regimen is adequate (Table 1)[4] and the patient is compliant (Table 4) and not consuming huge quantities of salt, that a curable cause has not been overlooked and drug interactions are not a factor (Table 3), and that the high readings are not just an office phenomenon, then a diagnosis of truly resistant hypertension is tenable (Table 2).[9]

The first steps in management usually consist of (1) adjusting diuretic therapy and (2) reexamining the drug schedule used. For the first, attention to dietary sodium may be as important as altering diuretic therapy; accurate estimates of sodium intake can be derived from 24-h urinary sodium excretion. If consistently high, dietary sodium chloride should be reduced to 2 g daily.

There is little additional benefit from increasing the dose of thiazide or related diuretics above the levels given in Table 1. If serum creatinine is elevated, furosemide should be substituted for the thiazide-type diuretic, and large doses may be required (up to 1 g daily). If serum creatinine is normal, the addition of spironolactone to the "thiazide" could be considered, but this step alone is unlikely to make resistant hypertension responsive. More potent in our experience is the addition of furosemide (80 to 120 mg/day) to the thiazide diuretic; this combination can lead to marked natriuresis and restore pressure control; because of its potency it should be used cautiously, i.e., only under adequate supervision and usually for not more than a few days at a time.

**Table 4.** Clinical and Laboratory Clues to Medication Adherence

| |
|---|
| Clinical clues suggesting nonadherence |
| Repeated missed appointments |
| Poor recall of medications and dosage schedule |
| Forgetting to bring medication bottles to the office |
| Neglecting to refill prescriptions regularly |
| Inadequate pill counts |
| Laboratory clues suggesting adherence |
| Diuretics (thiazide and loop agents) |
| Fall in baseline serum potassium concentration |
| Rise in baseline serum uric acid concentration |
| Sympathetic inhibitors |
| Reduction in resting heart rate (75 bpm) |
| Blunting of normal increase in heart rate with upright posture and exercise |
| Guanethidine: Orthostatic fall in blood pressure |
| Methyldopa: False elevations of urinary catecholamines when measured by the fluorescent technique* |

*Normal concentrations suggest that methyldopa has not been taken for the previous 48–72 h.
From Wollam GL, and Hall WD (1980) Resistant hypertension. In: Ferandes M (ed) Evolving Concepts in Hypertension, Biomedical Information, New York, pp 32–44.

### Basis for Readjustment of Therapy

Faced with a patient with none of the causes of pseudoresistance and following adjustment of gross errors in salt intake or diuretic therapy, readjustment of therapy should be undertaken, if necessary, on a rational basis. This includes both personal experience and objective evaluation of the pharmacologic and pathophysiologic features of each case. This need for a wisely balanced combination of art and science is the basis for any good practice of medicine. Thus, reexamination of the drug regimen should include an evaluation of the dosage prescribed, since patients labeled as resistant to a particular drug are not infrequently found to have been given only small doses of the drug.

A decision to increase a dose is usually based on personal experience; it is particularly indicated if one suspects problems with gastrointestinal absorp-

tion or rapid drug metabolism or wishes to use fully the dose-response characteristics of a drug. With some drugs, like propranolol, increasing dosage may recruit other mechanisms of action; Zacharias and associates have used doses of propranolol of as much as 1 g or more daily with surprisingly few additional side effects.[12] Methyldopa can be increased to 3 g daily, but beyond this there is little or no further effect on blood pressure, and side effects are usually prohibitive.

Increasing the dose of hydralazine above 300 mg daily may enhance blood pressure control but at the risk of the lupus erythematosus syndrome. Nevertheless, this could be an acceptable risk if a severe hypertension is thereby controlled; doses of hydralazine up to 1 g daily were not unusual in the past. Guanethidine has almost an infinite dose-response curve so that there is no theoretical upper limit to its dose, although side effects usually preclude doses of more than 150 mg daily. However, in some patients with severe or resistant hypertension, doses as high as 400 mg daily have been used.

This personal approach to dosage adjustments should be balanced by some investigations to determine objectively the pathophysiologic characteristics of that particular hypertension and the degree to which they were influenced by the current therapy. This again raises the question of the practical value of laboratory investigations in hypertension; I believe they are very important in guiding therapy of resistant hypertension. Their cost and inconvenience are outweighed by the benefits of a rational choice and of a well-planned follow-up adjusted to the needs of a complex situation. Since this indication concerns a relatively small population, the overall costs and logistics of the problem are of a much smaller and more manageable magnitude than in the case of all newly discovered hypertensives.

The tests are planned to evaluate the four main pressor mechanisms that could be responsible alone or in combination for persistent hypertension. Although it is often assumed that these specialized tests require hospitalization, it is possible, with proper organization, to have them performed during a single visit to an outpatient department. Thus, the patient is asked to bring in the morning a 24-h urine collection; this is used to determine the daily excretion rate of sodium, potassium, creatinine, and metanephrines as well as of aldosterone. Meanwhile, the patient, who came fasting, is asked to lie down quietly; after a half-hour rest, blood samples are obtained through an intravenous needle which had been inserted much earlier, for determinations of plasma renin and catecholamines as well as aldosterone if needed. Blood volume is then measured, and cardiac output and ejection fraction can be determined by one of the minimally invasive techniques which are now available. Following this, the patient undergoes a head-up tilt or is asked to move about to determine the effects of posture or exercise on blood pressure, heart rate, and plasma renin and catecholamines. The whole study can be completed around noon.

This approach allows an overall simultaneous assessment of the cardiac, renal, and humoral status of the patient as well as some index of the patient's neurogenic response to stress. Some investigators prefer to evaluate the role of different mechanisms functionally rather than biochemically by determining the effect of specific pharmacologic blockade rather than blood levels of neurohumoral factors. Thus, they would rely on the blood pressure response to some specific angiotensin antagonist like saralasin in place of measuring plasma renin activity; similarly, the blood pressure response to a ganglion blocker or to alpha-adrenergic and beta-adrenergic blockers (singly or in combination) may give an index of neurogenic participation in maintenance of arterial pressure. As expected, a significant correlation has been found between the level of circulating catecholamines and blood pressure response to neural blockers, as well as between plasma renin activity (PRA) and response to angiotensin antagonists. An important caveat in this context is the fact that acute responses to drugs may not always predict their long-term effects.

From the results of different tests, a pathophysiologic profile is established; the mechanisms apparently responsible for maintaining an elevated pressure despite treatment are identified, allowing a rational adjustment of therapy. Interpretations of hemodynamic or of renin estimates, however, rarely allow an "either-or" conclusion, because hypertension is a multifactorial process both in its development or maintenance and in its response to therapy. Thus in some cases of high-renin essential hypertension, the elevated renin activity can be the result of increased sympathetic nervous activity rather than the primary cause for the high blood pressure. Thus, the final decision is based both on the data gathered and on the physician's personal experience, and is rechecked at intervals depending on the patient's response. The number of variables involved precludes any dogmatic algorithm or "cookbook" formula; treatment of a resistant hypertension should nowadays not be based on "trial and error" of any available drug. Rather it consists of a wise adaptation of pharmacologic measures to pathophysiologic findings. In that therapeutic plan, a particularly important feature is *patience.* Frequent changes in medications (except for emergencies) are often counterproductive; any change must be carried out

in a deliberate manner—changing one therapeutic element at a time and allowing time for the new element to take effect. If two or three drugs are changed simultaneously, side effects are likely to develop; the physician becomes overly involved in the complaints of the patient; and before long the track is much too confused to follow.

In some instances, cases are encountered that defy most available drugs. For those particular situations, one can turn to newer drugs, to intensive parenteral therapy or, in near desperation, to surgical measures.

## Recently developed drugs

Of new developments, two are, in our opinion, particularly effective—a direct vasodilator, minoxidil, and oral converting enzyme inhibitors. Monoxidil is one of the most potent agents for resistant hypertension; most investigators have found it effective after all other agents have failed.[8] It must be given in association with a beta blocker or neural depressant to avoid tachycardia and with a diuretic to prevent fluid retention. This combination could go a long way toward eliminating resistant hypertension were it not for some occasional unacceptable side effects. Beta blockade is usually successful in blocking reflex tachycardia, but the potent fluid-retaining properties of minoxidil are barely controlled by diuretics in high doses. It also causes rather marked hirsutism, which is highly objectionable to many women and children (see Chaps. 32 and 33). The use of minoxidil in resistant hypertension is one of the best illustrations of the need to evaluate objectively the balance of action in the combination of drugs used. Ineffective or insufficient beta blockade will result in increased cardiac output with suboptimal blood pressure control and even hyperkinetic pulmonary hypertension. On the other hand, excessive fluid accumulation, possibly with the added effect of marked adrenergic suppression, may result in a congested circulation and even cardiac decompensation.

Inhibitors of dipeptidase—the enzyme that converts angiotensin I to angiotensin II—have been recently introduced. The first, captopril, has been used for over 3 years with remarkable effectiveness. The second, MK-421, is just being tried; it lacks the undesirable sulfhydril radical of captopril, but its effectiveness and side effects have not yet been as thoroughly tested.

Converting enzyme inhibitors have been effective in controlling most forms of clinical and experimental hypertension with the exception of primary aldosteronism and other mineralocorticoid types. The exact mechanism(s) by which hypertension is reduced are still unclear; Laragh has made a strong case for its dependency on interference with the renin-angiotensin system.[5] Indeed, the early response to captopril was clearly shown to depend on pretreatment levels of plasma renin activity; however, its long-term therapeutic effects did not demonstrate that relation. Captopril was found in many centers to be effective in both low- and high-renin types of hypertension. Its effectiveness is markedly enhanced by concomitant diuretic therapy; in our experience about 50% of patients will need combined therapy for optimal blood pressure control. Table 5 summarizes our findings over more than 3 years of studies.

**Table 5.** Long-Term Captopril Therapy in Hypertension

| | Hypertension | | | | | |
|---|---|---|---|---|---|---|
| | Type-*N* | | | | Total | |
| | RAD-13 | | EH-31 | | 44 | |
| Results | n | % | n | % | n | % |
| Good BP response: | | | | | | |
| 1. Drug alone | 2 | 15 | 6 | 19 | 8 | 15 |
| 2. With diuretics | 10 | 77 | 19 | 61 | 29 | 66 |
| 3. Totals | 12 | 92 | 25 | 81 | 35 | 80 |
| Maintained on $R_x$* | 9 | 69 | 20 | 65 | 29 | 66 |

*Treatment stopped because of side effects in six and non-drug-related causes in two.

Captopril appears to be effective in both essential and renovascular hypertension. It lowers blood pressure by reducing total peripheral resistance without significant changes in cardiac output, heart rate, or plasma volume. This is an unusual pattern that has not yet been fully explained; the lack of volume expansion might be related to control of secondary aldosteronism. Experience at the Cleveland Clinic showed that the initial reduction of high plasma aldosterone levels by captopril was maintained during long-term treatment; indeed, asymptomatic hypoaldosteronism was found in 8 of 31 patients. Hyperkalemia was not encountered, possibly because no potassium supplements or potassium-sparing diuretics were usually given with captopril. The absence of tachycardia suggested a possible interference with baroceptor mechanisms; this has yet to be clearly demonstrated. Whether used alone or with sodium deprivation or diuretics, captopril did not lead to significant orthostatic hypotension[10].

Still not fully clarified are the clinical dose response characteristics of captopril or its relationship to alterations of plasma converting enzyme levels. The doses used presently (25–100 mg t. i. d. to q. i. d.) are much lower than initial recommendations (up to 1.0 g/day). Also not fully explained is the

mechanism of reduced responsiveness in some cases to long-term captopril treatment, a late resistance that is not associated with volume expansion yet often responsive to added diuretics. Side effects reported to date include fever, rash, loss of taste and, more ominously, agranulocytosis and proteinuria. The latter has been related to a membranous glomerulonephritis which might or might not be reversible. The relation of those side effects to the chemical structure and SH group of captopril (remarkably similar to penicillamine) are under intense study.

Finnerty and co-workers have shown that resistant hypertension can be made responsive to oral regimens if arterial pressure is kept at nearly normal levels for 7 to 10 days by parenteral therapy with agents such as diazoxide.[3] They recommended repeating doses of diazoxide whenever the blood pressure rises above 170/110 mm Hg and postulated that this brings a "resetting of the barostats." Whatever the exact mechanism, it is worth a trial when everything else has failed. Sodium nitroprusside would probably be just as effective, but its prolonged administration is more cumbersome.

### Surgical treatment

One last resort for management of resistant hypertension is bilateral lumbodorsal sympathectomy, which is not a very satisfactory solution. The extensive bilateral lumbodorsal sympathectomy of Smithwick is a two-stage procedure accompanied by much morbidity. Unfortunately it is not often helpful for the patient who has truly drug-resistant hypertension. It is more frequently beneficial when failure to control hypertension is due to poor compliance or side effects from drugs and not due to drug resistance. However, the side effects of the operation are usually worse and more permanent than the side effects of drugs.

The one-stage subdiaphragmatic splanchnicectomy of Adson is a less formidable procedure with little morbidity. It is sometimes helpful in making hypertension easier to control with less medication; but this partial success is unlikely if the blood pressure has been totally resistant to large doses of appropriate drugs. The technical problems and morbidity associated with the carotid sinus nerve stimulator have markedly dampened the original enthusiasm for this form of treatment. Most patients in our experience have not obtained long-term relief from this modality.

Patients with end-stage renal failure sometimes present a high-renin, severe hypertension that cannot be controlled (or is made worse) by dialysis. Bilateral nephrectomy has been advised for this type of resistant hypertension, but the advent of minoxidil, and possibly of captopril, has replaced this radical approach (see Chap. 35).

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# Hypertension in the Dialytic Population

# 35

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## Introduction

Dialysis is a well accepted mode of therapy for end-stage renal disease. Years of experience and research have been rewarded with the development of various artificial kidneys and extracorporeal techniques. At one time a therapy rendered to a select few, dialysis is now offered to a large population of patients. This growth reflects not only an amelioration in techniques but also a rather impressive improvement in the 1-year survival statistics. In 1964, the 1-year survival rate was 50%; in 1979, despite a current higher mean age and the presence of systemic disease in 10% of the dialysis population, the 1-year survival rose to 86%. With improved survival and a growing population of patients came some new problems. The leading cause of death among dialysis patients now is cardiovascular in origin, with cerebrovascular accidents and myocardial infarction being the most frequent.

Several factors are known to contribute to this condition. There is ample evidence of rapidly advancing atherosclerosis in the dialytic population. In the nonuremic population such risk factors as cigarette smoking, lipid abnormalities, and hypertension were shown to be major factors in cardiovascular catastrophes. It would seem reasonable that these same risk factors would apply to the dialysis population. Some correlation between the underlying renal disease that brought the patient to end-stage and subsequent cardiovascular disease has been shown. Likewise, among the risk factors for the hemodialysis population hypertension has been found to play a major role.

## Pathophysiology

Classically, one may divide hypertensive patients with end-stage renal disease into those with sodium-volume–dependent hypertension and those with renin-dependent hypertension. As in many classifications, this is perhaps an over-simplification. There are patients with a hypertension that is both volume- and renin-dependent; further, the sympathetic nervous system has also been shown to play a central role, as we will see later. Moreover, the anephric population may differ substantially in the characteristics of its hypertension from patients with kidneys. Unresponsive to certain therapeutic attempts at blood pressure control prior to nephrectomy, the same patient may become highly responsive after nephrectomy. In order to render appropriate therapy, one must first understand the underlying pathophysiology that plays a role in the hypertension of dialysis.

### Sodium-Volume–Dependent Hypertension

Of the total dialysis population, 80% will be hypertensive when starting dialysis. This is defined by a diastolic blood pressure greater than 90 mm Hg or a systolic blood pressure greater than 160 mm Hg. Of this population, some 70% will be easily controlled by sodium restriction, and volume control and sodium removal during dialysis. This group is generally known as the sodium-volume–dependent hypertensive.

Vertes et al.[7] showed a good correlation between

approach to dry weight and blood pressure control. Dry weight is defined as that weight below which a normal albuminemic patient on dialysis will become hypotensive with fluid removal and above which this same patient will either be hypertensive or show subtle signs of fluid expansion. As weight is reduced by fluid removal, blood pressure drops gradually, finally approaching normal some 6 to 8 weeks after start of dialytic therapy. Exchangeable sodium has also been shown to play a significant role in control of this form of hypertension. Thus, the central role of dialysis therapy and sodium restriction in blood pressure control has repeatedly been demonstrated. Wilkinson et al., however, found no significant correlation between exchangeable sodium and diastolic blood pressure in 45 unselected dialysis patients.[2] His study reviewed 14 patients who, despite low exchangeable sodium level, were still maintaining diastolic pressures above 100 mm Hg.

Severa studies have attempted to explain the hemodynamic basis for this blood pressure response to volume expansion in chronic uremia. One theory, that of autoregulation, is perhaps the most quoted. Coleman and Guyton found in three anephric patients that increases in sodium and water led first to increased cardiac output resulting in higher blood pressure.[8] With time, however, total peripheral resistance rose as the cardiac output returned toward normal, while arterial pressure remained elevated. With return to normal hydration, the total peripheral resistance fell, preceded by a drop in cardiac output to below control values. They postulated tissue autoregulation as the underlying physiologic event and increases in cardiac output as the prime mover in the establishment of blood pressure elevations. Their conclusions were challenged by Onesti and co-workers who found no evidence for "autoregulation" in some anephric patients.[1]

The pattern of response to volume expansion can, however, be significantly modified by the presence or absence of the kidneys. Patients who are not responsive to volume depletion before nephrectomy often become volume-dependent hypertensives after the kidneys are removed. Moreover, Onesti reported that the blood pressure response to volume depletion following nephrectomy depended on the patient's previous history.[1] Studying a much larger group of patients, Kim et al. compared 75 uremics (52 hypertensive and 23 normotensive) with 45 normal controls.[13] The hypertensive uremics had a higher cardiac index than normal controls but did not differ significantly from them in level of total peripheral resistance. However, when hypertensive uremics were compared to uremic normotensives, total peripheral resistance was significantly higher in the hypertensives without a significant difference in heart rate, stroke index, or cardiac index. This, therefore, implied a primary role for peripheral resistance in uremic hypertension.

Total peripheral resistance was also implicated in a study by Neff and associates.[14] They first studied the hemodynamic state of 40 stable uremics; they confirmed the presence of a high cardiac output among uremics but also found a significantly higher total peripheral resistance in hypertensive uremics (compared to normotensive uremics). To investigate the role of the elevated cardiac output, six hypertensive patients were transfused to a hematocrit of 40% over a 6- to 12-week period. Despite normalization of their cardiac output, the patients' blood pressures increased. Cardiac output, therefore, played only a minor role in maintaining hypertension in these uremic patients. In these studies, however, no clear-cut distinction was reported in the volume status of the patients studied. Both types of hypertension, volume- and renin-dependent, were evaluated, thus leaving unclear the role of volume changes alone.

Nowhere are volume changes more constantly or rapidly accompanied by blood pressure changes than in the anephric population. Although increased sympathetic activity, as assessed by plasma catecholamine levels, norepinephrine concentration, and dopamine beta-hydroxylase activity, has been reported to play some role in renoprival hypertension, alterations in blood and extracellular fluid volume seem to be the major factor. Those who were hypertensive prior to nephrectomy also became hypertensive when volume expanded after nephrectomy, whereas those who were normotensive before surgery failed to elevate their blood pressure with sodium and volume loading after nephrectomy. Our own studies, however, have identified a small group of anephric patients who, although hypertensive prior to nephrectomy, failed to develop hypertension postoperatively despite levels of volume and sodium overexpansion that led to edema and even congestive heart failure. The explanation of that phenomenon is not yet clear; however, prior structural changes cannot be the entire explanation of Onesti's results.

In general, the uremic who approaches dialysis has an expanded extracellular fluid; in most patients, this will be translated into increased arterial pressure. Once dialytic therapy is begun, an attempt should be made to bring the patient down to his or her dry weight. This transition from volume expansion to dry weight may take several months and should not be attacked overzealously. Rapid removal of fluid may end by depleting intravascular volume faster than it can be refilled from the extravascular compartments. This will result in hypotensive episodes during dialysis, leading to an erro-

neously high estimate of dry weight. Once normovolemia is obtained, if the patient is volume-dependent, the blood pressure should be well controlled. With normal dietary salt and fluid intake during the interdialytic period, the patient's blood pressure will gradually rise to high levels predialysis. With adequate fluid removal and sodium balance during dialysis, these elevated blood pressures will be returned to normal.

## Renin-Dependent Hypertension[6,9]

Some 15% to 20% of the hypertensive dialytic population will need drug therapy along with sodium and volume control for normalization of blood pressure. This population generally has a higher peripheral renin activity than does the volume-dependent hypertensive. Despite vigorous sodium and volume removal, blood pressure may actually be increased along with plasma renin and angiotensin II levels during dialysis.

The exact relationship between renin and blood pressure is a controversial topic even today. Wilkinson et al., in a very precise and well-designed study, found a close correlation of plasma renin activity with diastolic and systolic blood pressures, as well as a significant difference in plasma sodium levels between hypertensive and nonhypertensive patients on dialysis.[2] It is generally agreed that the higher plasma renin levels are indeed associated with higher blood pressures, but the argument is still unresolved as regards patients with normal or slightly elevated renin levels. It is argued that renin is inappropriately high for the state of sodium balance or hydration. Weidman et al. found the same expected inverse relationship between renin and sodium state in hemodialysis patients as among normal subjects, but renin was consistently higher relative to the state of hydration in the hypertensive than in normotensive patients.[3] This was interpreted to mean that the higher blood pressures were in part related to an imbalance of the renin—volume relation.

Adding to the difficulty in interpretation of results is the question of changes in pressure mechanisms during dialysis. It is theorized that, as the patient loses intravascular volume, he or she shifts from a volume- to a renin-dependent state for blood pressure maintenance. Renin production seems to be higher in the volume-contracted patient on dialysis and lower in the patient with less weight reduction though there are studies, too, that found no relationship of blood pressure and body weight changes to alterations in peripheral plasma renin activity.

Weidman et al. reported that peripheral plasma renin activity could help select those dialysis patients who would best respond to nephrectomy.[3] Three groups of patients were described: those who were normotensive, those who were hypertensive but controlled by volume and sodium balance, and those who were uncontrolled by these techniques. The peripheral renin activity was significantly lower in the volume-responsive or nonhypertensive group than in the uncontrolled group. These latter patients were found to have a higher diastolic blood pressure as compared to volume-responsive hypertensives; their total peripheral resistance was also higher and their stroke index lower. The conclusion, therefore, was that in these patients the renin-angiotensin system was a primary cause of significant vasoconstriction.

If the renin-angiotensin system does in fact play a role in a proportion of dialysis hypertension, then those patients showing renin dependency would also show a hypotensive response to angiotensin II antagonism. Lifschidtz et al. found, indeed, the response of 15 hemodialysis patients to saralasin infusion could be subdivided into two groups;[15] one had a marked drop of systolic (greater than 20 mm Hg) and diastolic pressure (greater than 10 mm Hg) characterized by a higher peripheral plasma renin activity (PRA) with a further significant increase after saralasin infusion, and a second had no appreciable change in blood pressure during saralasin infusion and a lower PRA which did not respond to the antagonist. Again, however, patient volume status was not described. Earlier studies could not relate blood pressures to blood volume or plasma angiotensin II concentrations. Saralasin responsiveness was just as dependent on sulfate space as on the preinfusion renin activity or angiotensin II concentration.

Mimran et al. demonstrated an active role of angiotensin II in hemodialysis hypertension and found a correlation not only with plasma renin and plasma aldosterone activity but also with the response to saralasin infusion.[16] They concluded that saralasin nonresponders should be subjected to vigorous ultrafiltration for blood pressure control while those that did respond showed the central role of the renin-angiotensin system in their hypertension.

## Hypertension with Other Etiologies

The role of secondary hypertension should not be overlooked in the dialysis population. Such disease states as hyperthyroidism, pheochromocytoma, and coarctation of the aorta can coexist with renal disease. An increasing amount of evidence showing an

active role of the sympathetic nervous sytem and hypertensive disease has been reported.

Baroreceptor activity abnormalities have been noted in the uremic population, believed to be secondary to autonomic nervous system dysfunction.[4] There is evidence implicating a "reset" baroreceptor activity in the hypertensive patient which reverts to normal following nephrectomy. Plasma catecholamine activity, serum norepinephrine, and dopamine beta-hydroxylase activity have been used to assess sympathetic nervous system function, and conflicting results have been obtained. The role of the autonomic nervous system, therefore, in the hypertensive dialysis patient is still uncertain.

Prostaglandins have also been investigated as a possible factor in hypertension either through a direct effect on vessel contractility or via their ability to stimulate renin and thus angiotensin production. Finally, atherosclerosis per se and its consequent systolic hypertension can also be seen and is probably more frequent at any age group when comparing dialysis patients to nonuremic patients. The higher frequency of advanced atherosclerosis makes this later etiology a real factor in an already compromised patient population.

One can, therefore, conclude that hypertension in the dialytic population, although classically divided into renin-dependent and volume-dependent states, may in fact have a multifactorial basis. It is the physician's role to attempt to arrive at a logical basis for blood pressure elevation in any specific patient and then to treat the patient accordingly.

## Treatment

### Sodium and Volume Restriction

Virtually all patients approaching end-stage renal disease will be in need of some sort of dietary restrictions. Perhaps the most frequent is the sodium and volume restriction placed on these patients. Assessing the true need for these restrictions requires that patients be studied under two circumstances; first, after a high sodium intake for 24 to 48 h to determine the maximum sodium and volume excreted by the kidneys; then following a 48-h sodium-deficient diet when a 24-h urine collection will give the obligatory renal sodium and volume loss.

These determinations will allow accurate estimate of their dietary sodium and fluid allowance which should be set within this range. In general, however, barring the obligatory sodium waster, end-stage renal disease patients on dialysis need to be restricted to a 2-g sodium diet and an 800- to 1200-ml daily fluid intake. This will allow for a 0.5- to 1.0-kg/day weight gain during the interdialytic period and lead to stable dialysis runs.

This strict dietary regimen is unfortunately not followed by a significant portion of any dialytic population. Excessive thirst from secondary disease states such as hyperparathyroidism or underlying pathologic conditions such as the hyperglycemia of diabetes make fluid control difficult. Psychological denial of their renal disease and consequent dietary indiscretion play a role in noncompliance. One, therefore, loses the therapeutic benefit of dietary restrictions for blood pressure control.

### Extracorporeal Techniques

If dietary compliance is a problem, one must adjust the dialytic procedure to accomplish fluid and sodium removal. This will maintain the patient at his or her dry weight and thus control the volume-dependent hypertension. Generally accomplished by ultrafiltration techniques, these measures may take several forms, as noted below.

#### Ultrafiltration/dialysis

The most frequent method, ultrafiltration during dialysis, is accomplished by either osmotic gradients as in peritoneal dialysis or hydrostatic pressure difference as in hemodialysis. With these gradients being applied to whatever membrane (peritoneal or artificial) being used, one can accomplish fluid removal along with diffusion dialysis treatment. Once dry weight is established, these techniques can then be altered so as to remove only the amount gained by the patient during the preceding interdialytic period. This will be effective in the vast majority of patients on dialysis for control of fluid and consequent volume-dependent hypertension.

#### Isolated ultrafiltration and sequential dialysis

There is a population of hemodialysis patients who, despite expanded volume and increased sodium, will still become hypotensive during attempts at fluid removal by dialysis. The volume-dependent hypertensive who resists standard ultrafiltration techniques will need to be subjected to isolated ultrafiltration for fluid removal followed by diffusion dialysis with no ultrafiltration. This technique leads to a remarkable hemodynamic stability which is generally ascribed to lack of important osmolar changes during dialysis. In our experience the hemodynamic effects of this procedure are characterized by venoconstriction in response to fluid loss instead of the venodilation often associated with regular hemodialysis. The result is a stable cardiopulmonary volume and

hence a constant cardiac output which avoids the hypotension of dialysis and allows effective volume removal.[5]

### Hemofiltration and other methods

Some patients have been resistant to the above techniques but have been responsive to a new technique of dialytic therapy known as hemofiltration. In effect a total body water exchange, this carries ultrafiltration to its limit by removal of large amounts of body fluid and replacement of it by a smaller amount of fluid either in a pre- or postdilutional mode. Thus, blood pressure has been controlled in several patients who were previously thought to be dialysis-resistant hypertensive. Whether these patients were in fact volume-expanded and had their blood pressure controlled by this technique of fluid removal or whether this technique altered hormonal responses to some extent is not known.

A newer technique that we are currently studying is that of slow, continuous ultrafiltration/hemofiltration with removal of large volumes of fluid in a continuous manner and replacement both parenterally and orally. One avoids the need for volume restriction and effects a more stable physiologic method of fluid removal. Once this technique can be applied to the ambulatory population, the volume-expanded state and subsequent volume-dependent hypertension will become a rare occurrence.

## Medications

As in the therapy of most hypertensive diseases, the first step to pressure reduction is always fluid and salt control. The dialysis population is no exception to this rule. If these measures are not effective, the next step is the addition of drug therapy. Identification of the dominant pressure mechanism may help in the choice of treatment. If renin dependency plays a major role, then drugs aimed at reduction of renin release or at interference with the production or action of angiotensin II should be used. These include propranolol, converting enzyme inhibitors (CEI) and, to some extent, methyldopa. If, however, there is evidence of sympathetic overactivity, then methyldopa or clonidine or both may prove more advantageous. If a reduction in vascular tone is the major aim, then directly vasoactive medications such as hydralazine, prazosin, or minoxidil would be the drugs of choice. It is usually necessary, however, to combine these medications to obtain blood pressure control with smaller doses which reduce the side effects of each agent used alone.

### Drugs interfering with renin-angiotensin system

Propranolol is a beta-adrenergic blocking agent with multiple effects on the cardiovascular system, on renin release, and on central autonomic activity. Blood pressure control with this drug is probably multifactorial and not dependent on renin suppression alone. In our opinion, blood pressure reduction can be achieved by propranolol alone in a majority of dialysis patients. It was not found to reduce reticulocyte index, hematocrit, and red blood cell mass in uremic patients, despite experimental evidence that it might have an adverse effect on erythropoiesis in rabbits. However, it was particularly effective in a moderate dosage range (240 mg/day) for control of blood pressure in renin-dependent hypertensive patients.

Because propranolol metabolism is almost entirely via the liver and its excretion via the bile, no dosage adjustment need be made for patients on dialysis. Limiting factors for its use are no different in this population than in the nonuremic hypertensive. Bronchospasm in the patient with obstructive lung disease; precipitation of congestive heart failure secondary to negative inotropic and chronotropic effects; worsening of hyperglycemia or, on the contrary, a masking of hypoglycemic symptoms in the diabetic population; and worsening of peripheral arterial insufficiency and precipitation of nightmares are the major clinically important side effects of this drug. Dosage should be given on a twice per day regimen, usually from 40 to 320 mg daily. The use of megadoses (1–2 g/day) has been reported in the European literature but probably is not necessary. If dosage exceeds 600 mg/day, one should consider supplemental therapy with other drugs.

Two other areas of attack might be logically considered in renin-dependent hypertensives: blockade of angiotensin II by specific antagonists or inhibition of its production.[10] The first approach is used presently more as a diagnostic and prognostic test than as actual therapy. Saralasin (1-sar-8-ala-angiotensin II) is a competitive antagonist of angiotensin II; its hypotensive effect may be used as an index of the role of angiotensin in any particular hypertensive state. The recommendation has been made, therefore, to select those patients who would benefit from nephrectomy and/or therapy with CEI. However, recent studies have shown that hypertensive patients whose blood pressure was not lowered by angiotensin antagonists could still respond to CEI.[11] Hence a trial of captopril or other converting enzyme inhibitors should not be denied on the basis of a negative saralasin response.

Converting enzyme inhibitors are presently under clinical trials in several hypertensive conditions.

These are supposed to reduce circulating angiotensin II by inhibiting the enzyme necessary for conversion of angiotensin I to angiotensin II; the two available drugs are effective when given orally and thus would seem particularly suited for renin-dependent hypertension in patients on dialysis. Whether captopril acts *only* by reducing circulating angiotensin II is actively debated; conflicting reports have appeared regarding its effect in anephric patients or animals. Whatever the ultimate mechanism of its antihypertensive effect, this is markedly potentiated by fluid removal during dialysis, which may necessitate fluid replacement to control hypotension. Captopril and other converting enzyme inhibitors, although still investigational, have great promise as an alternative to multidrug regimens or to bilateral nephrectomy in the resistant-hypertensive dialysis patient. Daily dosage of captopril should not exceed 35 mg.

### Sympathetic inhibitors

Once used as the first agent when drug therapy was reached, methyldopa still enjoys a central role in the management of dialysis hypertension. Its major action depends on central alpha-receptor stimulation leading to reduction in sympathetic activity; the latter leads, among other effects, to some reduction in plasma renin activity.

It is this effect that allows it to be active in the systolic hypertension of atherosclerotic heart disease of both uremic and nonuremic patients. Adverse effects include impotency, lethargy, and drowsiness, and although the latter effects are generally more pronounced in early treatment periods, it still may cause confusion in clinical evaluation of the uremic state. Clonidine can be used for the same purpose as methyldopa. The hypotensive effects of both will be markedly potentiated by fluid withdrawal. There are reports of severe interdialytic hypotensive episodes in patients taking either of these drugs; it is therefore recommended that the dose prior to dialysis be omitted in an effort to avoid this effect. Contrariwise, there have been some reports of episodes of hypertension during dialysis secondary to removal of the drug; this latter condition is very rare in our experience.

The dosage regimen for methyldopa is usually 500 to 2000 mg divided over the day; we have found it as effective in a b.i.d. as in a q.i.d. regimen, perhaps because of increased patient compliance. The dose for clonidine is 0.1 to 0.2 mg on a b.i.d. regimen. Either drug has been effective in our experience in controlling predominantly systolic hypertension secondary to atherosclerosis in dialyzed patients.

Two major concerns with clonidine have made it less popular with our group; one is the rebound hypertensive phenomenon on abrupt withdrawal of the medication, and the other is the seemingly higher incidence of fatigue and mental depression among the uremic population. We have not encountered the paradoxical hypertension reported to occur in the methyldopa-propranolol combination.

Other drugs with a principally depressive action on the sympathetic nervous system are less frequently used; in fact, because of severe orthostatic hypotension, such classes of drugs as rauwolfia or guanethidine should probably be avoided. Phentolamine should be reserved for use only for very specific indications.

### Vasodilator drugs

One of the most frequently used hypertensive medications in the uremic population is hydralazine. This drug has a direct vasodilatory effect on the peripheral vasculature and thus reduces peripheral resistance. Reflex tachycardia may pose a problem for patients with coronary artery disease; this effect can generally be abolished or mitigated by the concomitant administration of propranolol or methyldopa. Again, this drug is metabolized principally by acetylation in the liver and, therefore, dosage adjustment for renal failure is not necessary. There is no increase in lupus-like reaction among the uremic population as compared to nonuremics at similar dosage schedules. Hydralazine has the advantage of being active after oral, im, and iv administration; it has been used in parenteral form for the treatment of hypertensive emergencies and occasionally for the rapid lowering of blood pressure during dialysis.

Two other parenterally administered drugs have shown clinical prominence over the past several years. Diazoxide, a potent direct vasodilator, has been used in clinical situations where there is a need for rapid reduction of the blood pressure. Although it is generally recommended to be given as a 300-mg bolus, we have preferred giving it in 100-mg dosage. The lower dose avoids the severe hypotensive effect that may occur especially while on dialysis and offers the advantage of being able to "titrate" down the blood pressure to some predetermined range. Once acceptable blood pressure has been obtained, this can be maintained by periodic redosage.

Sodium nitroprusside is a most effective and powerful hypotensive agent which should be used only in an intensive care nursing area where close patient observation is possible. Because it is converted in vivo to thiocyanate, toxicity is sizable with continued administration, especially in uremic patients; for this reason, they should not in general be treated for longer than 48 h with nitroprusside. Further fre-

quent thiocyanate plasma levels should be determined to avoid levels above 10 ml per 100 ml. have found this potential danger rare if the dr used with the proper setting and dosages.

A newer, potent, orally active vasodilator, minoxidil, has been recently released for use in the United States. It has proved to be quite effective in the treatment of dialysis patients with drug-resistant hypertension. Pettinger and Mitchell[12] studied 11 patients with accelerated hypertension refractory to conventional therapy; 7 had advanced renal disease. Minoxidil reduced blood pressure in all. Other investigators have confirmed the remarkable potency of this vasodilator for resistant hypertension; however, its side effects are not negligible. They include tachycardia and fluid volume retention requiring beta blockade and potent diuretic therapy, respectively. Among the dialytic population, the application of minoxidil therapy may avoid the need for bilateral nephrectomy for severe hypertension. Perhaps the major drawback of this therapy is hirsutism; this is not confined to any specific area of the body and may prove to be quite extensive and particularly objectionable in women and children. Dosage regimens are usually started at a 2.5-mg b.i.d. schedule and raised every 2 to 3 days until blood pressure control is effective or a total daily dosage of 40 mg is reached. In our experience 90% of previously resistant hypertensive patients will respond to this drug combined with adequate fluid removal during dialysis.

Finally, classified here as a vasoactive medication, prazosin is an alpha blocker which lowers arterial resistance and increases venous capacity. This, therefore, has the theoretical advantage of reducing both cardiac preload and afterload. Its dosage is not altered by renal failure, but its main disadvantage is orthostatic hypotension, especially following dialysis therapy. Syncopal episodes associated with tachycardia have often been noted with the first dose of this medication; the patients should therefore be asked to stay recumbent for a few hours after this first dose. The dosage is usually 0.5 to 1 mg b.i.d. This dosage may be increased by 0.5 mg/week to a maximum of 8 to 10 mg/day; dosage adjustment is dictated by pressure control and orthostatic hypotension.

### Nephrectomy

Despite the advent of potent drugs and advancements in dialytic technique, there still remains a minority of dialysis patients whose hypertension proves resistant to all therapeutic attempts. This small percentage of patients (5%) will respond only to bilateral nephrectomy. Comparisons of survival rates of nephrectomized vs. nonnephrectomized hypertensive dialysis patients revealed that control of blood pressure via bilateral nephrectomy was beneficial to long-term survival. Weidman and Wilkinson found a close correlation between response to nephrectomy and prospective peripheral plasma renin activity. In patients with low or normal renin, nephrectomy was not beneficial, whereas sustained improvement following surgery was obtained in patients who exhibited high renin activity.

Unfortunately, this therapy is not without its problems. With the loss of renal tissue, there is a loss of renal endocrine functions. Thus, the hematocrit can drop substantially, probably secondary to a lack of erythropoietin production; this increases the requirement for blood transfusions and consequently increases the risk of hepatitis. Evidence that calcium absorption is decreased in the anephric state raises the question of loss of 1-25 vitamin D conversion by the kidneys. Anephric patients are exquisitely sensitive to volume changes, which makes hemodialysis-associated hypotension a significant clinical problem. In addition, strict fluid restrictions are needed in patients whose kidneys previously might have been helping eliminate some fluid, which allowed an easier regimen of fluid intake.

Finally morbidity and mortality of the surgery is a consideration. The use of the posterior rather than the anterior approach has greatly reduced perisurgical morbidity. Some serious thought should also be given to the nonsurgical ablation of kidneys, via bilateral transarterial renal infarction. This latter technique may prove less invasive than surgery and equally effective.

## Conclusion

Hypertension in the dialytic population requires the same aggressive therapeutic management as it does in the nonuremic hypertensive. This may best be accomplished by recognizing the multitude of factors which can play a role in the hypertensive diseases of the dialysis population in general, and identifying which factor or combination of factors is dominant in the individual patient. Once this is determined, appropriate dialytic and drug management can be offered. Despite aggressive therapy, there will still remain a small but definite population who will require bilateral nephrectomy for blood pressure control. With further advancements in dialysis techniques and drug discovery and manipulation, it is

hoped that less surgical intervention will be needed and greater preservation of renal tissue may be possible.

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