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Relation between Change of Blood Pressure and Age

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Sixty years after the invention of the sphygmomanometer we still know little about the development of arterial hypertension. Few attempts have been made to study its natural history, because this cannot be done with hospital populations, and most epidemiological studies have been cross-sectional and therefore inappropriate for this purpose.

The conflicting views on the nature of unexplained hypertension remain unresolved. Platt (1961, 1963) and his followers, who believe essential hypertension to be a disease entity, think that there are two types of person, those whose pressures do and those whose pressures do not increase markedly in middle age, and that this is determined at conception by the presence or absence of a single pair of genes acting at a single locus. Their dissenters were unimpressed by the evidence, and were unwilling to attribute a disorder so common in old age to the effects of a single pair of genes. Pickering (1961, 1965) challenges this concept of essential hypertension on the grounds that evidence derived from many sources suggests that it is a graded characteristic, its effects depending largely on the level attained. His school believes that age and environmental factors are of major importance in determining blood-pressure levels and that the relatively small contribution from inheritance is polygenic. Those who disagreed were able to draw attention to considerable sections of some communities in whom pressure does not rise with age.

Longitudinal surveys of general populations provide an opportunity to study some of the outstanding questions. This paper reports analyses of data, collected over periods of 10 and 8½ years in two such studies in South Wales, in which the relations between change of blood pressure, the pressure already attained, and age are explored.

Population Samples and Surveys

The populations of a typical Welsh mining valley, the Rhondda Fach, and a neighbouring agricultural area, the Vale of Glamorgan, were selected by the M.R.C. Pneumoconiosis Research Unit for epidemiological studies of tuberculosis and pulmonary disease in contrasting occupational groups (Cochrane *et al.*, 1955, 1956). The population of the Rhondda Fach

was defined by censuses in 1950 and 1953, and a serially numbered card was prepared for each person over 5 years of age resident in the valley at either time. The cards were numbered in a geographical order, and one in every 100 was selected to give a systematic random sample of the population for the blood-pressure investigation; the cards of those who had died or left the area were replaced by random selection from the same batch of 100 cards. The final sample included about 1 in 90 of the total population of 23,889 residents in 1953. The population of the Vale of Glamorgan, where a census was taken in 1955, included 5,691 subjects over the age of 5 years. Random samples were selected from nominal lists to give groups of 200 subjects of each sex.

The first blood-pressure surveys were undertaken in the winters of 1954 and 1956 in the Rhondda Fach and Vale of Glamorgan respectively. The random samples were assumed to be representative of the general population and were used as the *propositi* for genetic studies in which measurements were made also on all their first-degree relatives living within 25 miles (40 km.). Over 95% of the *propositi* and over 95% of their relatives were examined in the initial studies.

Follow-up studies were carried out in the Rhondda Fach in the winter of 1958 and in the summer of 1964; the Vale of Glamorgan sample was followed up in the summers of 1960 and 1964. Of 1,216 subjects seen in the first Rhondda survey 909 (74.8%) were examined 10 years later, the death certificates of 130 (10.7%) who had died were studied, 149 (12.3%) had left the area, and 28 (2.3%) had refused follow-up. Of the 1,464 subjects seen at the first survey in the Vale of Glamorgan 1,142 (78.0%) were still being followed up eight and a half years later, the death certificates of the 139 (9.5%) who had died were examined, 144 (9.8%) had left the area, and 39 (2.7%) had refused further follow-up. By 1964 either the blood-pressure status or the cause of death was known for 2,320 (86.6%) of the original 2,680 individuals.

Details of the techniques used have been described in previous publications from these studies (Miall and Oldham, 1955, 1958, 1963). Casual blood-pressure measurements were made by one observer using a mercury sphygmomanometer in all surveys reported here. Observations were made in the subject's own home after he or she had been sitting quietly for at least five and usually more than ten minutes. Measurements were made at any time between 9 a.m. and 10 p.m., but the majority

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were done after 4 p.m. In the follow-up surveys measurements were made without having any recorded information of previous findings available at the time; data from previous surveys were transferred subsequently to the new record cards.

Comparison of Data Obtained at the Three Surveys

The curves relating mean systolic and diastolic pressures and age at each of the three surveys in the Rhondda Fach and Vale of Glamorgan are shown in Figs. 1 and 2. Data for people who died before 1964 have not been excluded from the earlier surveys, so the curves are comparable. They are not as exactly superimposed as they would have been had no secular changes occurred in either the pressures or their determination. The means for males in the Rhondda were somewhat lower at the first than at the second survey, and those at the third survey tended to be intermediate. For females also the pressures at the second survey in the Rhondda were slightly higher than those at the first survey, but at the third survey they were marginally lower. In the Vale of Glamorgan values in both sexes at the first survey were higher than those at subsequent surveys, which were almost superimposed.

FIG. 1.—Mean systolic and diastolic pressures at the three surveys; Rhondda Fach.

FIG. 2.—Mean systolic and diastolic pressures at the three surveys; Vale of Glamorgan.

Differences between the overall shapes of the curves relating pressure with age at the three surveys are small, but their slight displacements complicate the analysis. The first two Rhondda surveys were carried out in the winter during the same three months of the year, but the second (1958) survey was done during particularly cold weather with much snow. The third Rhondda survey took place in the summer. In the Vale of Glamorgan the first survey was done in the winter, the second in the spring, and the third in the summer. Temperature differences may have played a part in causing the changes between surveys—cold environments increase arterial pressure (Takahashi *et al.*, 1957), warm ones appear to lower it (MacPherson, 1949); Rose (1961) reported evidence of seasonal trends in arterial pressure. Similar findings were reported by McKeown *et al.* (1963) and attributed to temperature differences.

Though these small but definite secular or technical differences complicate the analyses, it seems likely that other longitudinal surveys of this kind will face the same problem. The similarity of the relation between pressure and age in the two sexes and in the two populations at each occasion makes it unlikely that these differences have important biological significance. Their effect on the analysis has been to make it impossible to pool longitudinal data from the two populations.

When the change of a biological characteristic is related to the initial measurement a difficulty arises because these are not independent variables. If the characteristic fluctuates, as does arterial pressure, those with atypically high or low values at first measurement will tend to show, respectively, lower or higher values when re-examined. This difficulty is overcome if the change is related to the mean of the two measurements; these are independent variables.

Results

Tables showing the change of pressure between the first and third surveys, according to the mean of the initial and final readings, were compiled for all subjects followed up to 1964 and will be made available on request. An examination of these Tables suggested that the change of pressure during these intervals was more closely related to mean pressure than to age. The relation between change of systolic pressure, mean systolic pressure, and age is illustrated in Figs. 3 and 4, where the mean change of pressure is shown for subjects with different ranges of mean pressure in separate 10-year age groups; the numbers at the foot of the columns indicate the number of subjects contributing to each mean.

Multiple regression analyses of change of pressure on mean pressure and age were carried out for each 10-year age group, excluding that for people who were over 75 at the first survey, where the numbers were small; the single regression coefficients of change of pressure on mean pressure, disregarding age, and on age, disregarding mean pressure, were also computed. The multiple regression coefficients and their levels of significance are shown in the Table. Since these analyses were suggested by an examination of the data, the calculated significances should be treated with some caution. The Table shows that in the multiple regression analyses

all but one of the seven significant age coefficients were negative, whereas all 25 significant mean pressure coefficients were positive.

The significant *single* regression coefficients of change of pressure on age (not shown in the Table) were also nearly all negative and almost confined to the 5–14 age group. The older subjects in this age group at the first survey would, 10 and 8½ years later, be over 20, and would have reached the age at which the rapid increase in pressure which accompanies growth ceases. Apart from this age group there were only two significant regressions of change of pressure on age, one positive and one negative, among the other 48 age/sex/pressure groups, and these were significant only at the 5% level. No trend was apparent and no significant heterogeneity was found in the

coefficients of change of pressure on age in subjects aged 15 and over.

There were 22 of the *single* coefficients of change of pressure on mean pressure which were statistically significant, and all were positive; nine were significant at the 0.1% level, seven at the 1% level, and six at the 5% level. Among these regressions of change of pressure on mean pressure in adults the larger and more highly significant coefficients tended to be found in the young and middle-aged, and in three of the four analyses of systolic pressure data (Vale males and Rhondda and Vale females) and in one of the four analyses of diastolic pressure data (Vale males) significant heterogeneity among the regressions was found.

FIG. 3.—Mean change of systolic pressure (mm. Hg) in 10 years according to mean systolic pressure and age; Rhondda Fach.

FIG. 4.—Mean change of systolic pressure (mm. Hg) in eight years according to mean systolic pressure and age; Vale of Glamorgan.

Multiple Regression Coefficients for Change of Pressure on Mean Pressure and Age

Age at First Survey	Rhondda Fach					Vale of Glamorgan				
	No.	Systolic		Diastolic		No.	Systolic		Diastolic	
		Mean B.P.	Age	Mean B.P.	Age		Mean B.P.	Age	Mean B.P.	Age
Males										
5-	73	0.35*	-1.23	0.25	0.19	119	0.47‡	-1.59‡	0.32*	-0.51
15-	71	0.04	-1.10*	0.13	-0.44	60	0.00	-1.30	0.09	-0.72
25-	84	0.19	-0.33	0.05	-0.56	97	0.22‡	0.45	0.34	0.61*
35-	75	0.42‡	-0.96	0.39‡	-0.22	129	0.37‡	-0.15	0.29‡	-0.51
45-	62	0.53‡	-1.25	0.09	0.02	105	0.45‡	-0.21	0.50‡	-0.41
55-	34	0.56*	0.07	0.59*	0.53	43	0.01	0.11	-0.06	0.82
65-	11	0.30	-3.89	0.69	-3.07	27	-0.01	-1.04	0.07	-0.05
Females										
5-	97	0.14	-2.29‡	0.37*	-1.11*	107	0.24	-2.53‡	0.19	-0.98‡
15-	85	0.21	0.18	-0.04	0.56	60	0.34‡	-0.64	0.51‡	-0.19
25-	96	0.62‡	0.06	0.23	-0.47	99	0.59‡	-0.15	0.32‡	0.01
35-	96	0.30‡	0.48	0.12	0.23	98	0.27‡	0.68	0.20*	-0.12
45-	65	0.35*	-0.03	0.27	0.40	92	0.24*	-1.33	0.22*	-0.35
55-	47	-0.04	0.14	-0.06	0.23	74	0.04	-1.00	0.14	0.46
65-	16	0.01	-0.07	0.37	1.66	41	0.32	-0.09	0.17	0.09

* Coefficient significant at 5% level.

† Coefficient significant at 1% level.

‡ Coefficient significant at 0.1% level.

The lower regressions of change on mean pressure in old people could be attributed to an effect of morbidity and the selective effect of mortality. As there was no evidence of an effect of age in determining change of pressure in any of these analyses, and as mortality seemed a likely explanation for the heterogeneity found among the mean pressure coefficients, adult age groups were pooled and multiple regression analyses of change of pressure on mean pressure and age carried out.

The multiple regression equations for the data for all adults were as follows:

Males

Rhondda Fach:
Systolic change = $-45.70 + 0.358 \times \text{mean systolic pressure}$
 $+ 0.145 \times \text{age}$
Diastolic change = $-16.86 + 0.256 \times \text{mean diastolic pressure}$
 $- 0.052 \times \text{age}$

Vale of Glamorgan:
Systolic change = $-28.81 + 0.243 \times \text{mean systolic pressure}$
 $- 0.056 \times \text{age}$
Diastolic change = $-14.45 + 0.198 \times \text{mean diastolic pressure}$
 $- 0.054 \times \text{age}$

Females

Rhondda Fach:
Systolic change = $-26.73 + 0.220 \times \text{mean systolic pressure}$
 $+ 0.145 \times \text{age}$
Diastolic change = $-6.71 + 0.123 \times \text{mean diastolic pressure}$
 $- 0.025 \times \text{age}$

Vale of Glamorgan:
Systolic change = $-23.64 + 0.235 \times \text{mean systolic pressure}$
 $- 0.107 \times \text{age}$
Diastolic change = $-15.97 + 0.243 \times \text{mean diastolic pressure}$
 $- 0.081 \times \text{age}$

These mean pressure regression coefficients were all significant at the 0.1% level with the exception of that for diastolic pressure Rhondda females, which was significant only at the 5% level. The age coefficients were not significant, with one exception; for diastolic change in Vale of Glamorgan females the coefficient, 0.081, was significant at the 5% level, but was negative.

The linear regression equations relating change of pressure to mean pressure, disregarding age, were as follows:

Males

Rhondda Fach:
Systolic change = $-47.11 + 0.409 \times \text{mean systolic pressure}$
Diastolic change = $-17.40 + 0.239 \times \text{mean diastolic pressure}$

Vale of Glamorgan:
Systolic change = $-28.92 + 0.227 \times \text{mean systolic pressure}$
Diastolic change = $-15.70 + 0.187 \times \text{mean diastolic pressure}$

Females

Rhondda Fach:
Systolic change = $-28.52 + 0.273 \times \text{mean systolic pressure}$
Diastolic change = $-6.58 + 0.110 \times \text{mean diastolic pressure}$

Vale of Glamorgan:
Systolic change = $-22.68 + 0.196 \times \text{mean systolic pressure}$
Diastolic change = $-15.96 + 0.201 \times \text{mean diastolic pressure}$

These regression coefficients were all significant at the 0.1% level with the exception of that for diastolic pressure in Rhondda females, which was again significant only at the 5% level. Significant regressions of change of systolic pressure on age, ignoring mean pressure, were found for the Rhondda males and females and the Vale females, but were spurious and due entirely to mean pressure, as is shown by the multiple regression analysis given above. Mean changes in pressure for Rhondda females according to their mean pressures are illustrated in Figs. 5 and 6. Those for Rhondda males and subjects of both sexes in the Vale of Glamorgan showed a similar pattern. In no case did the data deviate significantly from the regression line, but at higher mean pressures the scatter about the regression increased. This could be an effect of several different factors—small numbers, the influence of therapy, and the effect of such complications as cardiac failure, cerebrovascular accidents, and myocardial infarctions. Though rectilinear regressions appear to fit the data adequately, extrapolation below zero change of pressure is unwarranted; the equations suggest that below certain pressures the change in pressure is towards lower values, but, of course, this does not occur.

Since the pressures in the third survey were in general lower than those in the first survey, mean increments have been

underestimated and the absolute value of the (negative) constant terms inflated. These secular changes can have little effect on the regression coefficients. It is of interest that the regression equations suggest that change in pressure is less at lower pressures and greater at higher pressures for males than it is for females; this accords with other evidence that females tolerate high blood pressure better than do males.

FIG. 5.—Mean change of systolic pressure in 10 years according to mean systolic pressure; Rhondda Fach females aged 15 to 74 years at first survey.

FIG. 6.—Mean change of diastolic pressure in 10 years according to mean diastolic pressure; Rhondda Fach females aged 15 to 74 years at first survey.

Discussion

A number of longitudinal studies of blood pressure have been carried out in the past. Some of these have involved hospital populations—for example, Perera (1948), Bechgaard (1956), and Leishman (1959)—some have investigated insured populations—for example, Robinson and Brucer (1939)—and others have used a variety of general, working, or Service populations—for example, Ludwig (1956), Cruz-Coke (1959), Stamler *et al.* (1960), and Harlan *et al.* (1962). In most of these studies, as in our own, it has been shown that mean pressures are higher at each subsequent remeasurement, and that the mean increments in pressure accord with what would be expected from the cross-sectional studies. In some studies—for example, those of Robinson and Brucer (1939) and Stamler *et al.* (1960)—attention was drawn to subsamples who showed no increase in pressure over prolonged intervals. The technique of multiple regression analysis allows simultaneous examination of the relative contributions of age and pressure in predicting change of pressure. It would appear that no longitudinal blood-pressure data have been analysed in this way previously.

In the surveys reported here environmental differences and the slight secular changes in pressure or in its measurement which occurred between the surveys probably account for the differences between the findings in the two populations but do not affect the overall conclusion that change of pressure is related to pressure rather than to age.

Age, *per se*, plays no direct part in determining rate of change of pressure in these populations even though, as is seen in Figs. 1 and 2, mean pressures are much higher in the old than in the young and even though almost all old people in these populations have high pressures. Age appears to play a part solely because the blood-pressure changes on average are positive and increase with higher pressures.

The relation between change of pressure and mean pressure also appears to be a graded phenomenon—the higher the pressure the greater the rate of increase—and seems partially to reconcile the conflicting views on the nature of unexplained hypertension.

If this relation were found to be causal it could explain the observations that some individuals and some races show no apparent increase in pressure with age. For example, the populations in Oceania studied by Maddocks (1961) and Lovell (1963), where old people have the same pressures as young adults, have mean pressures below the levels at which our data suggest that a self-perpetuating mechanism could be implicated. But our analysis has shown only an association between change of pressure and mean pressure, not a causal relationship. It is possible that minor but sustained increases of pressure, due to a variety of environmental and genetic influences, could lead to changes in function and structure which perpetuate a vicious circle, but some other factor acting in a similar fashion may underlie the relationship found.

A controlled therapeutic trial might show whether the pressure attained determines the subsequent increments in pressure; if, for example, it could be shown that after a reduction in pressure effected by hypotensive drugs the subsequent changes in pressure of previously hypertensive subjects revert to those occurring spontaneously in subjects with lower pressures, this would be strong evidence for a causal relationship.

Summary

Data obtained from the longitudinal surveys of arterial blood pressure in two general population samples have been used to examine the relation between change of blood pressure, the mean pressure attained, and age.

It has been shown, by multiple regression analysis of change of pressure on mean pressure and age, that in these popula-

tions changes in pressure during intervals of 10 and 8½ years are highly significantly related to mean pressures, but only indirectly related to age. This implies that ageing plays no direct part in determining the rate of change of pressure; age appears to play a part solely because the blood-pressure changes are positive and increase with higher pressures.

If change of pressure is determined by attained pressure, this would explain the observation that some individuals and some races show no apparent increase of pressure with age, and would partially reconcile the conflicting views on the nature of unexplained hypertension. However, the evidence has shown only association, not causality.

We wish to record our thanks to the people of the Rhondda Fach and Vale of Glamorgan who so willingly continue to co-operate in these prolonged studies, and to Professor A. L. Cochrane and our colleagues in the M.R.C. Epidemiological Research Unit in South Wales, particularly Mr. F. Moore, who assisted with all the field work and much of the data preparation.

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Treatment of Polycythaemia Vera*

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The treatment of polycythaemia vera with radioactive phosphorus (³²P) was introduced in 1938 by Lawrence (1940); combined with venesection, it proved to be both effective and free from side-effects and was accepted as the best form of treatment (Scott, 1953; Harman, Hart, and Ledlie, 1955). Aplastic anaemia was its greatest hazard, but usually followed its use in unsuitable cases or in excessive dosage (Calabresi and Meyer, 1959). The association of acute leukaemia with the use of ³²P has been suspected for many years, and the evidence to substantiate this is considered. It is chiefly on account of this danger that some authorities (Perkins, Israëls, and Wilkinson, 1964) believe that ³²P should be replaced by chemotherapy (busulphan, thiotepea, nitrogen mustard, and pyrimethamine

being most frequently used); they regard this as equally effective but free from the risk of inducing acute leukaemia.

This paper reviews the results of irradiation (with ³²P or radiotherapy) in 81 patients with polycythaemia vera. Their survival, the incidence of acute leukaemia, and the causes of death are considered in detail, and the position regarding the use of ³²P is discussed.

Material

Polycythaemia vera was diagnosed when the haemoglobin was greater than 17 g./100 ml. or the red cell count greater than 6,000,000/cu. mm., together with one other feature—namely, a leucocyte count greater than 12,000/cu. mm., a platelet count greater than 300,000/cu. mm., or splenomegaly. Acute leukaemia was diagnosed when both blood and marrow were

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