As I review the extensive literature on the pathogenesis of primary hypertension published over the past 4 years since composing the previous edition of this book, a sense of futility arises. Hundreds of papers have been published describing the work of thousands of investigators who have spent many millions, perhaps billions, of dollars. Yet the pathogenesis of primary hypertension is as elusive and enigmatic as ever. The enthusiasm released by the elucidation of the human genome has quickly been dampened by the reality, as Sir George Pickering warned over 40 years ago (1964) that “elevated blood pressure is not a function of one gene, but rather a host of genes, each contributing a small effect.”

This overall pessimism should be lightened by the knowledge that a few new components, e.g., leptin, and a number of older ones, e.g., aldosterone and uric acid, have been added to the mosaic. However, these and other advances to be described seem only small pieces that will not solve the larger puzzle. Moreover, the puzzle may be unsolvable. In the words of Coggon and Martyn (2005):

Diseases that entail amplification of a microscopic or molecular event tend to be “all or none” in nature. Anyway, it is not difficult to separate cases of the disorder from most people who show no evidence whatsoever of disease. But for many other conditions, there is no clear dichotomy between those who have them and those that do not. Such cases, exemplified by hypertension, sensorineural deafness, and osteoporosis, represent the extreme of a physiological state whose variability is described by a continuous unimodal frequency distribution. Here, case definition is somewhat arbitrary, and understanding of causation amounts to identification of factors that modify this physiological state one way or the other. A full understanding of causation would mean the ability to predict P.51 accurately an individual's physiological state—their systolic blood pressure or bone mineral density, for example—from a knowledge of these modifying factors. However, the fact that these physiological states exist in a continuum in the population suggests that they are determined by the combination of factors, many of which might have only a small individual effect. This multiplicity means that complete understanding of causation is unlikely to be feasible, although it may be possible to identify some factors whose effects are large enough to offer scope for prevention.

GENERAL CONSIDERATIONS

Before considering the specific genetic and environmental factors that may be responsible for hypertension, a few generalizations are in order:

- A separation is necessary between primary, i.e., systolic and diastolic hypertension, and isolated systolic hypertension. As here defined, primary hypertension is the elevation of blood pressure (BP) seen in younger people which has a genetic foundation and is shaped by many environmental factors and which tends to be progressive if not treated but can usually be controlled. Isolated systolic hypertension (ISH), on the other hand, is the elevation of
systolic pressure which is almost exclusively seen in the elderly, which has no obvious genetic foundation, and is more loosely shaped by the same environmental factors that induce primary hypertension. Isolated systolic hypertension appears to be both less progressive and less responsive to treatment, in part because its duration is usually fairly short.

The distinction may be even simpler: Primary hypertension reflects both an increase in cardiac output and a functional, i.e., reversible, constriction of peripheral resistance vessels. Isolated systolic hypertension mainly reflects a stiffness of proximal, capacitance vessels (Safar, 2005).

Different precursors of these forms of hypertension can be identified in large populations (Franklin et al., 2005), but the multiple factors considered in this chapter mainly relate to primary hypertension.

- As noted by Coggon and Martyn (2005), although the concept of a single underlying abnormality that begins the hemodynamic cascade toward sustained hypertension is attractive, there may be no such single defect. In view of the multiple factors involved in the control of the BP, the concept of a multifaceted mosaic, introduced by Page (1963), may be more appropriate, as unattractive as it may be to those who prefer to believe that for every biologic defect there should be a single, specific cause.
- The relevance of data from animal models is highly questionable. Even though 70% of current research on hypertension is being done on rats or other small animals (Kwitek-Black & Jacob, 2001; Sugiyama et al., 2001), the relevance of such data to the human condition is suspect. For example, transgenic hypertensive rats develop fulminant hypertension at an early age despite low levels of renin in the plasma and kidney (Lee et al., 1996), quite unlike what is seen in humans. Therefore, this discussion will almost exclusively examine data from human studies.
- Few analytic techniques are available to measure accurately and repetitively small changes in various hemodynamic functions involved in the development of hypertension that may occur over many years. Cross-sectional observations may never be able to uncover the sequential changes that could be revealed by longitudinal studies.
- Even when studies are performed among adolescent and borderline hypertensives, the beginnings of the disease may have already been missed. In the absence of a marker to identify the prehypertensive individual, before the BP has risen, we may be viewing the process after the initiating factors are no longer recognizable, obscured by adaptations invoked by the rising pressure. An editorial some time ago in the Lancet (Anonymous, 1977) describes the situation aptly:

Blood pressure is a measurable end product of an exceedingly complex series of factors including those which control blood vessel calibre and responsiveness, those which control fluid volume within and outside the vascular bed, and those which control cardiac output. None of these factors is independent: They interact with each other and respond to changes in blood pressure. It is not easy, therefore, to dissect out cause and effect. Few factors which play a role in cardiovascular control are completely normal in hypertension: Indeed, normality
would require explanation since it would suggest a lack of responsiveness to increased pressure.

As we shall see, more and more differences are being identified within the population of patients with primary hypertension. For now, however, unifying hypotheses seem appropriate, with the recognition that there may be considerable variations in the role of various components at different times and stages and in different people. Before examining the specific hypotheses that may explain the development of hypertension, the role of genetics will be considered.

ROLE OF GENETICS

Family History

In the rush to discover specific genetic mutations responsible for hypertension, the relatively simple ascertainment of a family history is often neglected but should not be (Guttmacher et al., 2004). Former estimates of heritability based on office BPs were in the range of 20% to 40% (Dominiczak et al., 2000). More recent estimates based on ambulatory BPs are higher (Fava et al., 2004), reaching 61% in a large sample of twins (Kupper et al., 2005).

Genetic Associations

The current situation of the search for hypertension genes was characterized by Castellano (2004): … several different strategies have been adopted to dissect the genetic contribution to blood pressure, including investigations of specific candidate genes, genome-wide searches, the use of intermediate phenotypes, gene expression studies, comparative genomics and synteny in animal models. Overall, the candidate gene approach has been the main strategy utilized for searching for hypertension loci…. Recent studies conducted using another major strategy for identifying loci contributing to a complex trait (i.e. genome-wide scanning) strongly suggest that the genetics of human essential hypertension is probably characterized by many rare, recent-onset, population-specific alleles, carrying a genotype relative risk as little as 1.2–1.5. This scenario closely resembles the “geneticist's nightmare,” as hypothesized for other common diseases such as diabetes mellitus, and some scientists believe that, under these conditions, finding genotype-phenotype correlations is an almost impossible task. To give one example, assuming an odds ratio of 1.2 for the variant genotype in the development of hypertension, an 80% statistical power to detect an association with a P-value of 0.05 could be achieved only by studying close to 20,000 subjects (cases plus controls).

Lest Castellano be considered too pessimistic, Lohmueller et al. (2003) analyzed all of the 18 studies of the polymorphisms of the α-adducin gene described first by Cusi et al. (1997). They found only seven to be statistically significant and of those, five were of the same direction as the original report, the other two to be in the opposite direction. It seems apparent that “we are not there yet” in demonstrating specific genetic causation in complex diseases (Page et al., 2003) but the search will surely go on (de Lange et al., 2004) (Table 3-1).
Pharmacogenetics

Since individual patients' responses to any given monotherapy is so variable, pharmacogenetic approaches are being intensively pursued to predict the basis for response and thereby provide greater individualization and efficacy of antihypertensive therapy (Turner & Schwartz, 2005). As of now, a few tentative successes have been reported, as with polymorphism of the β-adrenergic receptor genes and response to β-blockers (Filigheddu et al., 2004). However, discrepancies abound. For example, the presence of the α-adducin Gly460→Trp polymorphism was found by one group to provide an odds ratio of 15.75 of being a responder to hydrochlorothiazide (Sciarrone et al., 2003) but the same polymorphism made no contribution to the BP response to P.53 diuretics by another group (Turner et al., 2003). Nonetheless, carriers of this particular polymorphism were found to have a lower risk of combined stroke and myocardial infarction (MI) with diuretic therapy than with other antihypertensive therapies (Psaty et al., 2002).

**TABLE 3-1 Some of the Candidate Genes for Which Polymorphisms Have Been Reported in Human Hypertension**

<table>
<thead>
<tr>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenosine type A2a receptor</td>
</tr>
<tr>
<td>α-Adducin</td>
</tr>
<tr>
<td>β2-Adrenergic receptor</td>
</tr>
<tr>
<td>Angiotensin type 1 receptor</td>
</tr>
<tr>
<td>Angiotensinogen</td>
</tr>
<tr>
<td>Atrial natriuretic peptide and receptor</td>
</tr>
<tr>
<td>Bradykinin type 2 receptor</td>
</tr>
<tr>
<td>Dopamine D1 receptor</td>
</tr>
<tr>
<td>Endothelial nitric oxide synthase</td>
</tr>
<tr>
<td>Endothelin 1 and 2</td>
</tr>
<tr>
<td>Epithelial sodium channel, β-subunit</td>
</tr>
<tr>
<td>G-Protein, β3 subunit</td>
</tr>
<tr>
<td>11β-Hydroxysteroid dehydrogenase type 2</td>
</tr>
<tr>
<td>Insulin growth factor 1</td>
</tr>
<tr>
<td>Insulin receptor substrate 1</td>
</tr>
<tr>
<td>Neutral endopeptidase</td>
</tr>
<tr>
<td>Prostacyclin synthase</td>
</tr>
<tr>
<td>Prostaglandin EP2 receptor</td>
</tr>
<tr>
<td>Renin</td>
</tr>
<tr>
<td>Sodium amiloride-sensitive channel</td>
</tr>
<tr>
<td>Sodium-chloride thiazide-sensitive cotransporter</td>
</tr>
<tr>
<td>Sodium-potassium-chloride cotransporter</td>
</tr>
<tr>
<td>Sodium-proton exchanger 3</td>
</tr>
<tr>
<td>Transforming growth factor - β1</td>
</tr>
<tr>
<td>20-HETE-synthase</td>
</tr>
</tbody>
</table>

The field looks promising, but as Califf (2004) notes: “The promise of genomics and proteomics is largely built on the theory that these technologies will be able to judge the risks and benefits of therapies in much smaller, focused groups of patients. While a few notable successes have occurred, progress has been slow, and many heralded advances have not been replicated in validation studies.”
Monogenic Hypertension

Unlike the problems of identifying the genes responsible for primary hypertension and those related to responses to drugs, the study of rare mendelian forms of hypertension in which mutations in single genes caused marked rises in blood pressure has been very informative (Nabel, 2003; Wilson et al., 2004). These are described in Chapters 12, 13, and 14 and most involve increased sodium reabsorption (Staessen et al., 2003). They include:

- Glucocorticoid-remediable aldosteronism
- Apparent mineralocorticoid excess
- Liddle's syndrome
- Hypertension exacerbated by pregnancy
- Pseudohypoaldosteronism, type 2
- Congenital adrenal hyperplasia (11β and 17α hydroxylase)
- Hypertension with bacbydactyly
- PPARγ missense mutations
- Multiple endocrine neoplasia-2 with pheochromocytoma
- Polycystic kidney disease
- Mutation in a mitochondrial tRNA

Scattered reports suggest that one or more of those monogenetic forms of hypertension may be more frequent, particularly in patients resistant to conventional therapies (Oparil et al., 2003) or with low renin levels (Carvajal et al., 2005). In the meantime, caution is advised in accepting such reports as reflecting real genetic differences (Crawford et al., 2004).

Limitations of Genetics

Even as the scope of genetic research is broadened, cautions about the limitations of what can be expected in the future are bringing the initial overenthusiasm about the “genetic revolution” into a more guarded perspective (Castellano, 2004). In addition to the fundamental problems of the complexity of BP regulation, Weatherall (1999) notes that “the complexity of the genotype-phenotype relationship has undoubtedly been underestimated…. It is far from certain that we will ever reach a stage in which we can accurately predict the occurrence of some of the common disorders of Western society at any particular stage in an individual's life.”

Genes versus Environment

As the complexities of the genotype-phenotype relationships are being addressed, a simple portrayal of the underlying interactions have been described by Carretero and Oparil (2000): Theoretically, in a population unaffected by hypertensinogenic factors, BP will have a normal distribution; it will be skewed to the right and will have a narrow base or less variance [Figure 3-1, continuous line]. When one hypertensinogenic factor is added to this population, such as increased body mass, one would expect the normal distribution curve to be further skewed to the right; consequently the base will be wider (more variance) and the curve will be flatter [Figure 3-1, broken line]. If a second hypertensinogenic factor such as alcohol intake is added to increased body mass, the
curve will be skewed more to the right and the variance will increase further, with more subjects classified as hypertensive [Figure 3-1, dotted line].

Discovering which genetic variations place BP on the left or right side of the distribution curve is of both theoretical and practical importance because it could help the physician to better treat or cure hypertension. Recognition of the hypertensinogenic factors may allow nonpharmacological prevention, treatment, or cure of hypertension. As will be noted in greater detail, the boundaries between genes and environment have been blurred further by the recognition of intrauterine growth retardation as an apparently strong predictor of subsequent hypertension. Obviously, it would be easy to mistake prenatal influences for genetic defects.

Promise of Genetics

Although a complete unraveling of the genotype-phenotype relationships involved in human hypertension may never be achieved, a great deal of good may come along the way. We can hope for another discovery such as the low-density lipoprotein receptor mutations underlying familial hypercholesterolemia that led to the development of the remarkably effective statin drugs. However, as Luft (2004) observes:

Compared with hypertension, lipid metabolism is a “no brainer.” Low-density lipoprotein cholesterol P.54 (LDL) and high-density cholesterol (HDL) can be easily measured, are relatively constant, and can be sent through the mail, in contrast to blood pressure measurements. We are able to account for almost all the genetic variance in the clinically relevant LDL/HDL ratio. These findings give us some grounds for optimism in terms of tackling complex genetic traits. However, lipid metabolism is a trivial academic pursuit compared with blood pressure.

FIGURE 3-1 Interaction among genetic and environmental factors in the development of hypertension. The left side of the figure shows how environmental factors and multiple genes responsible for high blood pressure (BP) interact and affect intermediary phenotypes. The result of these intermediary phenotypes is BP with a normal distribution skewed to the right. Continuous line indicates the theoretic BP of the population that is not affected by hypertensinogenic factors; shaded area indicates systolic BP in the hypertensive range. Broken lines and dotted lines indicate populations in which one (obesity) or two (obesity plus high alcohol intake) hypertensinogenic factors have been added. (Modified from Carretero OA, Oparil S. Essential hypertension. Circulation 2000;101:329–335.)

My colleagues at the University of Texas Southwestern Medical School, Drs. Michael Brown and Joe Goldstein, might take exception to the “no-brainer” depiction of lipid genetics, but it may still be possible to use gene therapy for complications of hypertension, as is being applied to patients with peripheral vascular disease (Morishita et al., 2004). Perhaps closer to practical application is the use of pharmacogenetics.
We will now examine various environmental factors, including stress, obesity, and electrolyte intake, that likely interact with multiple genes. These factors will be considered as part of a construct that covers multiple possible pathways to hypertension.

OVERVIEW OF PATHOGENESIS

The pressure required to move blood through the circulatory bed is provided by the pumping action of the heart [cardiac output (CO)] and the tone of the arteries [peripheral resistance (PR)]. Each of these primary determinants of the BP is, in turn, determined by the interaction of the “exceedingly complex series of factors” (Anonymous, 1977) displayed in part in Figure 3-2. Hypertension has been attributed to abnormalities in virtually every one of these factors. Each will be examined and attempts will be made along the way to integrate them into logical hypotheses. It is unlikely that all these factors are operative in any given patient; but multiple hypotheses may prove to be correct, because the hemodynamic hallmark of primary hypertension—a persistently elevated vascular resistance—may be reached through a number of different paths. Before the final destination, these may converge into either structural thickening of the vessel walls or functional vasoconstriction. Moreover, individual factors often interact, and the interactions are proving to be increasingly complex.

We will follow the outline shown in Figure 3-2, recognizing that the position of each factor in the outline is not necessarily in the order that the hemodynamic cascade follows in the pathogenesis of hypertension. Without knowing what starts the process, we can lay out only a preliminary blueprint that can be used by beginning at multiple sites.

An increased CO has been found in some young, borderline hypertensives who may display a hyperkinetic circulation. If it is responsible for the hypertension, the increase in CO could logically arise in two ways: either from an increase in fluid volume (preload) or from an increase in contractility from neural stimulation of the heart (Figure 3-2). However, even if it is involved in the initiation of hypertension, the increased CO likely does not persist, because the typical hemodynamic finding in established hypertension is an elevated PR and lower or normal CO (Taler et al., 2004a).
Heart Rate

Although an increased heart rate may not simply be a reflection of a hyperdynamic circulation or an indicator of increased sympathetic activity, multiple epidemiologic surveys have shown that an elevated heart rate is an independent predictor of the development of hypertension (Palatini & Julius, 1999). Moreover, both an elevated heart rate and decreased heart rate variability are predictors of cardiovascular mortality, at least in part because they are associated with other cardiovascular risk factors (Palatini et al., 2002).

Hyperkinetic Hypertensives

Numerous investigators have described hypertensives, mostly young, who definitely have high CO (Finkelman et al., 1965; Jiang et al., 1995). Using echocardiography to study young borderline hypertensives (average age, 33 years), 37 of 99 subjects were found to have increased heart rate, cardiac index, and forearm blood flow caused by an excessive autonomic drive (Julius et al., 1991c). It should be noted that most of these features could reflect anxiety over both the knowledge that they were hypertensive (Rostrup et al., 1991) and the procedures used in the studies (Marshall et al., 2002; Palatini et al., 1996). Moreover, these features have not been observed either in small groups of normotensive children who are likely to develop hypertension because both their parents were hypertensive (van Hooft et al., 1993) or in almost 500 participants in the Framingham Heart Study who developed hypertension (Post et al., 1994). In this echocardiographic follow-up in Framingham, initially increased heart rate and cardiac index were related to the subsequent onset of hypertension, but none of the hemodynamic evidences of a hyperkinetic circulation was a significant predictor of the development of hypertension after controlling for age and baseline BP. P.56

Cardiac Contribution

Nonetheless, significant increases in left ventricular mass have been recognized in the still-normotensive children of hypertensive parents (Koren & Devereux, 1993; van Hooft et al., 1993). Such left ventricular hypertrophy (described in greater detail in Chapter 4) has generally been considered a compensatory mechanism to an increased vascular resistance (afterload). However, it could also reflect a primary response to repeated neural stimulation and, thereby, could be an initiating mechanism for hypertension (Julius et al., 1991c) as well as an amplifier of CO that reinforces the elevation of BP from arterial stiffening (Segers et al., 2000).

Increased Fluid Volume

A second mechanism that could induce hypertension by increasing CO would be an increased circulating fluid volume (preload). However, in most studies, subjects with high BP have a lower blood volume and total exchangeable sodium than do normal subjects (Harrap et al., 2000).
Relation of Blood Volume to Blood Pressure

When the BP was correlated to the total blood volume in 48 healthy subjects and 106 patients with fairly early and mild primary hypertension, an interesting relationship was observed (London et al., 1977) (Figure 3-3). A negative correlation was found in the healthy subjects but not in the hypertensives, with 80% of the hypertensives being outside the 95% confidence limits of the normal curve. The authors interpret their data as indicating a quantitative disturbance in the pressure-volume relationship in primary hypertension (i.e., a plasma volume that is inappropriately high for the level of BP). Thus, even if absolute values are reduced, a relatively expanded blood volume may be involved in the maintenance of hypertension.

![View Figure](https://example.com/figure3_3)

**Figure 3-3** - Relation between diastolic blood pressure and total blood volume in 48 normotensive (open circles) and 106 hypertensive (solid circles) subjects. Only 20% of the hypertensive patients fell within the 95% confidence limits of the normal curve. The total blood volume definition (solid circles with arrow) represents the degree of the pressure-volume disturbance. (Modified from London GM, Safer ME, Weiss YA, et al. Volume-dependent parameters in essential hypertension. Kidney Int 1997;11:204–208.)

Even if CO is involved in the initiation of hypertension, once hypertension is established, CO usually is not increased, but PR is elevated (Taler et al., 2004a).

**Autoregulation**

**Definition and Description**

The pattern of initially high CO giving way to a persistently elevated PR has been observed in a few people and many animals with experimental hypertension. When animals with markedly reduced renal tissue are given volume loads, the BP rises initially as a consequence of the high CO but, within a few days, PR rises and CO returns to near the basal level (Guyton, 1992) (Figure 3-4). This changeover has been interpreted as reflecting an intrinsic property of the vascular bed to regulate the flow of blood, depending on the metabolic need of tissues. This process, called autoregulation, was described by Borst and Borst-de Geus (1963) and demonstrated experimentally by Guyton and Coleman (1969). With increased CO, more blood flows through the tissues than is required, and the increased flow delivers extra nutrients or removes additional metabolic products; in response, the vessels constrict, decreasing blood flow and returning the balance of supply and demand to normal. Thus, PR increases and remains high by the rapid induction of structural thickening of the resistance vessels, as described in the section Peripheral Resistance.

Similar conversion from an initially high CO to a later increased PR has been shown in hypertensive people (Andersson et al., 1989; Julius, 1988b; Lund-Johansen, 1989). In Lund-Johansen's (1989) study, younger (17- to 29-year-old) mild hypertensives were restudied both at rest and during exercise P.57
after 10 years on no treatment and then after 20 years following withdrawal of intervening therapy. As the overall BPs rose, the CO fell and PR increased (Figure 3-5).

![Progressive changes in important circulatory system variables during the first weeks in volume-loading hypertension. The initial rise in cardiac output is the basic cause of the hypertension. Subsequently, the autoregulation mechanism returns the cardiac output to almost normal and at the same time causes a secondary increase in total peripheral resistance. (Modified from Guyton AC. Kidneys and fluids in pressure regulation. Hypertension 1992;19(Suppl 1):12–18.)](image)

Problems with the Autoregulation Model Julius (1988b) considers autoregulation to be an unlikely explanation for the switch from high CO to increased PR and offers another: structural changes that decrease the cardiac responses to nervous and hormonal stimuli but enhance the vascular responses. His proposal states that the “hemodynamic transition can be explained by a secondary response to elevated blood pressure. The heart becomes less responsive as a result of altered receptor responsiveness and decreased cardiac compliance, whereas the responsiveness of arterioles increases because of vascular hypertrophy, which leads to changes in the wall-to-lumen ratio” (Julius, 1988b).

Nonetheless, the autoregulatory model does explain the course of hypertension in volume-expanded animals and people, particularly in the presence of reduced renal mass (Figure 3-4). Ledingham (1989) defends autoregulation as the “dominant factor” leading to the rise in PR in hypertension. Moreover, there is additional evidence in favor of volume expansion in the pathogenesis of the disease, reflecting the effect of too much sodium coming in and not enough going out, the latter because of a less-than-normal number of nephrons.

EXCESS SODIUM INTAKE

Figure 3-2 shows excess sodium intake inducing hypertension by increasing fluid volume and preload, thereby increasing CO. As will become obvious, sodium excess may increase BP in multiple other ways also.

Overview

After reviewing the available evidence relating sodium intake to hypertension, most investigators determine that “there is conclusive evidence that dietary salt is positively associated with BP and that BP can be lowered with reductions in sodium intake of 40 to 50 mmol [per day] in both hypertensive and nonhypertensive persons” (Chobanian & Hill, 2000). Some authors, reviewing the same evidence, do not agree (Brown et al., 1984), whereas others accept a role for sodium but question the wisdom of advocating sodium restriction in view of potential hazards (Alderman, 2004).
The basis for the generally accepted necessary but not, in itself, sufficient role of sodium excess was stated by Denton (1997):

Human prehistory as hunter-gatherers with inland savannah existence involved a paucity of salt. The hedonistic liking for it, physiologically apt in those circumstances, is maladaptive in Western metropolitan existence with processed food and cheap abundant salt sources. Above a threshold of 70–100 mmol Na per day, sodium intake may be directly causal of BP increase in sensitive individuals, and permissive of action of other factors such as low K and Ca intake, stress, obesity and alcohol to influence BP.

As will be noted, diets in industrialized societies contain many times the daily adult sodium requirement, an amount that is beyond the threshold level needed to induce hypertension (Figure 3-6). Only part of the population may be susceptible to the deleterious effects of this high sodium intake, presumably because these individuals have an additional renal defect in sodium excretion. As portrayed in Figure 3-6, because almost everyone in industrialized societies ingests an excess of sodium beyond the threshold needed to induce hypertension, it may not be possible to show a relationship between sodium intake and BP in these populations. The absence of such a relationship in no way detracts from the possible role of excess dietary sodium in causing hypertension.

Dietary Chloride

Chloride, and not just sodium, may be involved in causing hypertension. In two classic rat models of sodium-dependent hypertension, hypertension could be induced with sodium chloride but not with sodium bicarbonate or ascorbate (Kurtz & Morris, 1983; Whitscarver et al., 1984). In people, too, the BP rises more with NaCl than with nonchloride salts of sodium (Schorr et al., 1996). This issue is largely academic, as chloride is the major anion accompanying sodium in the diet and in body fluids.

Epidemiologic Evidence

The epidemiologic evidence incriminating an excess of sodium includes the following points:

- Primitive people from widely different parts of the world who do not eat sodium have no hypertension, and their BP does not rise with age, as it does in all
industrialized populations (Denton, 1997; Page et al., 1981). For example, the Yanomamo Indians of northern Brazil, who excrete only approximately 1 mmol of sodium per day, have an average BP of 107/67 mm Hg among men and 98/62 mm Hg among women aged 40 to 49 (Oliver et al., 1975).

- The lack of hypertension may be attributable to other differences in lifestyle, but comparisons made in groups living under similar conditions relate the BP most directly to the level of dietary sodium intake (Lowenstein, 1961; Page et al., 1981). Moreover, when primitive peoples who are free of hypertension adopt modern lifestyles, including increased intake of sodium, their BP rises and hypertension appears (Klag et al., 1995; Poulter et al., 1990).

- Significant correlations between the level of salt intake and the levels of BP and frequency of hypertension have been found in most large populations (Beard et al., 1997; du Cailar et al., 2004; Khaw et al., 2004; Stamler et al., 1996) but not in all (Smith et al., 1988). The strongest data come from the Intersalt study, which measured 24-hour urine electrolytes and BP in 10,079 men and women aged 20 to 59 years in 52 places around the world (Elliott et al., 1996; Intersalt Cooperative Research Group, 1988). For all 52 centers, there was a positive correlation between sodium excretion and both systolic BP and diastolic BP but an even more significant association between sodium excretion and the changes in BP with age (Figure 3-7). Few populations were found whose levels of sodium intake were in the 50- to 100-mmol per day range, wherein the threshold for the sodium effect on BP likely resides. However, the virtual absence of either hypertension or a progressive rise in BP with advancing age in populations with an average sodium ingestion of only about 50 mmol per day supports the concept of a threshold.

As noted by Denton (1997), our current high sodium-low potassium intake is a recent phenomenon in the span of human existence, beginning only a few hundred years ago and accelerated by modern food processing, which adds sodium and removes potassium. Table 3-2 shows that our herbivorous ancestors probably consumed less than 10 mmol of sodium per day, whereas our carnivorous ancestors might have eaten 30 mmol per day (Eaton et al., 1996). Human physiology evolved in a low-sodium/high-potassium environment, and we seem ill equipped to handle the current exposure to high sodium and low potassium.

Our current preference for a high sodium intake likely is an acquired taste, one that may develop early in childhood (Zinner et al., 2002). In the typical diet of industrialized societies, as little as 15% of total sodium consumption is discretionary, and even less is inherent to the food, with more than 75%