Genetics and the Nature of Essential Hypertension

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NO ONE now seems to doubt that essential hypertension "runs in families" and that this familial aggregation is in large part genetically determined. Evidence on the heritability of hypertension has been provided by family studies, comparisons in monozygotic and dizygotic twins, comparisons of different racial groups, and the demonstration of the genetic determination of essential hypertension in certain strains of rabbits.

The role of heredity in hypertension is of more than mere academic interest. The elucidation of genetic factors has a bearing on the answer to the questions: What is essential hypertension? Is essential hypertension a pathogenetic and etiologic entity? On the answer to these questions might depend how one will choose to approach the study of basic mechanisms in this common disorder.

Prior to the work of Pickering and his colleagues, most viewed essential hypertension as a distinct disease entity—a pathologic characteristic for which persons could be classed "plus" or "minus," affected or unaffected. Arbitrarily defining what elevations of blood pressure constitute hypertension, several workers such as Platt suggested that essential hypertension is a hereditary, Mendelian dominant characteristic.

The work of Pickering and his associates demonstrated that blood pressure describes a continuous frequency distribution which is unimodal, that no separation into a hypertensive class and a normotensive class is evident. Studies by Bøe in Bergen, Norway, by Comstock in Georgia, and by others corroborated the continuous distribution (fig. 1). Although the curves from all studies demonstrate a positive skew and leave open the possibility that two distinct populations are represented (fig. 2A), the conclusion of Pickering and his colleagues has been that blood pressure level is a multifactorial trait, comparable to stature, intelligence, ocular refraction, and many other traits. The corollary is that one does not inherit essential hypertension; rather one tends to inherit a particular level of blood pressure. "Essential hypertension is not a disease," is a dramatic way to put it. The persons labeled as suffering from essential hypertension are considered to be those whose blood pressure falls in the upper end of a "bell-shaped" continuous distribution. The genetic determination of hypertension is thought to be polygenic in nature and not susceptible to interpretation in terms of a simple Mendelian dominant or recessive. Presumably the multiple genetic factors operate, each through a different mechanism, to influence blood pressure. Although one could hope eventually to learn to define many or all of such multiple genetic mechanisms, the prospects are less bright than would be the case if genetic analysis suggested unifactorial inheritance and therefore a unitary biochemical defect.
Against this background the report of Platt et al., and that of Morrison and Morris et al., are of great interest. Both come to the conclusion that indeed two populations with reference to blood pressure are demonstrable and that there is bimodality consistent with the existence of a single major genetic factor in the etiology of essential hypertension.

Sir Robert Platt of Manchester reanalyzed the data of Pickering and his colleagues and of Søbye. The blood pressure of hypertensive probands and their sibs aged 45 to 60 years was used because (1) one could expect thus to exclude a certain number of cases of secondary hypertension which in Platt’s experience is more frequent than essential hypertension under the age of 40 years, and (2) the necessity for age correction is avoided. A bimodality was shown for systolic pressures and was suggestive for diastolic pressures. As a hypothetical example Platt pointed out that if hypertension affects about 19 per cent of middle-aged persons (figure...
chosen in part for convenience) and that if hypertension is a simple dominant trait then the incidence of the three genotypes becomes as follows:

\[ q^2 = 0.81 \text{ ('normal's')} \]
\[ 2pq = 0.18 \text{ (hypertensive subjects, heterozygous for dominant gene)} \]
\[ p^2 = 0.01 \text{ (hypertensive subjects, homozygous for dominant gene)} \]

And among the sibs of a hypertensive proband the proportion of hypertensive sibs is 0.58:

\[ 1 - \frac{pq^2(1-p/4)}{1-q^2} = 0.58 \]

The figure of 58 per cent is essentially the frequency among sibs in the data analyzed by Platt.

What clinical form hypertension would take in the person homozygous for this postulated dominant gene is interesting to speculate. Are persons with accelerated phase of essential hypertension, i.e., “malignant hypertension,” recruited from this group?

The old uncertainty about what level of blood pressure is hypertension might, Platt suggested, be resolved to some extent by these curves showing bimodality. If the antinode is taken as the threshold for hypertension in the 45 to 60 year group, then a blood pressure of 160/95 mm. is the approximate point above which hypertension can be said to be present in this age group.

As in Morris’ studies of coronary artery disease, data from the drivers and conductors of London buses were used by Morrison and Morris. The data of blood pressure had been collected previously without this particular analysis in mind. Although the curve for blood pressure in all cases was essentially continuous, that for those men in whom one or both parents had died in middle age was found to be bimodal (fig. 3A). This suggested the existence of two groups, one of which inherited the “dominant” gene and one of which did not. A reciprocal analysis involved the plotting of age of death in the fathers of hypertensive drivers. Here a distinct bimodality was demonstrated (fig. 3B), suggesting that part of the hypertensive drivers inherited the “dominant” gene from the father and part inherited it from the mother. The authors quoted a paper of Harris and Smith, who, in discussing a different problem, analyzed the considerations determining whether bimodality is evident in a distribution curve which in fact contains

\[ \text{Figure 3A} \]
\[ \text{Distributions of casual systolic blood pressures in bus drivers aged 45 to 60 years: (a) all} \]
\[ \text{drivers (186 men); (b) drivers with one or both parents dead in middle age (90 men)} \]
\[ \text{(middle age, 40 to 64 years); (c) drivers with both parents living to old age (96 men)} \]
\[ \text{(old age, 65 years or over).} \]
two populations: relative sizes of the populations, degree of separation of the modes, the standard deviations in the populations, etc.

If a single major genetic factor in essential hypertension is assumed, a unitary defect in a biochemical mechanism becomes plausible and seems worth seeking. (For example, Mendlowitz' suggestion of a defect in the enzyme 0-methyl transferase would be consistent with the genetic information.) It is possible to imagine that unitary biochemical defect, once found, could become the basis for preclinical diagnosis, definitive therapy, and prophylaxis.

As both Platt, and Morrison and Morris, have indicated, much needed are more longitudinal data to answer the question: Are there two types of persons, one in whom blood pressure rises with advancing years and one in whom blood pressure rises very little or not at all? Although mean pressure rises with age, it may be that only the average is raised by those individuals who for genetic reasons show a rise with age. The increase in variance of the blood pressure of groups with increasing age (fig. 4) could be so explained. Robinson and Bruce presented data consistent with the existence of two populations (fig. 5). Cruz-Coke, of Chile, from a study of civil servants spanning 12 years, found that persons hypertensive at the end of the period had had diastolic pressures in the normal range (although in the upper part of that range) at the beginning of the period.

Bimodality of blood pressure increment should be sought in longitudinal data. A study performed in a population as homogeneous as possible in racial background and environmental circumstances and designed to reduce extraneous sources of variability to a minimum might be ideal. Longitudinal studies among first-degree relatives of hypertensive patients would be expected to be particularly revealing because the two postulated populations should be more nearly equal in size.

The rebuttal to Platt and Morrison and Morris has taken the following arguments:

1. Cruz-Coke indicated that he would prefer the demonstration of bimodality in diastolic pressure, which he suggested is a better indicator of essential hypertension, being less affected by factors such as stroke volume and aortic rigidity.

2. Keen and Rose showed that bimodality among the offspring of parents dying in
middle age is not inconsistent with the polygenic hypothesis: The offspring of those dying of hypertension should demonstrate blood pressures distributed around a high mean and the offspring of those dying of causes other than hypertension should demonstrate blood pressures distributed around a lower mean approaching the mean of the general population.

3. In the follow-up data on blood pressure, collected in Wales by Dr. W. E. Miall, no differences in rate of rise of blood pressure in the relatives of "hypertensives" as compared with relatives of "normotensives" could be demonstrated by Oldham, Pickering, Roberts, and Sowry.

4. Pickering's group and Øbye began the studies which yielded the data analyzed by Platt with the bias that hypertension indeed is genetically unifactorial and that subjects can be classed without difficulty as affected or unaffected. Possibly there was a tendency unconsciously to shun the value of 150/90 mm. Hg. The medical mind may abhor uncertainty. Although the data of Morrison and Morris were collected without the analysis in mind the same psychologic factors may have been operative. The data of Miall and Oldham have the virtue that all pressures were taken by a single observer (Dr. W. E. Miall, a former student of Pickering at St. Mary's Hospital). At the time of their study the alternative multifactorial hypothesis had been advanced.
The other arguments of the rebuttal are restatements of points made earlier:

1. That the polygenic theory makes better physiologic sense in light of the multiple factors known to influence level of blood pressure.

2. That elevated blood pressure is per se not a clinical or pathologic entity but rather the complications of hypertension are responsible for clinical and anatomic abnormalities; and others.

That the correlation between the blood pressure of probands and first-degree relatives is the same (about 0.2) at all levels of pressure in the proband23 is possibly in keeping more with the polygenic hypothesis. So is the racial difference between Negroes and whites living under apparently similar circumstances in southern United States.5 However, with a considerable environmental factor in blood pressure, intrafamilial similarities and interracial differences in environment might be invoked to account for the data on a unifactorial genetic basis.

The difficulties in interpreting the genetics of hypertension—and in the opinion of one school, the ease of misinterpreting polygenic inheritance as unifactorial dominant inheritance—is illustrated nicely by the example of "distal hyperextensibility of the thumbs." When measured as the angle of maximal extension of the terminal phalanx of the thumbs the character displays a unimodal continuous distribution. Yet using an arbitrarily designated angle of extension as the point of separation between "affected" and "unaffected," Glass24 could demonstrate good agreement of family data with a dominant hypothesis. Arguments based on calculations of supposed gene frequencies (see above) are suspect, since a fit to a single gene hypothesis can be attained by manipulation of data on a polygenic trait.

It can be concluded that the evidence is sufficiently susceptible to conflicting interpretation to warrant an open mind. Certainly, even the existence of evidence for polygenic inheritance does not preclude the desirability of searching for a unitary, genetically determined biochemical defect, the expression of which is modified by environmental and other genetic factors.

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References


Heredity vs. Environment

We are all tattooed in our cradles with the beliefs of our tribe; the record may seem superficial, but it is indelible—Oliver Wendell Holmes, M.D. The Poet at the Breakfast Table, 1872.
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