The aim of this brief review is to provide researchers involved in investigating the pathogenesis of essential hypertension with a historical perspective of genetic studies on the subject and to list some of the problems that should be taken into account when considering the hypothesis that a given biochemical mechanism may be involved in causing essential or genetic types of hypertension. Because of obvious space limitations and the wide variety of problems involved, it will not be possible to provide a detailed, comprehensive review of all the published work on this topic. However, we will try to focus on some common beliefs that have been dominant in the literature and continue to influence the thinking of many students of hypertension, at least as indicated by discussions at scientific meetings and articles in the specialist journals. We will also briefly discuss the criteria for allocating a given biochemical finding to its probable position in the chain of events leading from a gene abnormality to increased blood pressure. Such criteria appear to be missing in most of the published work on genetic rat models aimed at elucidating differences in biochemical systems of blood pressure regulation between hypertensive strains and their various normotensive controls.

Many genes coding for proteins involved in blood pressure regulation (renin, atrial natriuretic factor, mineralocorticoids, and adrenergic receptors) have already been identified. In addition, molecular mechanisms that may affect the blood pressure level in humans and experimental animals are under investigation. For these reasons, any discussion of the genetic or primary mechanisms causing essential hypertension must include attempts to find links between these aspects at the different biological levels of organization—from the ultimate phenotypic level (blood pressure) to the protein level (gene products), and eventually, to the DNA structure. The extension of this strategy to humans might be possible if the complex interaction of genetic and environmental influences were understood. Even if the sophistication and the novelty of the techniques discourage many students of hypertension, this effort is justified by the demonstration that even diseases with similar phenotypes and identical modes of inheritance have turned out to be genetically heterogeneous at both the DNA and primary gene product levels. For all these reasons, our discussion of the genetic control of blood pressure will examine the results obtained thus far with the classic biometrical approach, which includes analysis of the frequency distribution of blood pressure in the population and more sophisticated quantitative methods (studies of families, likelihood analysis of pedigree data), to determine whether the large amount of data so furnished justifies a deeper investigation of the genetic control of essential hypertension and which genetic model best fits the experimental information. We will also address the following question: If genetic factors play an important role in determining the variability of blood pressure in the population, can a link with a given genetically controlled protein polymorphism be identified, and to what extent are such polymorphisms related to the variability of blood pressure?

The Biometrical Approach

When the blood pressure distribution of the human population is considered, those persons with blood pressure above a certain arbitrary limit are said to have essential hypertension if other causes of hypertension can be ruled out. Systolic and diastolic blood pressure levels are characteristics that can be defined as quantitative; they are measured on a continuous scale. It is clearly impossible to divide the population values into discrete categories on the basis of individual measurements. Nevertheless, from the clinical standpoint a sharp distinction exists: A portion of the population (a minority) is defined as abnormal (hypertensive) and the remain-
The Unimodal–Bimodal Controversy

The shape of the overall distribution of blood pressure levels was regarded with particular interest in the epidemiological surveys that dominated the literature of essential hypertension during the 1950s and 1960s. Platt8–9 claimed the existence of a bimodality in the distributions of blood pressure. He attributed this to the segregation of a single gene, even if there were large variations between the measurements, but he thought that environmental conditions played little or no part in the genesis of hypertension. This interpretation was in strong opposition to the views of Pickering’s group,10–12 which supported the existence of unimodal distributions in the detailed, large surveys of the London population. A unimodal distribution in a random-mating population would suggest the existence of many genetic factors segregating independently. An extensive interpretation was that hypertension is not a true disease, but that the risk arising from high blood pressure is simply proportional to its entity, environmental factors being responsible for the rate and pattern of the rise with age.13

The debate between bimodalists and unimodalists has now lost much of its importance, since the shape of a distribution is not sufficient to prove the existence of few or many segregating genes, at least if the environmental conditions cannot be controlled, as in animal and plant experiments. In fact, a bimodal distribution can be simulated in a polycyclically controlled trait by a secondary effect when the measured variable shows a tendency toward self-enhancement; for instance, above certain levels of blood pressure, kidneys can be damaged, leading to further increases in blood pressure.14 On the other hand, bimodality cannot be observed among closely overlapping distributions.15 Examples can be furnished by analyses of variability in enzyme levels caused by various polymorphisms, such as glutamate–pyruvate transaminase activities16 and red blood cell acid phosphatase activities.17 In such cases, the combined distribution of enzymatic levels in the population at large can be regarded as unimodal and interpreted as multifactorial in origin, even when the total population distribution is determined by the segregation of only two alleles. Finally, a more careful reexamination of epidemiological data from a large blood pressure survey in Bergen, Norway—when the data were stratified according to age and sex—has revealed, in an apparent unimodal distribution, the existence of two overlapping distributions with statistically different mean values at different ages.18

Analysis of Aggregation in Families

A genetic hypothesis cannot be based exclusively on the population distribution of the variable. Family data are also needed; in other words, the aggregation of the trait must be examined in relatives. The aggregation of a phenotypic trait among persons who share genes in common (parents and offspring, siblings) is a strong indication of the existence of genetic control of the trait if the environment can be considered neutral. The study of blood pressure levels in families has, however, no simple genetic interpretation, because family members share a common environment as well as genes. Many epidemiological data have been studied to clarify the relation between probands and, generally, their first-degree relatives by means of different coefficients of resemblance (correlation and regression coefficients). The most important studies dealing with the quantitative genetic analysis of blood pressure levels from large samples of the population yielded different estimates of the degree of association between parents and offspring and between siblings (Table 1). The comparison of these estimates is of interest. The correlation between siblings was higher than that between parents and offspring in the study of Miall et al.,19 lower in the Framingham study,20 but similar in the Evans County21 and Tecumseh studies.22 Furthermore, no correlation between siblings was found in the black population of Detroit,23 although the sample size was small. Moreover, a reanalysis of the Detroit data using more appropriate and sophisticated methods showed that a significant fraction of blood pressure variation is caused by genetic factors.24 The complementary information furnished by the analysis of the aggregation of blood pressure levels of adopted children as compared with the blood pressure of adoptive parents is included in the Montreal Adoption Study.25

An analysis in twins can corroborate the interpretation of the genetic control of a quantitative trait. Monozygotic twins represent the only model in which genetically identical humans can be com-
pared and where environmental effects may be detected; in fact, any differences between them are due to environmental influences. Comparison with the trait in dizygotic twins, in whom both genetic and environmental factors act, can quantify the extent of genetic control, which is estimated to represent as much as 82% of the variation in systolic blood pressure. Some caution should be observed because cultural influences are generally more similar in twins than in siblings. An analysis of the genetic control at the biometrical or phenotypical level based on the degree of association of the trait in relatives has recently been reviewed. All the data revealed a stronger correlation between genetically related persons than between spouses or between adoptees and have so far strongly stressed two major points. First, a familial aggregation of blood pressure levels, and consequently of hypertension, exists even when large differences in different populations have been taken into account. Second, the observed familiarity is due, in different proportions, to shared genes and shared environment. However, a large amount of indetermination is expected if the analysis is restricted to this approach. For instance, a parent-sib correlation may be lower than a sib-sib correlation for two reasons: a more similar level, they can greatly influence the interpretation of the results. As discussed in detail by Cavalli-Sforza and Bodmer, if a specific environmental effect on siblings can be excluded, the estimate of the fraction of blood pressure variance due to genetic factors will increase. An interpretation could be that relatively few genes are involved in the determination of blood pressure, since a consistent dominance effect of many genes seems unlikely. In the Montreal Adoption Study, however, the environmental effects were carefully investigated and a differentiation was made between a shared environment common to parents and children (the so-called across-generation environmental effects) and an environment shared by children only (within-generation effects). For instance, with regard to diastolic blood pressure, 30% of the phenotypical variability in siblings was due to genes, 11% to across-generation environmental effects, and 20% to environmental effects shared by the children alone.

Blood pressure correlates with potential confounding traits such as age, sex, and anthropometric characteristics, and this has also been observed for many biochemical and physiological factors involved in its control. The existence of such correlations can lead to two different biases in the use of the aggregation of the blood pressure among genetically related persons. First, groups of siblings and groups of spouses will be more uniform for age than other randomly selected persons. If the confounding variables are not considered in the analysis (a good approach is the use of residuals after fitting a multiple regression to the data), biased or distorted correlations can be the result of their joint variation instead of the variation of the main trait. Second, the estimate of heritability coefficients from the association coefficient is based on the assumption of random mating in the study population. If blood pressure can be influenced by concomitant variables, particularly by anthropometric or behavioral characteristics that can favor assortative mating, the basic assumption for the unbiased estimation may not be upheld.

**Analysis of Pedigree Data**

For all of the reasons mentioned, a promising strategy is to determine the relative contribution of genes and of environmental factors directly from pedigree data or, preferably, from data measured in individual members of a family whose links in the pedigree are known. The determination is made possible by fitting a specific genetic model to family data and by estimating its relative likelihood. Quantitative methods such as likelihood pedigree analysis and path analysis are commonly used in population genetics, but they have been employed only recently in the study of the genetics of hypertension. In this procedure, each genetic model (sporadic, monogenic, polygenic, or mixed with different subdivisions) can be represented by a set of genetic and environmental (familial or individual) factors. A likelihood function is used to combine the data from pedigrees with the parameters of the model. The values of parameters that maximize the function are chosen as representative of the model and, consequently, of the distribution characteristics in the overall population. Different models are compared with the sporadic one that does not include genetic parameters, and the model with the highest likelihood is chosen as that best fitting the observed data. The most extensive applications of the likelihood pedigree analysis can be found in the Utah Survey and in the Montreal Adoption Study. The maximal likelihood analysis of pedigrees has

<table>
<thead>
<tr>
<th>TABLE 1. Coefficients of Aggregation for Systolic Blood Pressure Among First-Degree Relatives</th>
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</thead>
<tbody>
<tr>
<td>Study and location</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Miall et al., South Wales, UK</td>
</tr>
<tr>
<td>Havlik et al., Framingham, MA, USA</td>
</tr>
<tr>
<td>Hayes et al., Evans County, GA, USA</td>
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<tr>
<td>Longini et al., Tecumseh, MI, USA</td>
</tr>
<tr>
<td>Shull et al., Detroit, MI, USA</td>
</tr>
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<td>Biron et al., Montreal, Canada</td>
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*Correlation coefficient.  †Intraclass correlation coefficient.
confirmed that a polygenic model is adequate to explain the observed variability of blood pressure.

The Molecular Approach

Since it has been established that a substantial portion of blood pressure variability is due to genetic factors and that a polygenic model best explains this variability, the question arises as to whether (and eventually how) it would be possible to identify, among the genes involved, the gene with the higher relative effect. According to genetic theory, a true difference does not exist between the so-called polygenes and a major gene at the primary product level and, consequently, between the genetic control of a quantitative and a qualitative trait. The distinction is based only on the difficulty of dissecting the complex phenotypical expression into the effects of individual genes that control the quantitative trait. One of the well-known examples of phenotypical changes in the expression of a genotypical difference according to the biological level of observation is provided by the phenylketonuria syndrome.35 This syndrome is related to the high level of phenylalanine in the plasma of affected persons as a result of a mutation of the gene coding for the enzyme responsible for the conversion of phenylalanine into tyrosine. The distinction between normal and affected persons is difficult to make if it is based on a complex phenotypical trait such as head size (Figure 1, bottom panel), because the effects of other genes and of environment are added (polygenic model). The contribution of the phenylketonuria gene to head size (the ultimate level in this example) is obviously smaller as compared with the total effect of other genes. The intelligence quotient (IQ) distributions (see Figure 1, middle panel) overlap slightly. In fact, the IQ is still highly influenced by different genetic and environmental factors. However, the effect of the phenylketonuria gene is already clear. If we consider a level of analysis closely related to the primary activity of the gene (see Figure 1, top panel), the distinction between normal and affected persons is clear, and even if a certain variability is present, the effect of the major gene is detectable in a qualitative way. If we consider the phenylketonuria gene as only one of the polygenes controlling head size, it acts at the primary product level as a "normal" gene with a clear qualitative effect.

Analysis of Biochemical and Physiological Components of Blood Pressure or Intermediate Phenotypes

Even if the formal model of quantitative inheritance implies the existence of many genes that all have similar and additive effects, a multifactorial model can comprise some genes with a larger effect on the level of the trait under study. The detection of such a gene or genes is difficult indeed if the analysis is restricted to the ultimate phenotype—in this context, blood pressure. The identification of major physiological and biochemical components, the variability of which must be analyzed in persons drawn from a population or pedigree, can be of help in understanding the genetic control of the ultimate phenotypical level and the nature and degree of interactions with the environmental effects. A basic prerequisite should be that the variability of a component trait or of the so-called intermediate phenotypes is significantly associated with the variability of blood pressure in the population. The numerous physiological and biochemical studies of the pathogenesis of hypertension have furnished an excellent basis for identifying important intermediate phenotypes. These characteristics, which are generally investigated as biochemical or physiological indicators of hypertension, concern different aspects of human physiology.36 To be of interest in the genetic dissection of a complex trait, the mode of inheritance of the intermediate phenotype must be investigated. The detection of a simple genetic control is more probable if the intermediate phenotype is close to the primary gene product. If we know the genetic control of an intermediate phenotype, its relevance to the variability of blood pressure levels, and its relative frequency in different pedigrees, it should be possible to predict the inheritance of blood pressure more accurately.

The dissection of a complex trait is shown in Figure 2. In this scheme, the path connecting the genes (at the bottom) to the ultimate level—blood pressure (at the top)—is represented by a number of different intermediate levels that "dissect" the complex trait; at each level one or more intermediate phenotypes can be determined. At the bottom, the genetic information can be subdivided into polygenes, the effects of which are not individually measurable but that act at each level of dissection,
and candidate genes, the effects of which must be determined. The paths connecting the intermediate components (shown as dotted lines in Figure 2) and the genetic interactions with regulatory effects (shown as continuous lines) may be extremely complex. Environmental effects (cultural and stochastic) act independently at each level.

The analysis of the intermediate phenotypes can produce useful information: an intermediate trait that shows Mendelian inheritance and that can be linked to the normal biochemical and physiological regulation of blood pressure can act as a marker for blood pressure. Of course, since blood pressure is under polygenic control more than one marker trait probably will be identified in the future. The information about simple intermediate phenotypes and their link with blood pressure can be used to identify the candidate genes, their number, the frequency of alleles, and the mode of action (regulatory or structural). If the genes (measured genotype) are known, then the final product (phenotypical complex trait) can be predicted in individuals. The so-called measured genotype approach of Sing and colleagues was followed. Moreover, it should be possible to distinguish between a true multifactorial model (which emphasizes the role of the interaction between multiple environmental characteristics and multiple genetic factors) and the so-called multiple unilocus model (which relates the high blood pressure to a mutation at any one of many possible controlling loci).

An Example of Analysis of Intermediate Phenotypes in Rats

The model shown in Figure 2 allows us to incorporate the individual findings at the different biological levels in a logical sequence of events, going from a possible gene difference to a blood pressure abnormality. However, this approach to the genetic mechanisms of human hypertension requires an experimental and theoretical foundation in animal models. For example, only after having demonstrated that renal artery constriction causes hypertension in animals was it possible to detect the renal causes of hypertension in humans. The same may prove to be true for identifying the genetic components of hypertension, although an enormously greater degree of complexity and sophistication will be necessary. The results accumulated thus far by studying the problem in the Milan hypertensive strain of rats (MHS) in comparison with its normotensive control strain (MNS) may help to illustrate this type of approach. These studies are proceeding along the following lines:

1. Identification of one or more biochemical or physiological traits (intermediate phenotypes) that are relevant to the blood pressure differences between MHS and MNS.
2. Identification of the protein polymorphisms underlying a given biochemical or physiological trait.
3. Identification of possible DNA polymorphisms underlying the protein polymorphisms.

To assess the first point, an approach similar to that suggested by Rapp for evaluating the role of 18-hydroxydeoxycorticosterone in Dahl rats or of the vascular smooth muscle response to some cations in spontaneously hypertensive rats was followed. To propose that a given trait may be relevant in explaining a blood pressure difference between two strains of rats, the following criteria must be met, at least in part:

1. A difference in the trait between the two strains must be demonstrated.
2. The trait must cosegregate with an increment of blood pressure significantly different from zero in an F2 population obtained from the cross of F1 hybrids (MHS x MNS).
3. Some logical biochemical or physiological link must exist between the trait and blood pressure.

These criteria were met for Na\(^+\)-K\(^+\) cotransport and cell volume in erythrocytes from MHS, mainly because several functional similarities exist between the erythrocytes and renal tubular cells, which are
more directly involved in causing blood pressure differences between MHS and MNS. Therefore, the dissection of these two traits proceeded in order to evaluate whether a protein polymorphism was responsible for the differences between the two strains. The results of these studies showed that the cause of the difference in cell volume and Na⁺-K⁺ cotransport probably was localized in the network of membrane skeleton proteins. Cross-immunization experiments between MHS and MNS with the use of these proteins demonstrated an immunological difference between MHS and MNS of a 105-kilodalton membrane skeleton protein. An erythrocyte complementary DNA (cDNA) library was screened with the antibody against this protein, and a cDNA probe coding for a 31-kilodalton protein was isolated. When injected into rabbit, this protein stimulated the production of an antibody that bound to the natural 105-kilodalton protein. Further studies are in progress to isolate the entire gene coding for the 105-kilodalton protein and to evaluate its possible polymorphism in the two rat strains.

Table 2 illustrates the most significant findings obtained in these two rat strains at the different biological levels, together with other gene products that may be considered candidates for causing other biochemical or physiological differences between MHS and MNS. When the links in sequence—gene to protein to biochemical functions to physiological function to organ function to blood pressure—can be proved to be true and the relative weights to each passage can be assessed in a given rat model of genetic hypertension, then we should have the theoretical and experimental background to approach this problem in human pedigrees, provided that the environmental factors can be evaluated as well in humans as in rats. The key question is how to prove that a given biochemical or physiological sequence is linked to a given gene and is really the cause, or an important part of the cause, of the blood pressure differences between the two strains of rats. The most straightforward approach to this question is certainly the use of transgenic animals. These are animals that have foreign DNA integrated into their germ line by experimental procedures. The most common methods of introducing foreign DNA are direct injection into the embryo or transfection by retro viral vectors. After introduction, the foreign DNA integrates into the host DNA and responds to the host environment. If

<table>
<thead>
<tr>
<th>Phenotypical (or biological) level</th>
<th>Intermediate phenotypes</th>
<th>Experimental findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body</td>
<td>Kidney cross-transplantation</td>
<td>Presor effect ↑ in kidney of MHS 41-42</td>
</tr>
<tr>
<td></td>
<td>H₂O and Na metabolism</td>
<td>Na retention in MHS 43</td>
</tr>
<tr>
<td></td>
<td>Kidney function in whole animal</td>
<td>GFR and Na tubular reabsorption ↑ in MHS 44</td>
</tr>
<tr>
<td>Organ</td>
<td>Isolated kidney</td>
<td>GFR, Na tubular reabsorption, and O₂ consumption ↑ in MHS 45, 46</td>
</tr>
<tr>
<td>Cellular</td>
<td>Structure and function of</td>
<td>Cell volumes or Na content ↓ in MHS 44, 47, 48</td>
</tr>
<tr>
<td></td>
<td>Erythrocytes</td>
<td>Cell volume or Na content ↓ in MHS 47, 49</td>
</tr>
<tr>
<td></td>
<td>Renal tubular cells</td>
<td>Na transport is equal between strains 50, 51</td>
</tr>
<tr>
<td>Subcellular</td>
<td>Inside-out erythrocyte vesicles (without membrane skeleton)</td>
<td>Volume ↓ in MHS 50</td>
</tr>
<tr>
<td></td>
<td>Resealed erythrocyte ghosts (with membrane skeleton)</td>
<td>Na transport ↑ in MHS 51, 52</td>
</tr>
<tr>
<td></td>
<td>Luminal renal membrane</td>
<td>Na transport ↑ in MHS (unpublished data)</td>
</tr>
<tr>
<td></td>
<td>Basolateral renal membrane</td>
<td>All these activities are faster in MHS 54, 51-54 (and unpublished data)</td>
</tr>
<tr>
<td>Biochemical</td>
<td>Na⁺-K⁺ cotransport in inside-out erythrocyte vesicles, erythrocytes, and luminal renal membrane</td>
<td>Immunochemical difference between MNS and MHS 55, 56</td>
</tr>
<tr>
<td></td>
<td>Na⁺-H⁺ countertransport in luminal renal membrane</td>
<td>Difference in isoelectric pattern 56</td>
</tr>
<tr>
<td></td>
<td>Calpain activity in erythrocytes and renal tubular cells</td>
<td>Concentrations 10 times ↓ in MHS 53, 54</td>
</tr>
<tr>
<td>Molecular</td>
<td>105-kilodalton protein in membrane skeleton of erythrocytes or 78-kilodalton protein in renal membrane</td>
<td>Unpublished data</td>
</tr>
<tr>
<td></td>
<td>32- to 34-kilodalton protein in renal membrane</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calpain inhibitor in erythrocytes and renal tubular cells</td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>Isolation of the entire gene coding for the 105-kilodalton protein in membrane skeleton of erythrocytes in progress</td>
<td></td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; ↑ or ↓ = higher or lower in MHS than in MNS.
*By type of experiment performed.
†The characteristics of erythrocytes and blood pressure are highly correlated in F₂ hybrids obtained by crossing the F₁ (MHS × MNS) hybrids. Moreover, bone marrow transplantation between MHS or MNS in irradiated F₁ hybrids has shown that the origin of the functional difference between erythrocytes of MHS and MNS is in stem cells.
integration occurs at an early stage in a germ cell precursor, the foreign DNA will be passed to future progeny. In this way, a difference between the two strains of rats in a given DNA sequence coding for a protein of interest may be tested as a possible cause of a biochemical or physiological sequence of events leading to hypertension (or to part of it). To be successful, this experiment must be performed between strains of rats whose genomes are similar except for the DNA sequence of interest.

The need for this condition to be met is clear from Figure 2. In fact, only if the polygenes forming the genetic background, apart from those regulating blood pressure, are identical between the two strains can we test the effect of a given candidate gene. Such strains of hypertensive and normotensive animals currently are not available. However, strains of rats with a reasonable approximation to the ideal situation can be selected. For instance, since normotension is partly dominant over hypertension in MHS and MNS, a strain of congenic normotensive rats is being selected by repeatedly backcrossing normotensive hybrids to MHS. Successive generations of rats obtained from consecutive backcrosses showed blood pressure values ranging from normotension to hypertension. The number of backcrosses needed to reach a true congenic strain is critical because of the possibility of linkage between the genes of interest. In fact, the closer the associated genes, the higher will be the number of backcrosses needed to separate them. For independent genes, however, seven or eight backcross cycles should be sufficient to attain more than 99% coisogenicity between the congenic normotensive strain and the MHS strain. At that point, virtually only the genes affecting blood pressure should differ between them.

If a DNA polymorphism can be detected between the two strains, the relative gene may be a suitable candidate for a transgenic experiment. However, the present methods used in transgenic animals must be improved before the application of this approach to understanding the genetic basis of hypertension can become practical. First, transgenic techniques also need to be developed in rats (the majority of studies have used mice). Second, a precise targeting of the foreign DNA into the host genome should be accomplished, along with the capability of “switching off” the endogenous gene. At present, the expression, if any, of the foreign DNA may occur at different times with different control mechanisms, as compared with the natural genomic situation.

Future Directions

These approaches involving transgenic animals are expected to be available soon. However, previously published results and future trends in research in animal models or humans that are likely to contribute to the identification of candidates, either as gene products or as DNA segments, involved in blood pressure regulation may be grouped into two categories.

First, genes coding for proteins already known as blood pressure regulators, such as renin, angiotensinogen, mineralocorticoid and glucocorticoid receptors, kallikrein, and kininogen, have already been described, while genes coding for other proteins of this type are probably under investigation. The study of polymorphisms both at DNA and protein levels, either in human pedigrees with hypertensive persons or in strains of rats with genetic hypertension, may provide information on their possible primary involvement in the determination of the set point of blood pressure. The previously mentioned biometrical methods (measured genotypes) can quantify the relative importance of these molecular differences as compared with the remaining genetic background.

Second, extensive measurements of intermediate phenotypes in human pedigrees, families, or strains of rats have already been carried out. These measurements regard blood cell volume, ion concentration, ion transport across the blood cell membrane mediated by different pathways (Na\(^+\)-K\(^+\) pump, Na\(^+\)-K\(^+\) cotransport, Li\(^+\)-Na\(^+\) countertransport, Na\(^+\)-H\(^+\) countertransport), and many other biochemical or physiological functions. These intermediate phenotypes are being measured either because of a logical link between them and some classic pressor mechanisms (such as the release of neurotransmitters, the sodium or calcium concentration in vascular smooth muscle cells, or the renal retention of sodium) or because they showed distinctive values in hypertensive subjects (or rats) as compared with values in their appropriate controls. To be relevant to the understanding of the genetic mechanisms according to the scheme shown in Figure 2, these studies should include a combination of as many biochemical and physiological tests as possible performed on all the individual subjects of the same pedigree or in different rat strains. In fact, we need to describe a substantial portion of the sequence illustrated in Figure 2 and Table 2 in persons belonging to the same pedigree (or rat strain) to be confident that a given genetic link or interaction is at work in that particular pedigree or rat strain. Of course, the closer the intermediate phenotype is to the DNA level, the lower the influence of other concomitant genetic and environmental factors is expected to be. Hypertension is so common and heterogeneous that it would not be surprising to find, even in a single large pedigree, different molecular mechanisms with individual genetic characteristics and polymorphisms.

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