5.
TWIN STUDIES IN HUMAN GENETICS

GENETIC VARIANCE IN BLOOD PRESSURE*

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The National Heart and Lung Institute Twin Study has examined 514 white adult male twin sets aged 42-56 with respect to blood pressure. The data were analyzed by a method of Christian et al. which eliminates possible biases in estimated genetic variances that could result from different total variances in MZ and DZ twins. Results of the test for the presence of genetic variance indicate that both systolic and diastolic blood pressure are to a considerable extent genetically controlled with an estimated heritability of 0.8 for systolic and 0.6 for diastolic pressure. Although these findings are at variance with some previous reports, it is thought that much of the discrepancy results from application of different analytic techniques, not in the data themselves. The application of these findings to our understanding of hypertension epidemiology and community hypertension control programs are discussed.

INTRODUCTION

The role of genetic factors in the genesis of essential hypertension has been under intensive investigation for several decades (Stocks 1930, Friedman and Kasanin 1943, Hines et al. 1957, McKusick 1960, Mathers et al. 1961, Schweitzer 1962, Harvald and Hauge 1963, Murphy 1964, Lundman 1966, Pickering 1968, Downie et al. 1969). Although clinicians recognize the familial aggregation in hypertension, this observation is not sufficient evidence that hypertension is a genetically determined disease. Nor is the well-known influence of environment on the level of blood pressure sufficient evidence to reject a genetic hypothesis. To the extent that blood pressure is a biological quantity, the deviation from normal in patients with hypertension is quantitative and not qualitative. Therefore, it would seem probable that, as pointed out by Pickering (1968), " ... arterial pressure is inherited as a graded character through the ranges hitherto decribed as normal blood pressure and hypertension... ". The evidence that provides information on heritability of hypertension is derived from four types of studies. These are studies of records of single families, studies of family histories in large series of patients with hypertension, studies of measurements of blood pressure in relatives of patients with hypertension, and studies of blood pressure in twins. Of all these, measurements of blood pressure among twins are perhaps the most revealing (Stocks 1930, Friedman and Kasanin 1943, Hines et al. 1957, Mathers, 1961, Lundman 1966, Downie et al. 1969, Vander 1970). Indeed, for a variety of reasons, studies of records of single families and studies of family histories of patients with hypertension are of little value in providing evidence of heritability of hypertension (Pickering 1968). Foremost among studies of measurements of blood pressure in relatives of patients with hypertension is the work of Miall and his colleagues (Miall and Oldham 1955, 1957, 1958, 1963; Pickering 1968). These investigators, in measurements of blood pressure in propositi and their first degree relatives, demonstrated that relatives of patients with hyper-

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tension have higher levels of blood pressure than relatives of controls; a similar relationship between the blood pressure of propositi and their relatives was demonstrated to exist in the general population. As useful as these findings are in studies of the genesis of hypertension, they do not provide convincing evidence on heritability of hypertension. Even though the resemblance between relatives in their levels of blood pressure can be explained by their "sharing genes", the influence of environment *cannot* be ruled out entirely. Indeed, it is estimated by Pickering that environmental factors contribute about 36 to 67% to the variation of blood pressure, and that the contribution of genetic factors is probably between one-third and two-thirds of the whole (Pickering 1968).

It is felt that of all four types of studies mentioned above, measurement of blood pressure among twins is the best available method that could shed light on the issue of genetics in the genesis of hypertension. Despite their utility, studies of blood pressure in twins are beset by a variety of problems. These problems arise, mostly, from the variable nature of the underlying blood pressure measurements, the definition of hypertension, and the methodological problems in studying twins (Dahlberg 1926, Newman 1928*a,b*, Rife 1938, Gedda 1961, Christian et al. 1974).

In view of the fact that the role of heredity in hypertension is "of more than academic interest" (McKusick 1960), and the resolution of the questions surrounding the issue of inheritance in the genesis of hypertension has significant implications for programs in community health, the studies of twins offer a unique opportunity that should be capitalized upon despite their shortcomings. For this reason, the National Heart and Lung Institute supported the establishment of a national collaborative study of twins in the United States. This study began in 1969. It is the purpose of the present communication to report on the results of this study, only as they apply to systolic and diastolic (fifth phase) blood pressure as quantitative variables.

METHODS AND MATERIAL

A multicenter collaborative study of adult white male twins, ascertained through the Twin Registry of the U.S. National Academy of Science-National Research Council, was organized in 1969. All the twins were members of a cohort born between 1917 and 1927; they served in the U.S. Armed Forces during World War II or the Korean Conflict. They were, therefore, between 42 and 56 years of age at the time of entry into the study.

A total of 514 twins participated in the study, 250 MZ and 264 DZ. Data in Table 1 present the number of MZ and DZ twins in each of the participating centers and the dates of their examinations. Although the details of the study design, protocol of physical examination, and the methods of determination of zygosity are presented elsewhere, Feinleib et al. 1974, a few features of the methodology, pertinent to the present communication, will be presented here for ease of reference.

An effort was made to examine both members of each twin set (cotwins) at the center and on the same day. There were only a few exceptions where this objective was not achieved. All subjects were examined in the morning, after an overnight (14 hours) fast. Systolic blood pressure and the fifth phase of diastolic blood pressure were measured in the sitting position and recorded three times, initially by a nurse, then by the examining physician prior to the physical examination, and finally by the same physician immediately after the completion of the physician examination. The first reading recorded by the physician was used for analysis. To assure the « blind » nature of the study, different physicians examined cotwins. We were aware that this procedure, aimed at eliminating the possibility of bias due to recognition of twins by their facial and/or anthropometric similarities, could introduce a new bias of inter-observer variation of blood pressure measurement; but, we considered the latter the best of the two evils.

Determination of the estimates of heritability and the statistical analysis of the data were based on a new method of estimating genetic variance (Christian et al. 1974, Feinleib et al. 1974). The principal advantage of this methods is that it does not require, a priori, that total MZ and DZ variances be identical; the method makes allowance for these variances, however, when they do differ. In this method of analysis, we ascribe differences in MZ-DZ total variance to different environmental variances in the two types of twins. If MZ twins have larger environmental variance, an estimate of genetic variance based on W_{DZ}-W_{MZ} will tend to be an underestimate. On the other hand, if the DZ twins have larger environmental variance, the estimate of genetic variance based on W_{DZ}-W_{MZ} will tend to be an overestimate. It should be emphasized that in using this method of analysis, the « among component » estimate yields, in our opinion, an *unbiased* estimate of genetic variance under either of the above-mentioned conditions. In presenting our findings, therefore, we have chosen to use the « among component » estimate, even though it has a larger variance than the « within component » estimates. It should be noted that due to the large sample size in our study, this drawback of the method is mediated. But, like other investigators, we must make the assumption that the environmental covariances between MZ and DZ twins were the same.

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RESULTS

The distributions of systolic blood pressure and the fifth phase of diastolic blood pressure for 1,026 individuals twins are presented in Figs. 1 and 2.

It can be seen that, despite the pairwise dependence of the observations, these frequency distributions are similar to those observed among other white males of the same age in general population studies. Both distributions demonstrate a unimodal form, with skewness to the right. Using a systolic blood pressure of 160 mm Hg and a diastolic blood pressure of 95 mm Hg as arbitrary cutoff points, about 8% of our subjects had " systolic hypertension" , and approximately 13% " diastolic hypertension." Figs. 3 and 4 present the distributions of pair mean values of systolic blood pressure and of diastolic blood pressure for MZ and DZ twins. Mean values of *systolic* blood pressure by zygosity and for each study center are presented in Table 2. Mean values of *distolic* blood pressure by zygosity and for each study center are presented respectively in Table 3.

Since the number of MZ and DZ twins were not the same in all participating centers and mean blood pressure level apperared to differ between centers, we examined the possibility of a difference in levels of blood pressure between MZ and DZ twins, using a two-way analysis of variance. After adjustment for center differences, *we found no evidence for any difference in SBP and DBP levels between MZ and DZ twins.*

Data presented in Table 4 show intrapair (within pairs) mean squares (difference between twin partners) as well as interpair (between pairs) mean squares (difference between pairs of MZ and DZ twins), for systolic blood pressure, and for each of the collaborating centers. Data presented in Table 5 show intrapair mean squares (difference between twin partners) and interpair mean squares (difference between groups of MZ and DZ twins), for diastolic blood pressure.

Since the estimation of genetic variance in this study is a function of the " within " and " between " pair mean squares for the two types of twins, we considered it important to determine whether the " mean squares " were homogeneous across all centers. As can be seen from data in Tables 4 and 5, the test of the degree of heterogeneity of the " mean squares " across all centers (Bartlett's Test) was, with but one exception (systolic blood pressure, interpair mean square for MZ twins, $p < 0.05$) not significant. We could not, therefore, reject the null hypothesis of no difference in the " mean squares " among centers.

Data presented in Table 6 show the results of the estimation and testing of a genetic component of the variance for systolic blood pressure, when it is considered as a quantitative trait. Table 7 presents similar data for diastolic blood pressure. In each table, the " among pair mean squares ", the " within pair mean square ", and the estimates of genetic variance for " among pair ", " within pair ", and the " among component " are presented. The " F " ratio for the among component variance is 1.50 for systolic blood pressure ($p < 0.001$), and 1.38 for diastolic blood pressure ($p < 0.001$).

It should be pointed out that data in Tables 6 and 7 present three possibilities for estimates of genetic variance; these are: the " among pair ", the " within pair ", and " among component ". The " among pair " estimate uses the difference of the MZ and DZ among pair mean squares; whereas, the " within pair " estimates the difference of the " within pair " mean squares. The value and the appropriateness of using either of these estimates in calculating the genetic variance depends upon the results of the test for equality in *total* variance between MZ and DZ twins.

Data in Tables 6 and 7 present this total variance for systolic and diastolic blood pressures between MZ and DZ twins. As can be seen, systolic and diastolic blood pressures show considerable differences in their estimated total variance. For systolic blood pressure there is a significant difference in total variance between MZ and DZ twins (F ratio $= 346.2/268.4 = 1.29$, $p = 0.008$); whereas, for diastolic blood pressure there is no difference (F ratio $= 135.9/131.3 = 1.04$, $p = 0.720$). Thus, in the case of systolic blood pressure, where there is a considerable difference in total variance between MZ and DZ twins, the only acceptable estimate of genetic variance is the " among component " estimate which in our study differs significantly from zero, as was demonstrated in Table 6 ($p < 0.001$). For

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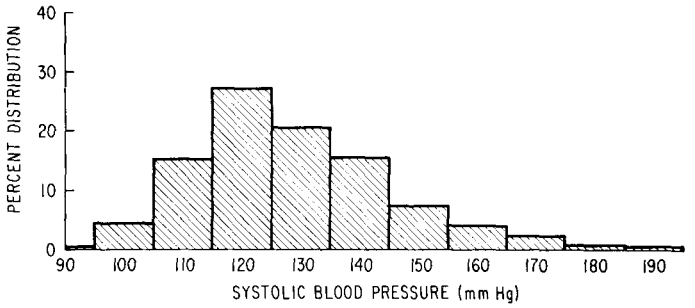

Fig. 1. Frequency distribution of systolic blood pressure in 1,026 individual MZ and DZ twins.

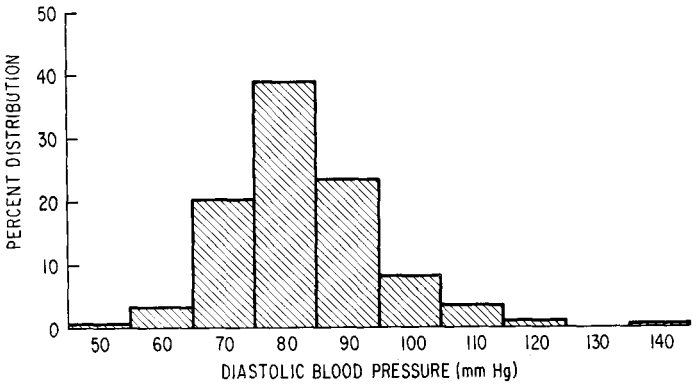

Fig. 2. Frequency distribution of fifth phase diastolic pressure in 1,026 individual MZ and DZ twins.

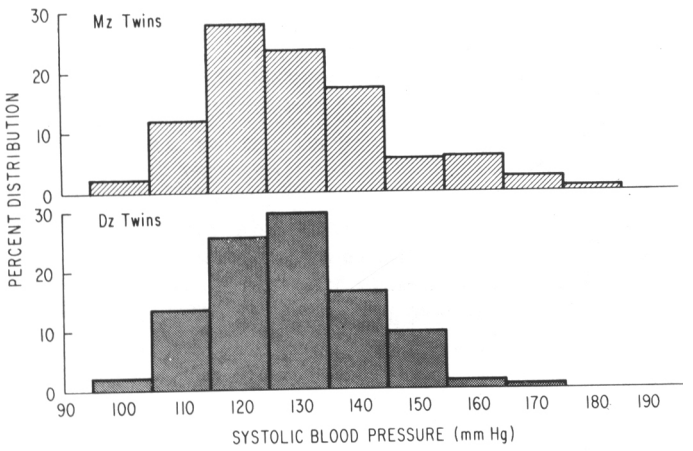

Fig. 3. Frequency distribution of pair mean values of systolic blood pressure among MZ and DZ twins.

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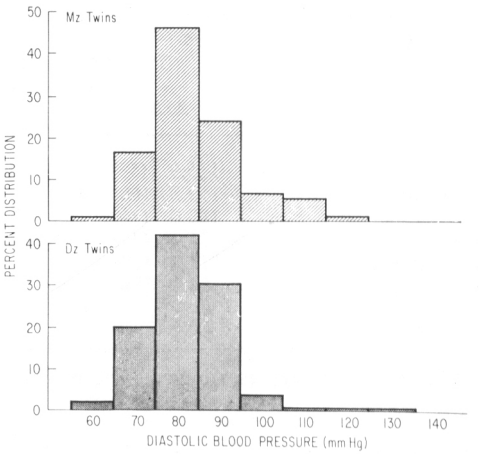

Fig. 4. Frequency distribution of pair mean values of fifth phase diastolic blood pressure among MZ and DZ twins.

Table 1. *Number of twins in each of the participating centers*

Study center	Date of examination	Number of twin sets		
		MZ	DZ	Total
Framingham, Mass.	1969-1970	55	50	105
Indianapolis, Ind.	1971-1973	68	73	141
San Francisco, Calif.	1970-1971	16	38	54
Davis, Calif.	1970-1973	33	45	78
Los Angeles, Calif.	1971-1972	78	58	136
All centers	1969-1973	250	264	514

Table 2. *Mean values of systolic blood pressure* (mm Hg), *by zygosity for each study center*

Study center	MZ	DZ	Total
Framingham (55,50)*	128.8	128.1	128.4
Indianapolis (68,73)	127.6	124.7	126.1
San Francisco (16, 38)	132.9	122.7	125.7
Davis (32, 45)	124.8	132.1	129.1
Los Angeles (77,58)	133.2	130.0	131.8
All Centers (248, 264)	129.6	127.4	128.5

* Numbers in parentheses indicate respectively the number of MZ and DZ twins.

Table 3. *Mean values of fifth phase diastolic blood pressure* (mm Hg), *by zygosity for each study center*

Study center	MZ	DZ	Total
Framingham (55, 50)*	81.4	81.1	81.3
Indianapolis (68, 73)	80.3	78.8	79.6
San Francisco (16, 38)	83.8	77.9	79.7
Davis (32, 45)	82.5	85.7	84.4
Los Angeles (77, 58)	86.0	82.5	84.5
All centers (248, 264)	82.8	81.1	81.9

* Numbers in parentheses indicate respectively the number of MZ and DZ twins.

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Table 4. *Intrapair and interpair mean square for systolic blood pressures, by zygosity for each study center*

Study center	Interpair mean square		Intrapair mean square	
	MZ	DZ	MZ	DZ
Framingham	155.9 (55)*	254.7 (50)	542.9 (50)	330.5 (49)
Indianapolis	159.5 (68)	212.9 (73)	555.8 (67)	337.9 (72)
San Francisco	182.0 (16)	156.8 (38)	529.0 (15)	270.0 (37)
Davis	77.4 (32)	182.9 (45)	225.8 (31)	328.7 (44)
Los Angeles	174.7 (77)	178.7 (58)	617.7 (76)	314.9 (57)
All centers	154.3 (248)	200.1 (264)	538.0 (247)	336.6 (263)
p-value	0.14	0.51	0.05	0.96

* Numbers in parentheses indicate the number of degrees of freedom associated with each mean square.

Table 5. *Intrapair and interpair mean square for diastolic blood pressure, by zygosity for each study center*

Study center	Intrapair mean square		Interpair mean square	
	MZ	DZ	MZ	DZ
Framingham	48.5 (55)*	79.9 (50)	219.3 (54)	122.0 (49)
Indianapolis	65.7 (68)	128.4 (73)	179.0 (67)	139.1 (72)
San Francisco	58.3 (16)	97.6 (38)	208.2 (15)	189.8 (37)
Davis	44.7 (32)	71.9 (45)	158.6 (31)	164.8 (44)
Los Angeles	62.5 (77)	85.8 (58)	241.0 (76)	173.8 (57)
All centers	57.7 (248)	95.8 (264)	214.0 (247)	166.7 (263)
p-value	0.63	0.18	0.62	0.56

* Numbers in parentheses indicate the number of degrees of freedom associated with each mean square

diastolic blood pressure, however, the disparity between the "among" and the "within" estimates of genetic variance is much smaller. Therefore, for estimation of genetic variance, both "within" and "among component" estimates are relevant, and both were significantly different from zero. Thus, for both systolic and diastolic blood pressure, there is evidence that a substantial portion of the total population *variability can be attributed to genetic differences.*

From these estimates of genetic variance, we calculated the "heritability" index for systolic and diastolic blood pressures. The details and method for this calculation are presented elsewhere (Feinleib et al. 1974), and will not be repeated here. As can be seen, the "heritability" indices were 0.82 and 0.64 respectively for systolic and diastolic blood pressures.

DISCUSSION

Results of our study are significant in that we find a highly significant estimate of heritability both for systolic and diastolic blood pressures. On the surface, these findings of strong genetic components are not entirely consistent with those of some previous studies (Newman 1928*a*,*b*, Stocks 1930, Miall and Oldham 1955, 1963, Pickering 1968). The difference between these findings and those of previous investigators are difficult to reconcile. But, two reasons could be cited as a reasonable explanation. One is the different analytic method we used in our study for assessing the genetic component; the second is that our population differed considerably from the twin populations used in other studies, in its degree of homogeneity and the age compositions.

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Table 6. *Estimated mean squares and genetic variances: Systolic blood pressure*

Variance	MZ twins	DF	DZ twins	DF
Among pair mean square	538.0	247.0	336.6	263.0
Within pair mean square	154.3	248.0	200.1	264.0
Total variance	346.2	378.0	268.4	494.5

Estimates of genetic variance	Estimates	*F* ratio	*p* value
Among pair	402.8	1.60	< 0.001
Within pair	91.7	1.30	0.019
Among component	247.3	1.50	< 0.001

$$\frac{\text{Genetic Variance (A. C.)}}{\text{Total Variance (Pooled)}} = \frac{247.3}{302.1} = 0.82$$

Table 7. *Estimated mean squares and genetic variances: Diastolic blood pressure*

Variance	MZ twins	DF	DZ twins	DF
Among pair mean square	214.0	247.0	166.7	263.0
Within pair mean square	57.7	248.0	95.8	264.0
Total variance	135.9	371.2	131.3	490.7

Estimates of genetic variance	Estimates	*F* ratio	*p* value
Among pair	94.6	1.28	0.023
Within pair	76.2	1.66	< 0.001
Among component	85.4	1.38	< 0.001

$$\frac{\text{Genetic Variance (A.C.)}}{\text{Total Variance (Pooled)}} = \frac{85.4}{133.3} = 0.64$$

A frequently used method of testing for the presence of genetic variance in twin studies of blood pressure has been the test of the DZ and MZ intrapir variances. Utilizing this method of analysis, Downie et al. (1969) and Mathers et al. (1961) were unable to reject the hypothesis of equal intrapair variance (difference between the two twin partners); thus, they concluded that there was no consistent evidence of genetic control over the variance of blood pressure. It is intersting to note that while our number of twins was substantially greater than theirs, we were able to reject the hypothesis of equal intrapair variance (within pair), for systolic blood pressure, *only at the* $p = 0.02$ *level.* Had we, in the present study, examined less than 168 pairs of MZ and DZ twins, a difference in the within-pair variance as large as we observed would not have been statistically significant. Thus, we believe the large number of twins we examined, and of course, the difference in analytic methods mentioned above, could explain the difference between our data, demonstrating a clear impression of a major genetic determination in blood pressure variation, and those reported by other investigators in previous twin studies of blood pressure and hypertension (Stocks 1930, Friedman and Kasanin 1943, Hines et al. 1957, Mathers 1961, Lundman 1966, Downie et al. 1969, Vander 1970).

Unfortunately, it is difficult to identify, much less to measure, as pointed out by Pickering (1968). the influence of environmental factors on blood pressure distribution. Also, there is always the possibility of overstatement of genetic influence on blood pressure. Regrettably this latter factor is not easily controlled, unless MZ and DZ twins pairs under study are separated since birth. However, we believe that overestimation of genetic factors should not occur simply because the environmental factors influencing blood pressure are associated within twin pairs. These estimates will be affected only when such associations differ between MZ and DZ twins. Thus, if MZ twins tend to share an environmental factor that influences their blood pressure more than do DZ twins, the genetic variance found would tend to be artificially elevated. In the present study, nearly all twin pairs were separated from each other around age 20. Therefore, if such a factor is in operation in biasing our results towards an impressive degree of genetic variation, it is fair to assume that such a factor must have exerted its influence at a very early age, i.e., infancy and childhood. Obviously, the design of the present study does not permit such an evaluation.

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