Etiology of Essential Hypertension

RICARDO CRUZ-COKE, M.D.

SUMMARY It is not possible to understand the etiology of hypertension without considering the role of inheritance. Epidemiological evidence indicates that the development of high blood pressure in the population at large depends on the interaction of different types of genes and several environmental influences. The sources of genetic variation in blood pressure distribution are polygenes, polymorphic genes, and dominant idiomorphic genes. The main environmental sources are weight gain, excess salt (Na) intake, and psychosocial stress. Only those individuals with a specific genetic predisposition may develop high blood pressure when exposed to excessive environmental influences. (Hypertension 3 (suppl II): 11-191—11-194, 1981)

KEY WORDS • ecology • hypertension • high blood pressure • etiology • human genetics

THERE is universal acknowledgment that it is not possible to study the etiology of essential hypertension without considering the role of inheritance. Unfortunately, a genetic approach to this problem has been hampered by the fact that not a single deleterious recurrent mutation has been detected in the structural idiomorphic genes which synthesize the enzymes of the renin angiotensin-aldosterone and kallikrein-kinin systems in mammals. Similarly, physiologists and biochemists have been unable to discover a single polymorphic genetic system that relates to blood pressure (BP) regulation. Thus, unable to obtain a direct approach to the genetic sources, geneticists have used indirect epidemiological methods to investigate the genetics of BP in human populations.

Models

Polygenic Model

The epidemiological evidence currently available indicates that the development of high BP in the population at large depends on the interaction of several genetic and environmental influences. The sources of genetic variation of the BP phenotype originate from polygenes, polymorphic genes, and possibly idiomorphic genes. The sources of ecological or environmental variation originate mainly from weight gain, salt (Na) intake, and psychosocial stress. All the genes may be grouped and explained on the basis of a polygenic model.

Polygenic or multifactorial inheritance of a quantitative trait assumes that multiple factors, both inherited and acquired and acting independently, lead to a distribution that is correlated in relatives of patients. The distribution is continuous in the population at large and is the expression of the interaction of "minor" or "common" genes and multiple environmental factors.

The degree of quantitative resemblance (correlation and regression coefficients) among relatives is proportional to the number of genes in common shared by all the individuals within the family.

The polygenic evidence is the following: 1) distribution of levels of BP in relatives of hypertensive patients, compared with controls, shows that the relatives of hypertensives have significantly higher mean blood BP levels at all ages than the relatives of controls.

2) After suitable adjustment for age and sex, it has been found that the tendency of the first degree relatives of hypertensive patients to resemble one another is the same at all levels of BP from the lowest to the highest ranges. The higher the pressure of the patient, the higher the pressure of the relative.

3) The degree of BP resemblance between relatives is a function of the corresponding degree of parentage. First-degree relatives (parents and sibling) show higher correlations and regression coefficients than the second-degree (uncles and grandfathers) and third-degree (cousin) relatives.

All the correlation studies of BP between relatives have found low degrees of resemblance around $r = 0.20$, against an expected 0.50 for total genetic determination. This familiarity is present early in life; the maternal infant correlation at birth is also 0.20. This resemblance is maintained with increasing age until adulthood, with a "tracking coeffi-
cient" near 0.70. In multivariate analysis, this familial coefficient of resemblance is maintained independently of the influence of environmental factors. Consequently, the polygenic evidence is supported by a constant, continuous, and permanent genetic determination detected throughout life.

Monogenic Model

The hypothesis that BP is inherited as a graded characteristic (minor genes) does not exclude the possibility that major genes (polymorphic and idiomorphic) may affect its continuous distribution. Analysis of the genetic variance of BP distribution within families shows that correlation between siblings \( r_{\text{M}} \) is higher than between parents and offspring \( r_{\text{po}} \). According to quantitative genetic theory, this fact demonstrates that a high proportion of the genetic component of BP variability is due to dominance. This suggests that there may be few genes involved in determining BP distribution, since a consistent dominant effect of many genes seems unlikely.

The hypothesis that there are few dominant genes influencing BP distribution has been recently demonstrated with the discovery of abnormal cation fluxes in the red cells of patients with essential hypertension. It has been demonstrated that red cells of essential hypertensives showed a low ratio of Na-extrusion to potassium uptake, and exchanged lithium for Na more rapidly than normals. These abnormalities are inherited according to a dominant pattern in the families of hypertensive patients.

This genetic evidence is also supported by recent studies on the genetic influence played by the renin-angiotensin-aldosterone system on the control of Na balance. Following Na load, relatives of hypertensives differed from controls in that they had higher BP levels, greater plasma renin activity values, and sluggish natriuretic responses. A measurable and significant influence of genetic variance is evident.

There exist many polymorphic genes whose effect upon the level of BP can be detected by marker phenotypic analysis. Associations between polymorphic genes and BP have been detected along all the range of the genome in the following chromosomes: Chromosome 1 (Rhesus), Chromosome 2 (MN), Chromosome 6 (HLA and C3), Chromosome 7 (Kell), Chromosome 9 (ABO) and Chromosome 16 (Gm). A true association between genes and BP implies a genetic involvement in BP variability, but not genetic linkage. Nonindependence of traits in a population is merely association, whereas linkage implies that the transmission of the two traits from parent to child is not independent. Association is an attribute of genes; linkage is an attribute of loci. The association method has no power to distinguish between monogenic and polygenic transmission.

Environmental Factors

The multiplicity of environmental factors such as nutritional, psychological, and social, acting simultaneously, makes it very difficult to determine the effect of a single factor on BP variability. Nevertheless, after half a century of epidemiological research, a consensus has been reached that the following main environmental influences may predict the rise of BP in the human population at large: a) weight gain, b) Na intake, and c) psychosocial stress.

Weight Gain

The experimental evidence of weight gain showed that the correlation between BP and weight is highly significant in all types of human societies, geographical regions, ages, and sexes. Moreover, longitudinal studies demonstrated that individuals who gain more weight show a greater BP and weight reduction is accompanied by a fall in high BP. Finally, in multivariate analysis of correlations between different parameters and BP, weight maintains the highest significance.

Na Intake

The influence of Na is demonstrated by the fact that an excess of salt intake induces hypertension in genetically susceptible individuals. There is a correlation between average daily Na intake and prevalence of hypertension in world populations. In primitive peoples, the prevalence of hypertension is inversely correlated with the degree of Na intake, and Na restriction and diuretic therapy reduced high BP.

Nevertheless there are some facts that are against the lines of evidence: 1) investigations of Na intake within populations has failed to demonstrate a correlation between Na intake and an individual's BP; 2) excessive Na intake does not have a significant effect on the rise of BP in rats and men; 3) other elements such as calcium, cadmium, potassium, and lithium also have significant effects in BP variability. The separate effects of these elements has not yet been disentangled.

Psychosocial Stress

The effect of short-term psychosocial stress on BP distribution was clearly demonstrated with the emigration of British soldiers from their peaceful Brit-ain to the desert warfare in Africa during World War II. Their mean diastolic arterial pressure increased from 75.8 to 90 mm Hg, and more than 40% of the soldiers became hypertensives (BP > 95 mm Hg). The possible effect of long-term psychosocial stress on BP variability has been detected during the process of migration of primitive peoples to Western civilization. Certain isolated small communities living in peaceful ecological niches showed an absence of hypertension. When these people migrated to developed cultures, they were submitted to the stress of new environments and developed hypertension. On the contrary, those individuals who remained in their native land remained normotensive.

Studies of migrant populations have shown that weight gain and Na intake are also correlated to psy-
chosocial stress and BP. In primitive peoples both BP and weight did not rise with age. They had a habitual low Na intake (no-salt cultures) and a low calorie intake. In their new environments, the migrants simultaneously increased their BP, their Na intake, and their weight. Investigations are in progress trying to disentangle the single effects of these three main environmental factors of BP variability.

Genetic Environmental Interaction

If the genetic effect upon BP is conditioned by environmental factors, then greater differences in BP might be expected between blood group phenotypes at certain loci in migrants than in non-migrants. The evidence is the following: 1) in a single locus analysis, NN phenotypes showed higher BP increase than MM phenotypes, when natives of Easter Island and Atiplano migrated to civilization, and 2) in a two-loci analysis of blood group Rhesus and Kell, double heterozygotes CcKk gave significant interaction effects between migrants and nonmigrants of Tecumseh, Michigan.

This evidence is supported by the method of path analysis which showed that there is an increasing degree of genetic determination in the migrants indicating a subpopulation of genetically predisposed “responders” to the changes in the new environment.

SOURCES OF ECOLOGIC VARIATION

Psychosocial stress
Weight gain
Na intake

POPULATION
Primitive
Acculturated

PHENOTYPE
Hypertensives

GENETIC PREDISPOSITION
Idiomorphic genes?

POLYMORPHIC GENES
Rh MN ABO K

CHROMOSOMES

SOURCES OF GENETIC VARIATION

Conclusion

Figure 1 summarizes the genetic environmental model to explain the etiology of essential hypertension. The basic hypothesis is that the hereditable component, a complex genetic predisposition, is expressed only when high risk genotypes are exposed to excessive environmental (ecological) influences. Three types of genes are the sources of genetic variability. Polymorphisms operate quantitatively. Polymorphic genes, distributed along the entire genome show the extent of genetic participation. Idiomorphic genes, probably acting as dominant and controlling Na transport, operate qualitatively in the hypertensive segment of BP distribution.

References

2 Falconer DS Introduction to Quantitative Genetics New York, Ronald Press, 1960
4 Cruz-Coke R The hereditary factor in hypertension Acta Genet (Basel) 9: 207, 1959
5 Miall WE, Oldham PD The inheritance of arterial blood pressure Acta Genet (Basel) 7: 114, 1957
6 Cruz-Coke R, Covarrubias E Blood pressure correlation between relatives in an endogamic population Acta Genet (Basel) 15: 87, 1965
10 Cavalli-Sforza LL, Bodmer WF The Genetics of Human Populations San Francisco, Freeman, 1971
14 Gram CE, Luft FC, Miller JZ, Rose RJ, Joe CC, Weinberger MH An approach to the evaluation of genetic influences on factors that regulate arterial blood pressure in man Hypertension 2 (suppl I) 1-24, 1980
15 Murphy EA Genetic in Hypertension Circ Res 23 (suppl I) 1-137, 1973
16 Fraser GR, Thurs RS, Bernini LF, Degreve WB, Van Loghem E, Mena Khan P, Went LN A search for associations between genetic polymorphic systems and physical, biochemical and haematological variables Human Heredity 24: 424, 1974
17 Smith DG, Sing CF Genetic environmental interactions in the variation of blood pressure in Tecumseh, Michigan J Chrom Dis 30: 781, 1977
23 Graham JDP. High blood pressure after battle. Lancet 1: 239, 1945
24 Cruz-Coke R. Environmental influences and arterial blood pressure. Lancet 2: 885, 1960
Etiology of essential hypertension.
R Cruz-Coke

Hypertension. 1981;3:II-191
doi: 10.1161/01.HYP.3.6_Pt_2.II-191

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/3/6_Pt_2/II-191

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/