Relative Roles of Genetic and Environmental Factors in Control of Blood Pressure in Normotensive Subjects

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Following the observation by Allbutt (1915) that hypertension often occurred in the absence of preceding renal disease, it has been generally accepted by clinicians that "essential hypertension" constitutes a discrete clinical disease entity, and is the result of the interaction of genetic and environmental factors.

This view has been supported by the work of Platt (1947, 1948, 1959, 1961, 1963, 1964) who further suggests that the disease is manifest in middle life through the action of a single pair of genes behaving as Mendelian dominants with incomplete penetrance.

The entire concept of the status of "essential hypertension" was challenged initially by Hamilton *et al.* (1954a, b). The results of their investigations indicate that blood pressure is inherited as a graded characteristic, and that the genetic influence is multifactorial in nature. They also suggest that subjects with alleged essential hypertension merely represent those at the upper end of a frequency-distribution curve for blood pressure in a population.

The controversy aroused by these conflicting opinions has stimulated many epidemiological studies of varying magnitude (Miall and Oldham, 1958, 1963; Morrison and Morris, 1959; Lowe and McKeown, 1962; Ostfeld and Paul, 1963; Armitage *et al.*, 1966; Miall *et al.*, 1967).

That there is no clear-cut division between physiological and pathological levels of blood pressure is evident from all the surveys performed. As Pickering (1965) pointed out, various arbitrary levels have been chosen by different authors to indicate the upper limit of normality, and in the resulting confusion it is difficult to compare these results. In the search to discover the magnitude and nature

of the genetic factor in hypertension, it seems possible to investigate only the hypothesis of multifactorial inheritance, because of the above limitations.

In investigating the magnitudes of the genetic and environmental components of any given characteristic, the epidemiologist is provided with a human biological model by the study of the degree of concordance of the characteristic under observation in monozygotic (identical) and dizygotic (non-identical) twins. Sir Francis Galton was the first to appreciate the value of the twin study method, and several such studies have been performed on blood pressure in twins.

Stocks (1930), Verschuer and Zipperlen (1929), and Kahler and Weber (1940) found closer resemblance in the blood pressures of monozygotic twin pairs than in the dizygotic pairs, suggesting the existence of an important genetic component. Case reports of hypertension existing in identical twins have come from Platt (1963) who reported 3 pairs, and Hames, McDonough, and Elliott (1964) and Heizer and Lewison (1964) who each reported one pair.

Osborne, De George, and Mathers (1963) investigated 53 pairs of normotensive twins, measuring basal and casual blood pressures, and analysed the data by comparing the intrapair and interpair variance in the monozygotic and dizygotic groups. They failed to show a sizeable genetic factor involved in determining basal or casual levels of blood pressure in normotensive subjects, but suggested that the cardiovascular response to environmental variability might be under genetic influence.

The purpose of the present study was to investigate the magnitude of the genetic influence on blood pressure in a series of normotensive twins, using a single casual measurement of blood pressure.

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TABLE I
AGE AND SEX DISTRIBUTION OF TWIN GROUPS

Twin group		No of twin pairs	Age (yr.)		
			Mean	Range	SD†
Monozygotic	Female	34	24.1	12-66	17.8
	Male	16	27.1	13-65	13.6
Dizygotic	Female	19	23.8	12-70	13.5
	Male	12	26.3	13-47	15.4
Dizygotic unlike-sex		28	21.7	13-64	12.7

† SD = Standard deviation.

SUBJECTS AND METHODS

Twin sample. A sample of 109 healthy twin pairs was obtained by advertisement in local newspapers, on radio, and on television, by advertisement in out-patient departments of hospitals in Glasgow, and by writing to the parents of twin schoolchildren in Glasgow. The names of the twin schoolchildren were obtained from the headmasters of the schools. The twin sample was originally collected to study the relative roles of genetic and environmental factors in the production of auto-antibodies (Buchanan *et al.*, 1966).

The twins who replied to the advertisements and accepted the invitation to participate in the study were seen irrespective of known disease. Osborne and De George (1959) have commented that it is probably impossible to avoid bias in the selection of a twin sample, but it is important to know the direction of the bias. The ascertainment campaign mentioned rheumatoid arthritis, but did not mention hypertension or cardiovascular disease. It seems unlikely, therefore, that the twin sample contained a disproportionate representation of hypertensive subjects. It is not apparent that other departures from random sampling, such as an excess of female monozygotic pairs (Table I), or the fact that the twins were co-operative and probably of above average intelligence, would influence the results of the study.

Determination of Zygosity. The criteria used in determining zygosity were those of Newman, Freeman, and Holzinger (1937). The like-sex pairs were examined with respect to their general appearance and likeness, colour and texture of hair, eye colour, skin colour, facial likeness, types of teeth, hands, fingers, and types of nails. The presence of reversed asymmetry in handedness and hair whorls was also taken as confirmatory evidence of monozygosity. Fingerprints and palm prints were examined for zygosity using the criteria of Holt (1961), and in some pairs examination of dental casts and cephalogram x-rays of the head were taken. The following blood group antigens were examined A1, A2, B, O; M, N, S, s; C, D, E, c, d, e; Kell; Duffy (a) and P.

The following Gm and InV groups were determined: Gm (a), Gm (x), Gm (b¹), Gm (b²), Gm (b³), Gm (b⁴), and Gm (C) and InV (b) (Alepa and Steinberg, 1964).

The likelihood of a correct diagnosis is probably greater than 90 per cent for every twin pair accepted as

being monozygotic on the above criteria (Dencker *et al.*, 1961), and in the case of the dizygotic twins the likelihood of a correct diagnosis is 100 per cent. Reciprocal split-skin grafts were performed in 15 twin pairs diagnosed as being monozygotic: the skin grafts were rejected in only one of these 15 twin pairs.

The sex and age distributions of the different categories of twins are shown in Table I. The majority of twins were young and with the exception of a slightly disproportionate number of monozygotic female pairs in the 20 to 30 decade, the age distribution was similar in all groups. Other workers (Osborne and De George, 1959) have noted an increased preponderance of female monozygotic twins in twin samples obtained by advertisement.

Measurement of Blood Pressure. Each twin pair was seen together, and a single measurement of casual arterial blood pressure was made on the right arm of each twin using a standard mercury sphygmomanometer. All measurements were made by one observer (W.R.G.) and readings were taken to the nearest 5 mm. on the scale. The readings from each member of a twin pair were made within 5 minutes of each other and approximately 30 minutes after the interview had begun.

RESULTS

The composition of the study sample is shown in Table I. It can be seen that apart from a slight preponderance of female monozygotic twins, the various groups are similar in composition, mean age, and age ranges.

Table II shows the mean and standard deviations of the blood pressures, intrapair variances, F ratios, and p values for the like-sex twin pairs. The calculation of intrapair variances for the twins was performed as described by Osborne and De George (1959), and Mathers, Osborne, and DeGeorge (1961). Allen (1966), in a review of problems in twin research, has commented that when one is dealing with continuous variables, the variance ratio method is preferable to the heritability index, *h*, of Newman *et al.* (1937). The differences between the two members of the twin pairs are ex-

TABLE II
RESULTS OF BLOOD PRESSURE MEASUREMENTS (mm. Hg) IN 81 LIKE-SEX TWIN PAIRS

	Females							
	No.	Mean		SD		Intrapair variance*	F ratio*	p value
		Twin 1	Twin 2	Twin 1	Twin 2			
<i>Systolic pressure</i>								
Monozygotic	34	131.9	131.1	13.49	14.13	57.12	1.20	NS†
Dizygotic	19	135.5	130.6	18.55	16.47	68.58		
<i>Diastolic pressure</i>								
Monozygotic	34	83.5	84.0	8.57	10.64	39.34	1.56	NS
Dizygotic	19	83.2	79.7	10.82	10.34	61.18		

	Males							
	No.	Mean		SD		Intrapair variance*	F ratio*	p value
		Twin 1	Twin 2	Twin 1	Twin 2			
<i>Systolic pressure</i>								
Monozygotic	16	132.8	135.3	15.91	16.98	78.13	1.21	NS
Dizygotic	12	125.8	133.8	11.84	14.78	94.79		
<i>Diastolic pressure</i>								
Monozygotic	16	80.6	81.6	10.30	10.28	27.34	1.38	NS
Dizygotic	12	79.6	79.2	8.65	13.62	19.79		

* See text for explanation of this function.

† NS = not significant.

TABLE III
MEAN BLOOD PRESSURES AND STANDARD DEVIATIONS OF DIZYGOTIC
UNLIKE-SEX TWIN PAIRS

	No.	Mean		SD	
		Female	Male	Female	Male
Systolic (mm. Hg)	28	136.3	126.2	17.03	11.75
Diastolic (mm. Hg)	28	80.5	76.6	11.25	9.91

pressed as mean intrapair variances, where the mean intrapair variance is $\sum x^2/2n$, where x is the difference between the two members of a pair of twins, and n represents the number of pairs of twins. The F distribution is used to obtain the probability level of the ratios of the different mean intrapair variances.

The mean systolic blood pressures for monozygotic female twins were $131.9 \pm \text{SD } 13.49$, and $131.1 \pm \text{SD } 14.13$ mm. Hg. For the dizygotic twin pairs the corresponding values were $135.5 \pm \text{SD } 18.55$, and $130.6 \pm \text{SD } 16.47$ mm. Hg. The respective intrapair variance values were 57.12 and 68.58, and F ratio 1.20, which is not statistically significant.

The mean diastolic blood pressures for monozygotic female twins were $83.5 \pm \text{SD } 8.57$, and $84.0 \pm \text{SD } 10.64$ mm. Hg. The corresponding values for the dizygotic twin pairs were $83.2 \pm \text{SD } 10.82$, and $79.7 \pm \text{SD } 10.34$ mm. Hg. The respective intrapair variance values were 39.34 and 61.18, and the F ratio 1.56, which again is not statistically significant.

The mean systolic blood pressures for monozygotic male twins were $132.8 \pm \text{SD } 15.91$, and $135.3 \pm \text{SD } 16.98$ mm. Hg, and for the dizygotic male twins the values were $125.8 \pm \text{SD } 11.84$, and $133.8 \pm \text{SD } 14.78$ mm. Hg. The values for the intrapair variances were 78.13 and 94.79, respectively, and the F ratio 1.213, once more not statistically significant.

The mean diastolic blood pressures for monozygotic male twins were $80.6 \pm \text{SD } 10.30$, and $81.6 \pm \text{SD } 10.28$ mm. Hg, while the corresponding values for the dizygotic male twins were $79.6 \pm \text{SD } 8.65$, and $79.2 \pm \text{SD } 13.62$ mm. Hg. The intrapair variance values were 27.34 and 19.79, respectively, and the F ratio 1.381, which is again not significant.

Table III shows the mean systolic and diastolic blood pressures with standard deviations for the dizygotic unlike-sex twin pairs. These values were not included in the over-all analysis, and are shown purely for interest.

It can be seen that on superficial examination of the mean blood pressure values, there appears to be a closer correlation between the values for the monozygotic twin pairs than for the dizygotic pairs, but statistical examination shows that this is not significant.

DISCUSSION

The results of the present study indicate that at normal levels of blood pressure there is no significant genetic component which can be detected by a single casual measurement of blood pressure. It might be argued that if basal measurements had been made, the results would have shown a significant degree of correlation in the monozygotic pairs, but the study of Osborne *et al.* (1963) has indicated that this is not so. This finding is at variance with that of Hines, McIlhaney, and Gage (1957) who claimed to have demonstrated a genetic component in measurement of blood pressure in normotensive twins under basal conditions, but the studies of Osborne *et al.* (1963), and Hines *et al.* (1957) agree on the existence of a genetic factor in the response of blood pressure to environmental variability. In the former survey, the comparison was based on the differences between basal and casual measurements, and in the latter on the reaction to the cold pressor test.

Hines and his colleagues (1957) also claimed to have shown a genetic component in hypertension occurring in twins. However, the numbers studied were small (17 twin pairs), and the determination of zygosity was based mainly on physical characteristics, which is generally considered a somewhat inaccurate method. Also one pair of the eight hypertensive twin pairs had hypertension secondary to polycystic renal disease which already has a strong genetic background (autosomal dominant).

The significance of our conclusion is apparent when one considers that most of the large population surveys of blood pressure are performed on the basis of single measurements of blood pressure. The fallacies involved in single measurements of blood pressure were studied by Ayman and Goldshine (1940) who showed that the examining physician was the largest single factor involved. More recently, Armitage and Rose (1966) and Armitage *et al.* (1966) have measured the magnitude of the error inherent in studies of blood pressure based on single measurements, and have shown in a field survey that approximately 17 per cent of subjects may be wrongly classified as "hypertensive" if only one measurement of blood pressure is taken, and an arbitrary cut-off point of 160/90 mm. Hg is taken to separate normotensives from hypertensives. However, the use of the single casual measurement

of blood pressure can be justified in a study such as the present one, since the blood pressure measured in this way is probably biologically more meaningful. Moreover, if, as has been suggested (Hines *et al.*, 1957; Osborne *et al.*, 1963), the variability of blood pressure in response to environmental changes is under genetic control, such a genetic factor should be obvious in our study.

What is important to the clinician investigating the nature and nurture dichotomy is not whether there is a genetic factor and/or an environmental factor, but how strong these factors are. For instance, in glucose-6-phosphate dehydrogenase deficiency, which is associated with haemolytic anaemia after ingestion of fava beans or administration of antimalarial drug therapy, the genetic and environmental components are considered to be roughly equal. In haemophilia, the genetic component is extremely strong (resulting in lack of anti-haemophilic globulin), but even here, environmental factors are still important, e.g. trauma. Tuberculosis is caused by an environmental agent, mycobacterium tuberculosis, but a genetic susceptibility has been proven, at least in animals (Lewis and Loomis, 1928). In the control of normal blood pressure, it appears that the genetic factor is weak, and probably of no clinical importance.

It is impossible to extrapolate from this study in normotensive twins, the vast majority of whom are in the recognized "pre-hypertensive" years, to "essential hypertension" in the older age-groups.

It is not possible at the present time to state whether "essential hypertension" is a distinct disease, as suggested by Platt, or whether it represents purely a quantitative rather than a qualitative difference from the norm, as Pickering insists. Because of the small numbers involved in existing twin studies in hypertension, and the subsequent lack of critical statistical analysis, it is difficult to interpret the results in either way.

Because of the precision of the twin study method, it seems useful to investigate larger numbers of hypertensive twins in order to investigate the magnitude of the genetic component, since it has been shown that in hypertension the environmental contribution is probably weak (Gearing *et al.*, 1962; Johnson, Epstein, and Kjelsberg, 1965).

SUMMARY

A single measurement of casual blood pressure was made on 109 pairs of healthy twins. The values obtained in 81 like-sex pairs were analysed by the intrapair variance method.

The results indicate that, at normal levels of blood pressure, there is no evidence of a strong

genetic component which can be detected by a single measurement of casual blood pressure.

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