HIGH BLOOD PRESSURE

**A longitudinal population study of men born in 1913,
with special reference to development and consequences for health**

by

Kurt Svärdsudd

Göteborg 1978

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CONTENTS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Svärdsudd K & Tibblin G: A longitudinal blood pressure study. Change of blood pressure during ten years in relation to initial values. The Study of Men Born in 1913.
Submitted for publication.

II. Svärdsudd K & Wedel H: Factors associated with the initial blood-pressure level and with the subsequent blood-pressure increase in a longitudinal population study. The Study of Men Born in 1913.
Submitted for publication.

III. Svärdsudd K: Change of blood pressure in relation to change of other variables and to development of hypertensive disease in a longitudinal population study. The Study of Men Born in 1913. Submitted for publication.

IV. Svärdsudd K & Tibblin G: Mortality and morbidity during 13.5 years' follow-up in relation to blood pressure. The Study of Men Born in 1913.
Submitted for publication.

V. Svärdsudd K, Wedel H, Aurell E & Tibblin G: Hypertensive eyeground changes. Prevalence, relation to blood pressure and prognostic importance. The Study of Men Born in 1913.
Acta Med Scand 204: 159, 1978.

INTRODUCTION

Ever since the introduction of blood-pressure measurements as a routine measure in clinical practice it has been known that high blood pressure is associated with an unfavourable prognosis as to survival[122]. To-day hypertension is considered to be the most serious risk factor for the development of cerebrovascular disease[15, 59] and one of the most serious for the development of ischaemic heart disease[15, 57, 112]. High blood pressure is a prevalent condition, affecting 10–15 per cent of the adult population in the Western world[8]. High blood pressure and its sequelae have been described in terms of an epidemic[112].

In clinical medicine biological traits are often described in qualitative terms like healthy – ill, normal – abnormal, normotensive – hypertensive. This dicotomy suggests that the two contrasting groups are qualitatively different. Hypertension was generally regarded as an entity qualitatively different from normotension until twenty-five years ago, when Pickering proposed that the blood pressure is continuosly distributed in the population and that hypertension merely represents the upper end of the distribution[90]. This hypothesis was challenged by Platt[92]. On the basis of an observed irregularity of the blood-pressure distribution curve, which was interpreted as evidence of bimodality, he proposed that there are two populations, one normotensive and one hypertensive. Platt further suggested that hypertension was probably a genetically determined disease with dominant inheritance.

The information on the blood-pressure distribution in the general population, and on the relationships between blood pressure and other variables, that was accumulated during the following years favoured Pickering's standpoint. Although the bimodality was the most often used argument during the Pickering-Platt controversy, it is of minor importance. Bimodality of the distribution is neither a prerequisite for nor evidence of two overlapping populations. The concept of hypertension as a quantitative disorder is mainly based on the finding that most hypertensive traits, including prognosis, physiological aberrations, chemical aberrations and so on, occur with increasing frequency and/or degree from the lowest blood pressures to the highest. To-day this concept is almost universally accepted.

A closely related issue is the limits of the normal blood pressure. Since the blood pressure is continuously distributed, there is no natural or given point in the distribution which separates a "normal" blood pressure from an "abnormal". Furthermore, normality can be defined in at least four different ways[99]. In a statistical sense normal means "most common" and is a purely descriptive term, with little or no medical significance. Normal in a clinical sense means the range within which the population is free from

symptoms. From a prognostic point of view normal means the ideal pressure range, that associated with the best prognosis. But since the blood pressure is a graded characteristic, neither of the two latter definitions provides sharp limits. Normality may also be defined operationally, e.g. as the range within which the disadvantages of treatment are greater than the advantages. With that definition, normality may be expected to vary from time to time. The blood pressure or "degree of hypertension" has therefore been regarded in this study as a continuous variable.

It has been known for more than half a century that the blood pressure tends to increase with increasing age[105, 127]. During the last twenty-five years a number of studies of the blood pressure in samples representative of the general population have shown that the mean value of the systolic and of the diastolic blood pressure increases in a somewhat irregular fashion from childhood up to high age[17, 19, 33, 43, 55, 61, 72, 76]. This trend has generally been interpreted as a normal physiological process, possibly caused by an increased rigidity of the vessel walls with increasing age. However, in 1929 Donnison published a paper on the blood-pressure level in Africans living on a reserve in Kenya[27]. In that group the blood pressure did not increase with increasing age. Donnison's interpretation was that since these people lived a life quite different from that of Western so cieties, the way of life might be involved in the development of hypertension. But the result could equally well be the effect of a number of biases such as selective mortality, bias in the selection of the study group, difficulties in estimating the age of the subjects, and so on. Later, a number of other populations with a similar stable blood-pressure level throughout life have been found[16, 20, 60, 62, 66, 70, 81, 84, 88, 93, 107, 108, 110]. To-day it seems reasonable to assume that the observation is a real one and not a product of selection or other bias[39].

These observations lend support to the hypothesis that the blood-pressure increase with age observed in Western societies is perhaps not an inevitable part of the biological ageing process. It might rather be caused by the influence of environmental factors. The blood-pressure level may be a reflection of the (genetically determined?) susceptibility to that influence[39]. If so, manipulation of the responsible environmental factor or factors may have a profound effect on the blood-pressure level in the community.

During the last few years increasing interest has been focused on factors associated with the development of hypertension and on the possibilities of primary prevention of the condition. For more than fifteen years preventive cardiological research has been carried out in Göteborg, Sweden, with the aim of developing primary and secondary preventive measures against hypertension and its sequelae. This thesis is one of the results of these efforts.

AIMS OF THE STUDY

The aims were:

1. To describe the blood pressure change over ten years and to study the relationship between the blood-pressure level at the start of the study and the subsequent blood-pressure change.
2. To describe the relationship between anthropometric, physiological, blood chemistry and psycho-social variables on the one hand and the blood-pressure level at the start of the study and the subsequent blood-pressure change on the other.
3. To describe the relationship between the change of blood pressure concomitant with the change of anthropometric, blood chemistry and psycho-social variables, and the development of indices of hypertensive disease.
4. To describe the consequences of different blood-pressure levels for health, measured as sick leave, disability pension, morbidity and mortality.
5. To describe the consequences of hypertensive arteriolar disease, additional to those of the blood-pressure level, for mortality and morbidity.

STUDY POPULATION

The original cohort

All inhabitants of Sweden have a National Registration Number that includes their date of birth and other vital statistics. Names, addresses and registration numbers are registered by the County Census Bureau and were accessible before the sample was drawn for the present studies. The study population was recruited from men living in Gothenburg, Sweden, who were born in 1913 and were still alive at the age of 50 years (1963). All men meeting these criteria who were born on a date divisible by three – the third, sixth, ninth day, and so on, of each month – comprised the study sample. 973 men met these criteria. Of these, 855 (88 per cent) agreed to be examined in 1963 at Sahlgren's Hospital, Gothenburg.

The basic population and the participants have been described in detail elsewhere[118]. Of the 118 men who did not participate, 40 agreed to be examined at home, 7 had died, 4 were in hospital and 9 had moved away from the city at the time of the investigation. The remaining 58 men declined examination for various reasons, in most cases owing to a negative attitude to medical care. Compared to the participants, non-participants had a lower mean income, were more frequently unmarried and were more often registered by the Temperance Board for alcoholic intemperance, indicating a higher frequency of alcohol problems. Slightly more non-participants had received sickness benefit[117]. During 13.5 years of follow-up the 40 non-participants examined at home had the same mortality rate and pattern as the participants, while the 78 men not examined had a higher mortality rate from both cardiovascular and non-cardiovascular causes (study I).

Comments: The loss of the latter group has probably introduced a selection bias in the study. But since the group is small, the error will also bee small, even if the group is markedly different from the participants. This is illustrated numerically in study I.

The followed cohort

Of the 855 men who participated in 1963, 792 were re-examined in 1967 and 703 of the latter were re-examined again in 1973, figure 1. The 855 and the 792 men constitute the study population of study V.

In addition to the 703 men examined on all three occasions, 15 men participated in 1963 and 1973 but not in 1967. 26 men who participated in 1963 and, in certain cases, in 1967, were not able to attend the examination in 1973 but replied to a postal questionnaire of the same type as that answered by the men attending the examination. The population of study IV consists of the 855 men who were followed with respect to mortality from stroke and myocardial infarction, and of the 703 + 15 + 26 = 744 men, who were followed in respect of other morbidity variables.

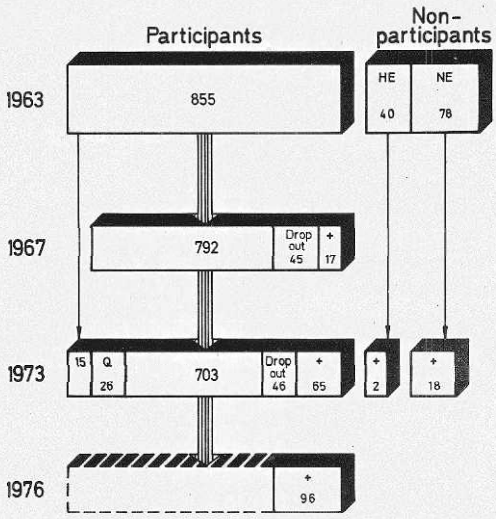

Figure 1. Composition of the population in the Study of Men Born in 1913. HE = home examination group. NE = not examined. + = died.

Comments: The 744 men constitute 94 % of the survivors from the 1963 investigation and 84 % of the survivors of the original sample. The effect of drop-out on the results is therefore probably small.

Antihypertensive treatment

All men found to have a systolic blood pressure ⩾ 175 mm Hg and a diastolic pressure of ⩾ 115 mm Hg at one of the examinations and at a subsequent control examination were offered antihypertensive treatment. 78 of the 703 men examined on all three occasions were receiving treatment on one or more occasions. The remaining 625 men constitute the population of studies I, II and III.

Comments: There are several reasons why only the 625 men were used. All three studies dealt with blood-pressure change. To reduce the error of the estimate of the pressure change, it was considered essential to have as many blood-pressure measurements as possible in each subject. Therefore, only individuals attending all three examinations were included. Since antihypertensive treatment was assumed to affect the blood-pressure change, all individuals receiving such treatment at the time of any examination were excluded.

The extent to which the 625 men represent the 855 men originally examined was analyzed in studies I and II. Those who died, were lost or were excluded from the study tended to have a higher blood pressure in 1963, a higher parental mortality from cardiovascular diseases before 1963 and a lower mean income in 1961 than those who remained in the study (table 1). They also probably had a greater blood-pressure increase during the ten-year period than those who were followed. In studies I and II an effort was

Table 1. Characteristics of four variables among the 855 men of the initial investigation and the 625 men untreated for hypertension and followed through the study.

	A history of		Mean systolic blood pressure in 1963	Mean income in 1961
	Mother dead in CVD	Father dead in CVD		Skr
	%	%	mm Hg	
The 855 men	19.6	22.0	138.3	16,988
The 625 men	17.0	20.3	134.4	17,664

made to estimate the extent to which the bias affected the results. Generally, the effect seems to be an underestimation of the strength of the "true" associations.

METHODS

On methodology in general

A large number of variables were measured in the five studies summarized here. They may broadly be grouped into blood pressure, anthropometry, ophthalmoscopic findings, blood chemistry, urine chemistry, physiology, psycho-social data and mortality and morbidity follow-up data. In most instances generally accepted standard methods were used.

Comments: To be practicable in an epidemiological study, a method must be 1) simple and cheap enough to be employable on a large scale; 2) safe enough to be used in apparently healthy individuals; 3) accurate enough, both as to the precision of the estimate and to the extent to which the method measures what it is supposed to measure; and 4) stable enough to permit the study to go on over a long time. The methods used in this study were selected according to these criteria.

Standardization

The methods used were standardized on several levels. All subjects were examined at the same time of the day on each occasion. They were all following the same time schedule [65, 118]. They all underwent the investigations in the same order. To reduce the observer error, the number of observers was kept as low as possible. For several variables a single observer made all the measurements on each occasion. All the measurements were performed according to a protocol specifying what to measure, where to measure it and how to measure it. Blood samples and urine samples were immediately taken care of and transported to a laboratory where all the analyses were carried out. Regular checks were

made to determine the accuracy of the laboratory methods[65, 118]. History-taking was carried out using a self-administered questionnaire[100] and by interview according to interviewer-administered questionnaires. The results of all measurements were recorded on data sheets for computer processing.

Methodological problems in longitudinal studies

On all three occasions the examinations were performed over approximately one year, with a break from the middle of June to the middle of August. In 1963 the subjects were examined in order of place of employment, and in 1967 and 1973 in order of date of birth. In 1963 and 1973 the examinations were performed in the morning, and in 1967 in the early afternoon. The same observer (GT) read all the blood pressures in 1963 and 1967 and 60 % of the pressures in 1973. The remaining 40 % of the blood-pressure measurements in 1973 were carried out by two more observers (BL and KS).

Comments: In a longitudinal study the population followed should be re-examined under conditions as identical as possible to those at the initial examination. This problem is often more difficult to solve than the methodological problems in cross-sectional studies. It is, for example, often impossible to use the same observers all through a study if it is as long-term as this one. In the Study of Men Born in 1913 the main methodological within-study differences were the addition of two more observers for blood pressure in 1973, differences in the time of the day at which the measurements were carried out in 1967 compared to 1963 and 1973, and differences in the time of the year for certain individuals in 1963 compared to 1967 and 1973. The effect of the change of observer is illustrated in study I. BL read the pressures higher than GT, and KS higher than BL. If KS had read all the blood pressures in 1973 the blood-pressure change during the study would have been considerably overestimated and the relationship between pressure change and the initial pressure level would not have been found since the observer error makes the standard error of the relationship larger.

A number of individuals were examined in different seasons during the study. This bias is counteracted by the break since the seasonal variation, at least for blood pressure, is most extreme during this period[98]. The bias is probably small and the main effect is to make individual blood-pressure readings more variable. The different time of the day for the examinations in 1967 compared to 1963 and 1973 may be responsible for the larger observed mean yearly blood pressure change during 1963–1967 compared to 1967–1973. But since most of the conclusions in the five studies are based on the ten-year period and the results from the partial periods are the same as for the whole period, the bias is probably small. The main effect is once again to make individual readings more variable.

Mortality and morbidity follow-up

Mortality data for all the 973 men in the original sample were followed up continuously

during the study by scrutiny of death certificates and periodic checks on vital statistics with parish offices (the authority which has primary responsibility for the census register), or the corresponding authority for men resident abroad. Death certificates were available for all men who died. Postmortem examination was carried out in 83 % of those who died up until 1976.

Morbidity data for stroke and myocardial infarction for all 855 men who were followed up were obtained by interviews, examination of hospital records and death certificates and, from November 1968, from the Myocardial Infarction[32] and Stroke Registers[46]. These registers cover the city of Göteborg and include more than 94 % of all infarcts and strokes. Special arrangements were made for men who had moved out of the area. All suspected cases were assessed by the same observer, according to the criteria for stroke and myocardial infarction specified in studies IV and V.

MODEL OF THE BLOOD-PRESSURE CHANGE WITH AGE

Description

The model of the blood-pressure change with age used here is a modification of a model for change of pulmonary function described by Fletcher et al.[37]. The blood-pressure change over time for most people is assumed to be a gradual process, occurring over decades, rather them a sudden, irreversible one. The rate of change is furthermore assumed to be continuously distributed in the population. The resulting model of the blood-pressure change in the study population is shown in figure 2*a*. For the sake of simplicity the pressure change over time was assumed to be linear even though it may have been irregular, as in figure 2*b*, at least in the short-term perspective.

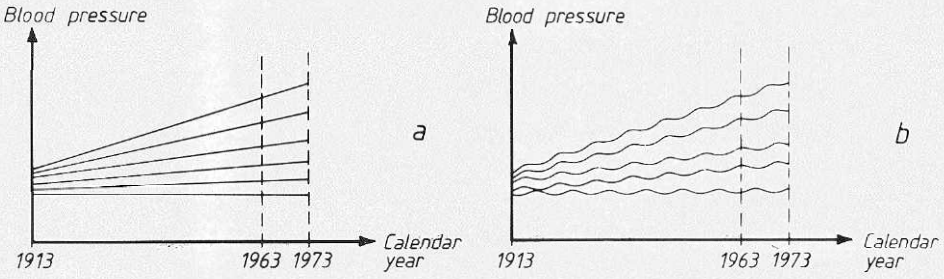

Figure 2. The presumed course of the blood-pressure in the study population under ideal (a) and under more realistic conditions (b).

Comments: Published blood pressure records over long time (e.g.[34, 49]) support the validities of the model. Other factors indirectly supporting it are the changes of the blood-pressure distribution with age and the stable blood pressure ranking. The blood-pressure distribution at young age is approximately normal. With increasing age the upper end of the distribution extents towards higher values while the lower end is relatively unaffected[7, 11, 31, 35, 45, 75, 131].

Several studies have shown a relatively stable blood pressure ranking, i.e. individuals in a group tend to retain their relative positions in the blood-pressure distribution of the group on successive measurements[25, 35, 44, 45, 50, 97, 102, 131]. An individual with high blood pressure at the first reading thus tends to remain at the upper end of the scale, an individual with moderate pressure remains in the middle of the scale, and so on. This stable ranking is observed in age-groups from two years of up to 70. The stability of the ranking decreases with increasing time interval between the measurements but it is still observable after 30 years[44].

Consequences

As a consequence of the model, a positive relationship should exist not only between the blood pressure increase and the pressure level attained but also between the attained level and subsequent blood pressure change. This is called the horse-racing effect, in analogy with a horse-race[37] where there is a close correlation between the speeds of the horses and their positions in the race. No satisfactory investigation of the horse-racing effect in blood pressure data has been published but the results from some studies suggest the existence of such an effect[69, 75].

Another consequence of the model relates to the interpretation of cause and effect. If a factor X, which causes a blood-pressure increase, is active for a sufficiently long time it will show a relationship both to the blood-pressure level and to the subsequent blood-pressure change when the level is taken into account. But if factor X is a consequence of the raised blood pressure, a relationship may be expected only to the pressure level, not to the blood-pressure change when level is taken into consideration. For parallel phenomena, i.e. if factor X and the blood-pressure change have a common cause but are otherwise unrelated, the same pattern of relationships would be observed as if factor X were a cause of the pressure change. On the basis of a known causal relationship a certain pattern of associations may thus be expected. In reality, however, the situation is the reverse. From the analysis a pattern of relationships is obtained which is used for the interpretation of causality. The absence of a statistically significant association is no evidence that no true relationship exists. Therefore, the pattern of relationships indicated above must be interpreted with caution.

The model also has implications for the study of the consequences of high blood pressure. Because of the stable blood-pressure ranking, a blood-pressure reading at the start of the study may be expected to reflect the blood-pressure level during the follow-up period fairly well, even if the duration of follow-up is long.

STATISTICAL CONSIDERATIONS

Measurement of change

As a measure of the blood-pressure change over the ten-year period, the difference between the pressure in 1963 and the mean value of the pressures in 1967 and 1973 was used (studies II and III). The change in blood pressure from 1963 to 1967 and from 1967 to 1973, and the change in other quantitative variables has been measured as the difference between the final and the initial value. For qualitative variables (infarction) morbidity, development of albuminuria etc.) conventional epidemiological principles have been used, the number of new cases being related to the population at risk.

Comment: The blood-pressure increase may be measured in two ways: qualitatively, as the proportion of individuals in an originally "normotensive" population who develop hypertension (according to a specified criterion) during the period, or quantitatively as the blood-pressure change in mm Hg during the period. The former method has been used in most earlier studies. With the model for increase of blood pressure used here, however, the majority of the individuals who "developed hypertension" during the follow-up period may be assumed to have been close to the arbitrary borderline already at the start of the study. Preliminary analyses confirmed this assumption. An advantage of the qualitative method is that patients who have received antihypertensive treatment during the period can be used. A disadvantage is that the information obtained from individuals whose pressures rose but did not reach the limit for hypertension is not used. Since the interest in this study was focussed on blood pressure change irrespective of the initial level, this method is rather insensitive. The blood-pressure change in mm Hg is for this purpose a more sensitive measure of change even though individuals on antihypertensive treatment must be excluded because the treatment interferes with measurement of the pressure change. This method of measuring change has been used in this study.

Since the blood pressure exhibits great intra-individual variation, a pressure change based on only two blood-pressure readings is subject to large measurement errors. In reality, two-thirds of a blood-pressure change recorded in this way is due to random errors (study I) if the short-term biological variation is included in "random errors". The more measurements a measured change is based on, the smaller the measurement error will be. The method of measuring the blood-pressure change during 10 years used here made it possible to reduce the mean measurement error somewhat (study III).

Regression towards the mean

The regression-towards-the-mean phenomenon is described in the appendix to study I and has been discussed in more detail in a previous report[116]. The phenomenon was of

importance in the analysis of the horse-racing effect (study I) and also in analyses in which change of a variable was studied (studies II and III). To reduce or eliminate the regression effect, a method developed in Göteborg was used in the former case and multivariate analysis in the latter.

Comments: In analyses of the change of a variable, the regression-towards-the-mean effect means that the change in subjects with high and low initial values is not comparable. The result will often be that true relationships between the change and other variables are not detected. The simplest way of overcoming this problem is to take the initial value for the change variable into account in the analysis. This was done consistently in studies II and III, even though this is not always explicitly stated in the text.

In the study of the horse-racing effect the regression-towards-the-mean phenomenon cannot be eliminated as easily since the initial value is one of the two variables in the analysis. Although the phenomenon has been known for almost a hundred years[40], no satisfactory method of measuring or eliminating the effect for this purpose has been found. Of the two methods previously used, one[83] has such important limitations that it should preferably be avoided. The other[35] only partly eliminates the regression phenomenon[10]. A new method has therefore been developed[9] and was used in this study. It is the most efficient method of eliminating the regression-towards-the-mean effect found so far[10, 116].

Confounding variables

A confounding variable is usually defined as a variable which is associated with both of the variables in the analysis. Standard confounding variables like age and sex were eliminated by the design of the study. Exchange variables, i.e. variables which measure approximately the same thing as one of the variables in the analysis, were not regarded as confounding variables. The number of confounding variables possible to handle in the analysis programs is limited. Only the strongest and most obvious variables were therefore considered.

Statistical methods

Differences in mean values between groups were tested using the two-sample t-test. The analysis of variance components in study I, the life table method used in study IV and the multiple stepwise linear regression in study V were all performed using standard techniques. In study IV multiple logistic regression technique was used, as described by Wilhelmsen et al.[130]. In study IV a test of linear trend in 2 x n tables was used. The test is equivalent to Fischer's permutation test[82]. In studies II and III a non-parametric test for partial correlation analysis was used. In the analysis, subgroups of men were formed according to the confounding variables. The associations between the investigated variables were tested in each subgroup. The results from the subgroups were pooles using a special technique described by Mantel[71]. The method has certain advantages compared

to linear and logistic regression for the analyses in these two studies. The same is true for isotonic regression, which was used in study II for construction of the regression surfaces. In contrast to the linear and logistic regressions, the isotonic model does not require any specific functional form for the dependent variable. It was assumed that the dependent variable, in this case blood pressure in 1973, increased or decreased with each independent variable when the other variables were fixed. The problem of estimating the dependent variable with this method is complicated. The minimum lower sets algorithm described by Barlow et al.[2] was used.

In all these methods two-tailed tests were used. Values of $p \leqslant 0.05$ were generally regarded as statistically significant. The problem of mass significance was in study V solved by demanding an extremely low p-value in the separate test. In study II it was solved by combining p-values and by comparing the relationships between similar factors and the blood pressure and comparing the relationships between a factor and the blood pressure on different occasions.

RESULTS

Blood-pressure change over ten years (study I)

The mean systolic blood pressure change for the 625 men who were not treated for hypertension was + 6.6 mm Hg during 1963–1967, + 2.9 mm Hg for 1967–1973 and thus + 9.5 mm Hg during 1963–1973. All these changes were significantly different from 0 ($p < 0.001$). The corresponding diastolic blood pressure changes were + 0.42 mm Hg, + 0.44 mm Hg and + 0.86 mm Hg. None of these mean changes differed significantly from 0. The variance was considerable both for the systolic and for the diastolic pressure change.

The distribution of the systolic blood pressure changed successively. The lower end of the distribution appeared to be fixed while the upper end became extended towards higher values and an increasing positive skewness occurred. The diastolic pressure distribution changed in a different way. It became broader at both ends, but the peak was located at the same value.

The change of both the systolic and the diastolic blood-pressure during 1963–1973 was strongly negatively correlated to the initial blood pressure, owing to the regression-to-the-mean phenomenon. After correction for that effect, the relationship between the systolic blood-pressure change and the initial value was positive while that for the diastolic pressure remained negative (figure 3).

Comments: Similar changes of the blood-pressure distributions and of the mean blood pressure have been found in other studies[7, 11, 35, 75, 114]. In younger age groups the diastolic blood-pressure change is similar to that of the systolic pressure, but smaller in magnitude[45, 114]. The expected horse-racing effect was found for systolic but not for

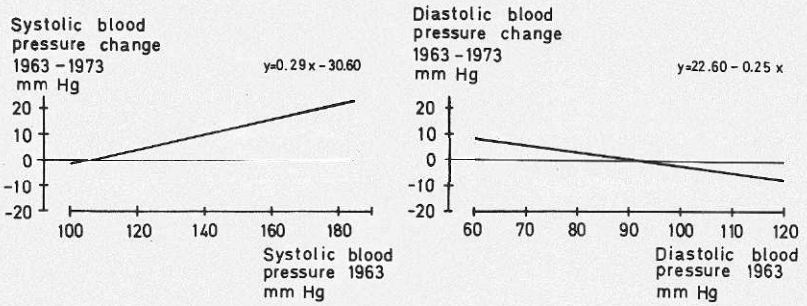

Figure 3. Regressions for change of blood pressure in relation to initial level after adjustment for regression towards the mean.

diastolic blood pressure. On the other hand, no significant diastolic blood-pressure change occurred during the period.

Factors associated with the initial systolic blood-pressure level and the subsequent pressure change (study II)

Weight and body mass index, which is a measure of relative weight, were both correlated to the blood-pressure level in 1963 and 1967 and also to the subsequent blood-pressure change between 1967 and 1973. Skinfold thickness was positively correlated to both the initial pressure level and the change even when weight was taken into account. When skinfold was taken into account weight was not related to the initial pressure level or the change. In 1967 a number of circumference measures were used as indices of obesity. They were all correlated both to the initial pressure level and to the pressure change, but only waist circumference was of importance when weight was kept constant. Uric acid, a history of maternal death from cardiovascular disease, total serum protein and systolic and diastolic blood pressure during exercise and at rest five minutes after work were all positively correlated to the initial pressure level and the change.

Blood glucose, serum triglycerides and cholesterol, haematocrit, heart rate, eyeground changes, heart volume, serum transaminases, urine albumin and pulse-rate during work were all positively correlated to the initial pressure level but not to the subsequent pressure change. Smoking was negatively correlated to the initial pressure level but was not correlated to the pressure change. Urine osmolality, sinus arrhytmia and coffee consumption were not correlated either to the initial pressure level or to the pressure change.

A multivariate analysis was performed in which the variables related both to the initial pressure level and the pressure change were introduced. The result is shown in table 2. Skinfold thickness, maternal death from cardiovascular disease, the serum-protein level and systolic blood pressure during exercise were independently correlated to the blood-pressure change when the initial blood pressure level was taken into consideration. However the blood-pressure increase that could be explained by these factors was rather small, as indicated by the regression coefficients. The effect of the strongest of them,

subscapular skinfold thickness, is shown in figure 4. The thicker the skinfold in 1967, the higher the blood pressure in 1973, regardless of the blood-pressure level in 1967.

Table 2. Regression analysis of suspected risk factors to blood-pressure increase during 1963–1973 and during 1967–1973 taking the initial blood-pressure level into account.

	Regression coefficient	$p \leqslant$
The period 1963–1973		
Subscapular skinfold thickness (mm)	0.46	0.001
Weight (kg)	– 0.21	0.005
Mother died from cardiovascular disease	3.36	0.05
Income (Skr)	– 0.0001	n.s.
Uric acid (mg/100 ml)	0.79	n.s.
The period 1967–1973		
Subscapular skinfold thickness (mm)	0.36	0.001
Systolic blood-pressure at 600 kpm/min (mm Hg)	0.10	0.01
Serum protein level (g/100 ml)	2.04	0.05

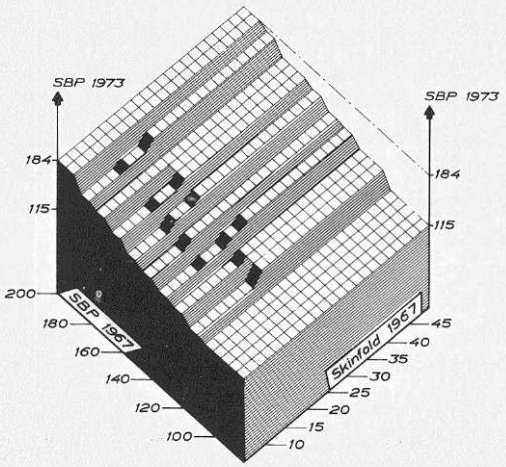

Figure 4. Systolic blood-pressure in 1973 in relation to systolic blood-pressure and skinfold thickness in 1967.

Comments: An association between a factor and both the initial blood-pressure level and the subsequent pressure change was in this study considered to support the hypothesis that the factor might be causally related to the blood pressure. An association to the level only or to the change only was considered not to support the hypothesis, al-

though the possibility that the factor is a causal one was by no means ruled out. However, in the case of a correlation to the pressure level only it is more probable that such a factor is a consequence of the pressure rather than the cause of it.

Weight and skinfold thickness were both used in this study in an effort to differentiate the influence of obesity from that of body mass or volume. The finding that skinfold thickness at a given weight was of importance for the pressure increase but that weight at a given skinfold was not, supports the hypothesis that body fat and not body volume per se is the variable related to the blood pressure. The findings were the same in another report from this study[65] using more sophisticated measures of body fat and lean body mass.

Father's and mother's death from cardiovascular disease was used as an indirect measure of the family history of high blood pressure. Only mother's death in CVD was significantly related both to the initial pressure level and to the change. The reason for this is obscure but the finding has been reported earlier[3]. The familial aggregation of high blood pressure has been analyzed in more detail in another report from this study [121].

Change of blood pressure in relation to change of obesity indices and related variables (study III)

The changes of a number of the variables used in study II were in this study analyzed in relation to the blood-pressure change to illustrate the course of events associated with the blood-pressure increase. The changes of weight, body mass index, skinfold thickness, waist circumference, heart rate, blood glucose and serum triglycerides were all positively related to the blood-pressure change but the changes of serum cholesterol and haematocrit were not. When weight was kept constant, all the significant correlations were weaker but still significant except for triglycerides, which were now nonsignificant (table 3). When the change of skinfold was kept constant, the change of weight was no longer significantly correlated to the blood-pressure change.

Comments: Once again, body fat rather than body mass or body volume seems to be the variable correlated to blood pressure. The change of blood glucose was related to the pressure change even when weight was kept constant. This is, however, true only under the assumption that correction for differences of weight abolishes the influence of body fat completely or almost completely. With this reservation, a higher blood glucose, indicating a more "diabetogenic" metabolism, seems to be associated with a higher blood pressure independently of the greater amount of body fat. This has been reported earlier[5]. Triglycerides, on the other hand, did not seem to exert any independent influence in this respect.

Table 3. Correlations between the changes of anthropometric, physiological and metabolic variables and the change of blood pressure during ten years except for change of waist circumference, which was over six years.

	Change		Correlation to systolic blood pressure change		Ditto given weight
	mean	s	direction	$p \leqslant$	$p \leqslant$
Weight (kg)	1.7	5.3	+	0.005	–
Body mass index (kg/m^2)	0.6	1.7	+	0.001	–
Skinfold (mm)	1.3	4.4	+	0.01	0.01
Waist circumference (cm)	6.3	5.8	+	0.001	0.05
Heart rate (beats/min)	2.2	12.8	+	0.001	0.05
Blood glucose (mg/100 ml)	5.4	22.6	+	0.01	0.01
Triglycerides (mmol/l)	– 0.02	0.7	+	0.05	ns
Cholesterol (mg/100 ml)	7.0	40.8		ns	ns
Haematocrit (%)	1.5	3.8		ns	ns

+ denotes a positive (direct) correlation. ns = not significant.

Change of blood pressure in relation to psycho-socio-economic variables (studies II and III)

In study II the relationship between education, social class, income, occupation, shift work and subjective stress according to self-rating on the one hand and the blood pressure on the other was analyzed. No relationships to the pressure level or change were found except for income, which was negatively correlated to the pressure change when the initial pressure level and smoking were kept constant ($p < 0.05$).

In 1973 a number of psycho-socio-economic variables were evaluated by interview. Among the questions answered, seven, relating to a worsened job situation, were chosen for study III. From these a worsened-job-situation score was constructed. This score was negatively correlated to the pressure change, implying that men who reported the greatest deterioration in their work situation during the period had the slowest blood-pressure increase. A score based on self-rating in fifteen questions relating to change in different aspects of the subjects' life situation was not correlated to pressure change. An affirmative answer to the question "have you been unable to make full use of vacation periods during the last ten years?" and "have you had a divorce during the last ten years?" was positively correlated to the pressure change ($p < 0.05$ and < 0.01, respectively). Other types of conflicts within the family, change of subjective stress and receipt of sickness benefit or a disability pension were not correlated to the pressure change.

Comments: The psycho-socio-economic variables were thus by and large unrelated to the initial pressure level and subsequent change. This is not to say that they are unimportant. It may be that these variables are too inaccurately measured or that they do not measure what they are supposed to measure. For example, income is probably a good measure of social class, perhaps better than occupation, but it may also be a measure of occupational exposure to noxious agents that may affect the blood pressure e.g. noise[54]. Income was of interest since it was correlated to the pressure change and the lack of correlation to the initial pressure level might be caused by selection bias. However, it had no independent significance.

The relationship between the 1973 psycho-social variables and the pressure change has to be interpreted with caution, firstly because the data are retrospectively collected and secondly since it is debatable what they actually measure. However, the presence of these items was assumed to put an increased mental load on the subject which might affect his blood pressure. The reverse was actually found for "worsened job situation" and for the score relating to a worsened life situation. Inability to make ful use of vacation periods was not included in the former two scores since it is possible that it measured something else, e.g. work satisfaction, form of employment or personality. The divorce item was also kept separate since it might be confounded by e.g. the subject's financial situation or alcohol consumption. If the two items are measures of stress, the results support the hypothesis that stress is associated with a long-term blood-pressure increase. But if so, it is remarkable that the other two possible stress items showed a correlation in the opposite direction.

Blood pressure and alcohol (studies II and III)

In study II reported consumption of beer, wine and spirits was not found to be correlated to the initial blood-pressure level. Wine consumption showed a weak correlation to the pressure change when smoking was taken into account. Being registered for alcohol intemperance was not correlated to the initial pressure level or the change. No correlation was found between reported change of beer, wine or spirits consumption and the pressure change (study III). An admission of past drinking problems was negatively correlated to the pressure change, while an admission of current drinking problems was not.

Comments: In an earlier report from the Study of Men Born in 1913 registration for alcohol intemperance was shown to be related to the blood pressure level, using the same systolic-diastolic pressure classification as in study IV[118]. Other studies have found similar relationships[23, 41, 42, 64, 78, 79]. In the two largest, the Framingham Study and the Kaiser-Permanente Multiphasic Health Examination[23, 64], an effect on blood pressure was seen only in those subjects taking more than two drinks a day. The relationship is difficult to interpret since the consumption estimate is based on selfreporting and there is reason to believe that the consumption is underestimated and that the bias increases with increasing consumption. The negative correlation between past drinking

problems and the pressure change is compatible with the hypothesis that alcohol affects the blood pressure since those who decreased their consumption should have a slower blood-pressure increase than those with unchanged habits.

Consequences of a high blood-pressure level (study IV)

The blood pressure in 1963 was classified according to both the systolic and the diastolic pressure, proposed by Tibblin[118] and shown in figure 5. The resulting 16 blood-pressure groups were re-grouped as follows: 1, 2–5, 6, 7–15, 16. The blood pressure in 1963 was strongly correlated to the mortality during the following 13.5 years (figure 6a). More than 35 % of men at risk in the highest blood-pressure group died, compared to less than 5 % of those in the lowest pressure group. As regards the specific causes of death, the blood pressure was correlated to mortality from myocardial infarction and cancer. There was a tendency towards correlation to mortality from stroke. The blood pressure was also strongly correlated to morbidity from myocardial infarction and stroke (figures 6b and 6c). 46 % of men at risk in the highest pressure group had a myocardial infarction, compared to none in the lowest pressure group. More than 20 % of those at risk in the highest pressure group had a stroke, compared to none in the lowest pressure group. The blood pressure was also correlated to the incidence of angina pec-

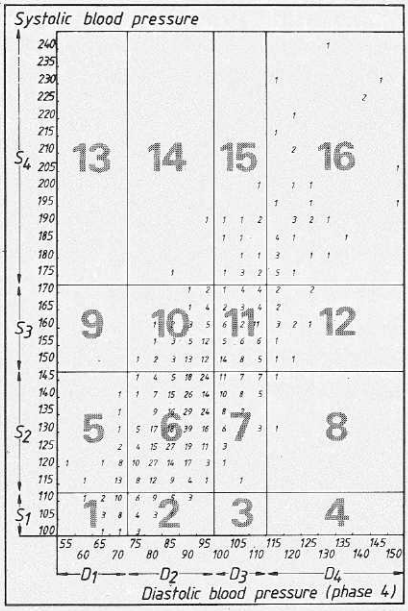

Figure 5. Systolic and diastolic blood pressures for the 855 men examined in 1963. The men have been divided into 4 groups according to both systolic and diastolic blood pressure. The resulting 16 groups have then been numbered as shown in the figure. See text. Also non-existing squares like 3 and 4 and empty squares like 9 and 13 are indicated for the sake of clarity.

toris and there was a tendency towards a correlation to claudication and kidney stone. There was a positive correlation to receipt of a disability pension (figure 6d) but not to sick leave.

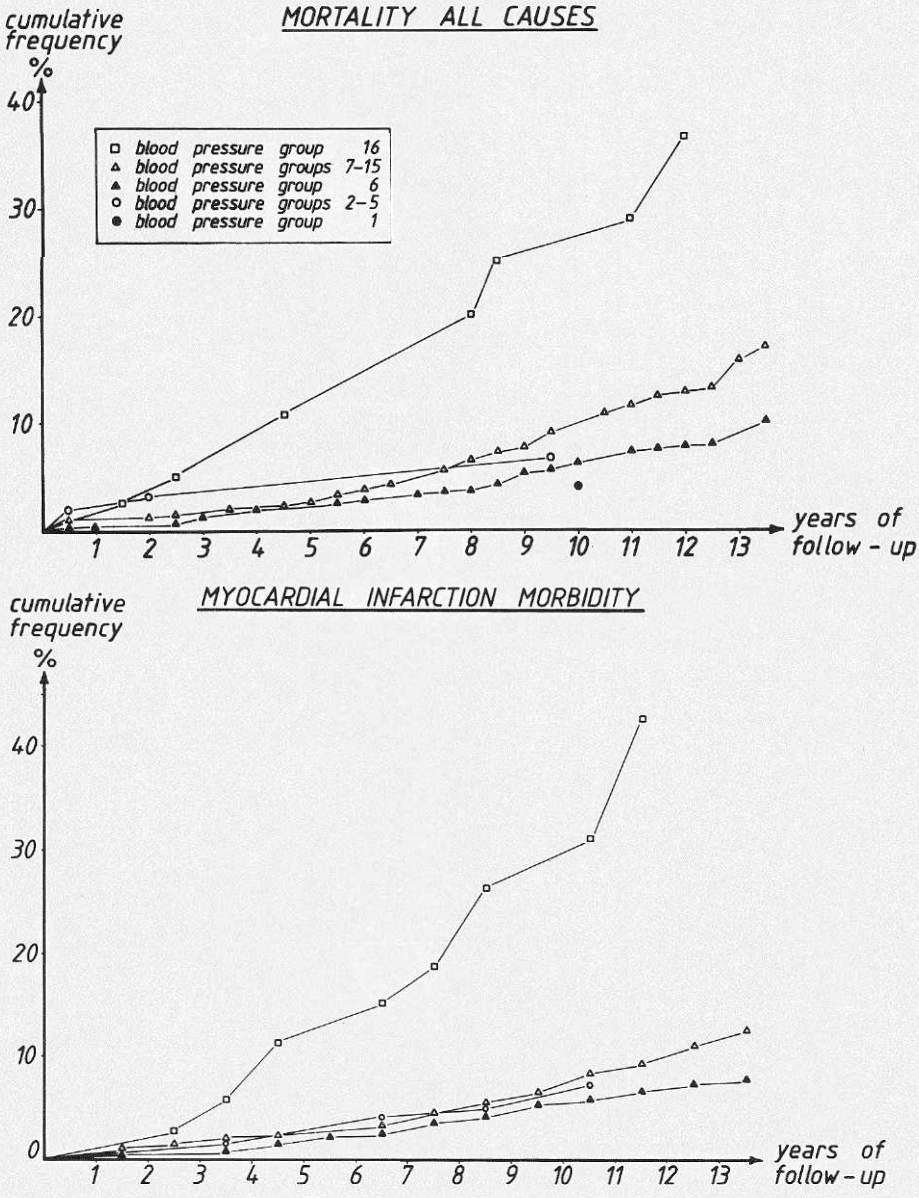

Figure 6. Cumulative frequencies in relation to time of death irrespective of cause, infarction morbidity, stroke morbidity and retirement in the Study of Men Born in 1913. The analysis was performed using the life-table method.

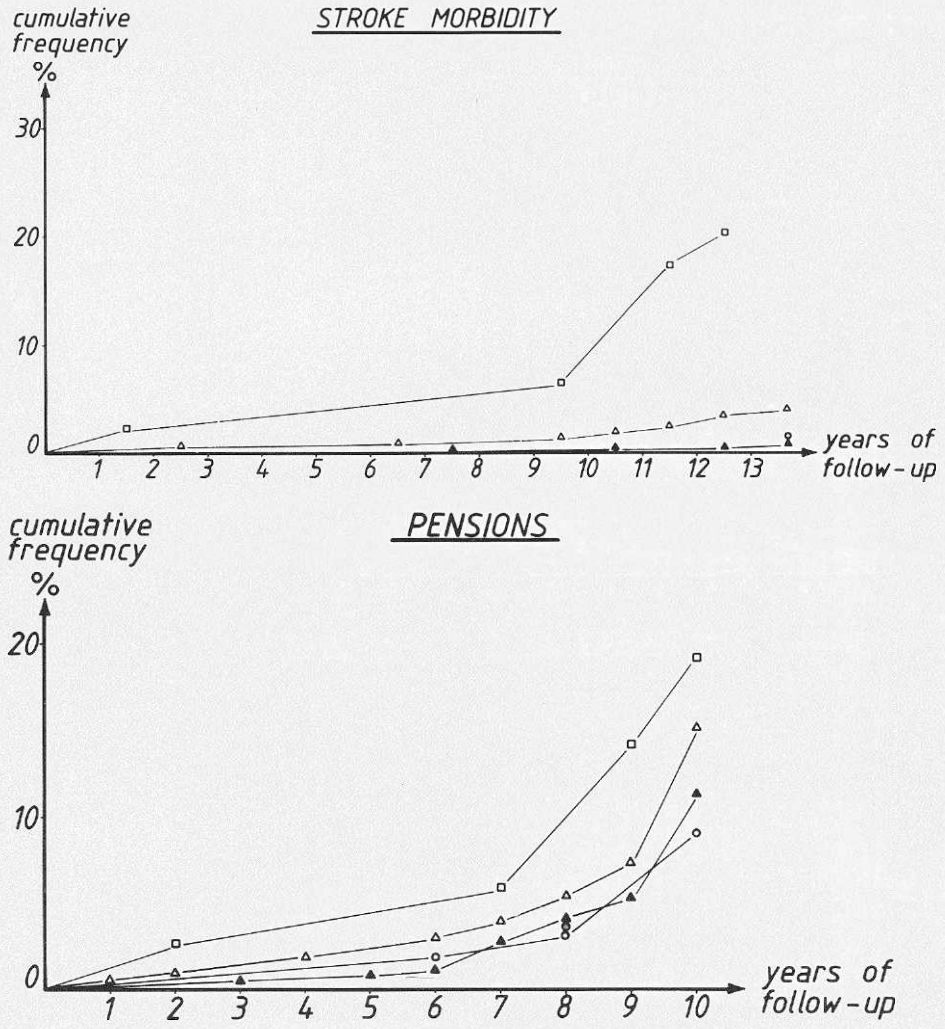

Figure 6. Cumulative frequencies in relation to time of death irrespective of cause, infarction morbidity, stroke morbidity and retirement in the Study of Men Born in 1913. The analysis was performed using the life-table method.

Comments: The blood-pressure grouping used in this study is unconventional. Using both the systolic and diastolic pressure has an effect similar to using duplicate measurements. The blood-pressure level is more accurately estimated. In this was the extreme groups could be made large enough and extreme enough.

The excess mortality and morbidity attributable to the blood pressure has been well documented previously[12, 24, 26, 29, 47, 51, 57, 68, 73, 85, 89, 101, 109, 113, 122] except for the correlations to cancer mortality and to receipt of a disability pension, which have been described only occasionally[30, 52, 67]. It should be kept in mind that the cohort followed in this study had received antihypertensive treatment according to fixed criteria and was therefore undoubtedly treated more often than the general population of corresponding age and sex. In spite of the high excess mortality and morbidity attributable to the high blood pressure in this study, it is most probably an underestimation of that in the general population.

Consequences of a blood-pressure increase with the pressure level taken into account (study III)

In study III an analysis was carried out to see whether the blood-pressure change had any importance over and above that of the blood-pressure level for the development of hypertensive disease. The change of blood pressure was significantly positively correlated to the development of general attenuation of the eyeground arterioles, to focal narrowing and to broadened light reflex but not to crossing phenomena or increased heart volume during 1963–1967. It was also positively correlated to the development of albuminuria during 1967–1973 and to development of ECG abnormalities during 1963–1973. The change of blood pressure was not correlated to the development of myocardial infarction, stroke or angina pectoris during 1963–1973 or to intermittent claudication during 1967–1973.

Comments: The absence of a correlation between the incidence of myocardial infarction, stroke, angina pectoris and claudication and the blood-pressure change is difficult to interpret. Men who suffered myocardial infarction may have had a different blood-pressure course after the infarct than before[129]. Whether or not the other three conditions affect the blood pressure is unclear. Another possible explanation in these instances might be that ten years is not long enough for development of the diseases with the moderate pressure increase exhibited by the sample.

Consequences of hypertensive vascular disease indices with the blood-pressure level taken into account (study V)

The hypertensive eyeground changes were in this study used as indices of hypertensive vascular disease. The features used were general attenuation and focal narrowing of the arterioles, crossing phenomena and broadened light reflex. Each of these four features was significantly correlated to the initial blood-pressure level ($p < 0.001$). Subdivision

of the sample into groups according to the presence of the eyeground variables or combinations of them in 1963 gave the result shown in figure 7. The groups with focal narrowing, regardless of other signs, had the highest blood pressure, followed by those with attenuating arterioles. Men with isolated crossing phenomena and/or broadened reflex had the same blood pressure as those with no changes at all. The results were the same

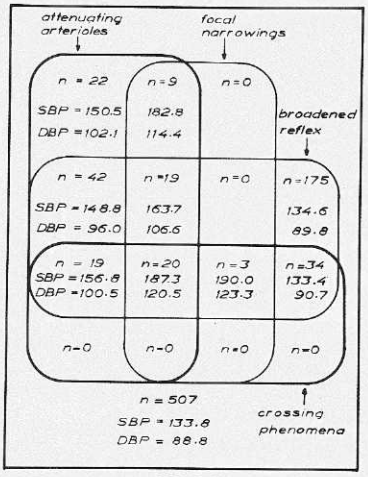

Figure 7. Grouping according to presence of eye ground findings and combinations of findings at the examination in 1963. SBP = mean systolic blood pressure. DBP = mean diastolic blood pressure.

when the data from 1967 were used. Of the four eyeground features, attenuating arterioles and/or focal narrowings discriminated the blood-pressure levels best (figure 8). Addition of crossing phenomena and/or broadened reflex worsened the discrimination.

A multivariate analysis was carried out in order to see whether the presence of eyeground changes in 1963 influenced the mortality during 1963–1975 when blood pressure, smoking and serum cholesterol were taken into consideration. Focal narrowing and crossing phenomena contributed significantly to the total mortality ($p < 0.05$ and $p < 0.01$, respectively). To see if this result was linked to any specific disease or group of diseases, the mortality end-point was subdivided into myocardial infarction, other coronary heart disease, stroke, malignancy and other causes. A myocardial infarction group was formed by pooling the fatal group with a group of survivors, and the same was done for stroke. New multivariate analyses were performed, one for each end-point. The result is given in table 4. When blood pressure, smoking and cholesterol were taken into account, none of the eyeground variables seemed to be of importance for myocardial infarction. Focal narrowing was of importance for stroke morbidity and cancer mortality. Crossing phenomena were important for fatal coronary heart disease, stroke morbidity and mortality

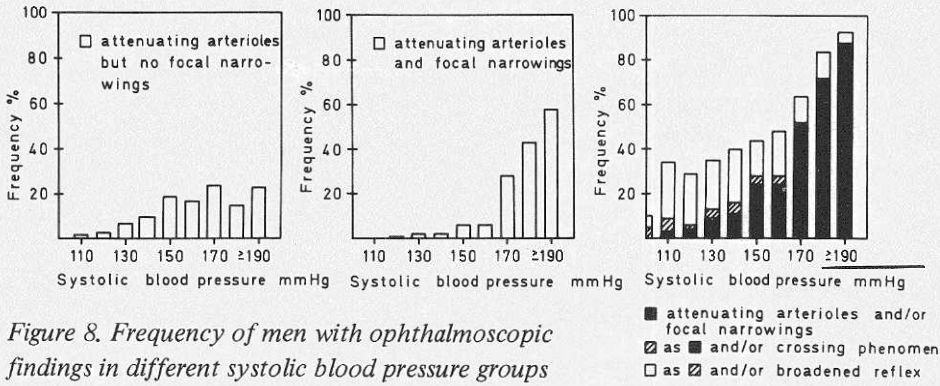

Figure 8. Frequency of men with ophthalmoscopic findings in different systolic blood pressure groups in 1963.

Table 4. P-values (indicated if $p \leq 0.05$) for the relations of eye ground variables to mortality and morbidity after correcting for smoking, blood pressure and cholesterol in multiple logistic regression analyses (all relations are positive).

	Myocardial infarction ($n=54$)	Fatal coronary heart disease ($n=22$)	Stroke ($n=16$)	Fatal malignancy ($n=20$)	Other causes of death ($n=29$)
Attenuating arterioles					
Focal narrowing			0.05	0.05	
Crossing phenomena		0.03	0.02		0.02
Broadened reflex			0.05		

from causes other than coronary heart disease, stroke or malignancy. Broadened reflex was of importance for stroke when smoking, blood pressure and cholesterol were kept constant but there was no significant correlation when crossing phenomena were taken into consideration.

Multiple linear stepwise regression analyses were performed to compare the predictive power of the significant eyeground variables in the table with the predictive power of smoking, blood pressure and cholesterol. The significant eyeground variables were consistently the first variables included and were thus the best single predictors for these end-points.

Comments: Attenuating arterioles and focal narrowing are generally interpreted as vascular damage due to the hypertensive process, attenuation being an early lesion and focal narrowing a more advanced one[106, 122]. Broadened reflex and crossing phenomena are considered to be caused by arteriolosclerosis, crossing phenomena being the more pronounced feature[122, 124]. Breslin et al.[13] showed that a modified Wagener & Keith

classification was of prognostic importance for mortality even when blood pressure was taken into account. No study seems to have analyzed the importance of the separate eyeground features. Presence of hypertensive vascular disease indices indicating a more advanced disease thus seems to be of prognostic importance over and above the blood-pressure level. In addition, since the eyeground variables are of differing and supplementary importance, any grouping of them, as for example in the Keith & Wagener classification, means loss of information and should be avoided.

DISCUSSION

Blood pressure and ageing

The model for blood-pressure change with increasing age used in these five studies only shows *how* the pressure rises with time, not *why* it rises. One possibility is that the pressure rise is part of the normal biological ageing process. As stated in the introduction to this summary, however, there are several examples of populations in which the blood pressure does not rise with increasing age. A further indication that the blood-pressure rise is not an inevitable consequence of ageing was found in study I. Although all the subjects had aged ten years during the study, by no means all of them exhibited a blood-pressure rise, even when the effect of random errors was eliminated as far as possible. There is no doubt that the mean blood pressure in Western populations rises with increasing age. But it is by no means certain that the pressure rises *because of* ageing. The increasing mean blood pressure in the population with increasing age might equally well be an effect of increase of the pressure with time, irrespective of which factor is responsible.

Blood pressure and the environment

Another possibility is that the blood pressure is influenced by internal and/or external environmental factors. In studies II and III the importance of a number of such factors was analyzed. Certain factors which could not be evaluated in these studies will also be discussed here.

Weight and obesity: All studies in this field have shown that weight and weight change are of importance for the blood-pressure level and blood-pressure change[14, 18, 29, 36, 53, 56, 58, 63, 69, 74, 86, 94, 111]. Intervention studies[14, 18, 36, 53, 56, 58, 63, 74, 86, 94, 111] have shown that weight reduction is followed by decrease of blood pressure. Subsequent weight regain is accompanied by increase of the blood pressure[18, 63]. The weight-pressure relationship thus fulfils the normal criteria for a causal relationship. Whether the relationship is direct or indirect, and which mechanism is responsible, is not known. The results from the Study of Men Born in 1913 indicate that it is the amount of adipose tissue and not the body mass as such which is of importance. Dahl found that weight loss also led to a reduced salt intake, which might explain the blood-pressure reduc-

tion[21]. Other workers, however, have found a relationship between weight change and blood-pressure change even when the salt intake, measured as excretion, remains constant[94].

Serum proteins: It is known that the serum protein level is correlated to the blood pressure[119]. In this study the protein level also had predictive power for continued rise of the blood pressure. The increased serum protein level in hypertensives, as well as the increased haematocrit level, has previously been interpreted as a filtration effect at the capillary level, leading to haemoconcentration. The relationship to the blood-pressure change would be unexpected if the protein level were solely an effect of the high blood pressure. The most probable explanation is therefore that the protein level in some way reflects causal mechanisms behind the blood-pressure rise even though the protein level as such is not of causal significance.

Blood pressure during exercise: The blood pressure during exercise was correlated to the resting blood-pressure level and to the blood-pressure increase when the initial level was taken into consideration. The effects are the same as in the "cold pressor test"[1] and the "handgrip test"[80]. The underlying concept for these tests is to increase the blood pressure by some form of provocation. The presumptive hypertensive is expected to respond with a greater blood-pressure rise than individuals who will remain normotensive. The physiological background has been described by certain authors[e.g. 28, 87] as an increased vascular reactivity in the resistance vessels. Folkow et al.[38] believe that an elevated blood pressure leads to adaptive changes in the walls of the resistance vessels, resulting in increased wall thickness. This will lead to a greater blood-pressure rise in response to provocation than that occurring in a vessel of normal wall thickness. A greater blood-pressure rise during exercise therefore probably indicates that the individual already has adaptive vascular changes. The blood pressure at rest is generally somewhat higher than in an individual who does not increase his pressure as much during exercise even if, owing to the blood-pressure variation, the two subjects happened to have the same casual blood pressure at the screening.

Stress: It is widely believed that stress causes high blood pressure. Stress kan be defined in several ways, however. Sometimes the term is used to signify mental strain, anxiety and sometimes to describe the alarm-defence reaction as defined by Selye. Irrespective of definition, it is assumed that stress will initially cause a transient blood-pressure rise and that if the stress stimulus is repeated sufficiently often it will eventually lead to a permanently elevated blood pressure.

There is a good deal of evidence that stress does lead to a transient blood-pressure rise. The effect in the more long-term perspective is more questionable, however. Numerous studies have found an association between stress, measured as anxiety, neuroticism and personality traits, and blood pressure. In a review from 1971, Davies[22] pointed out, however, that most of these studies were small case-control studies in which cases and controls were recruited from different sources and were therefore not fully comparable. In

the larger case-control studies in which cases and controls were recruited from the same population[91, 103, 104, 128], and in population studies[4, 95, 96] no association between blood pressure and stress, measured in this way, has been found. Hypertensives treated at hospital and hypertensives in the general population differed, however. Davies concluded that since the studies in which an association was found generally compared hospital hypertensives with normotensives from the general population, the association found between blood pressure and stress, measured as personality traits, neuroticism and anxiety, was probably due to selection and iatrogenic factors.

The long-term effect of stress as defined by Selye is more difficult to assess. The suggested mechanism for the stress effect assumes, however, that the stress is so frequent or of such long duration that it should be measurable as personality traits and/or occupational exposure. No definite association between these two factors and blood pressure has been demonstrated. The results from studies II and III do not support the hypothesis that stress influences the blood pressure in the long term, although such an effect cannot be ruled out.

Salt intake: Salt intake was not studied in this series of studies. The factor will be discussed, however, as it makes it possible to explain the blood-pressure model in a simple manner.

The documentation on the importance of salt for homeostatis is extensive. Numerous findings suggest that salt intake may have a decisive influence on the blood-pressure level. Freis has published a review[39] of the evidence and reached the following conclusions: 1) epidemiological studies in unacculturated peoples show that the prevalence of hypertension is inversely correlated to the salt intake; 2) haemodynamic studies suggest that the development of chronic experimental hypertension is a homeostatic response to a maintained increase in extracellular fluid volume (ECV); 3) evidence has been put forward that the ECV of "salt-eaters" is expanded in comparison to that of "no-salt eaters"; 4) investigations in hypertensive patients receiving either diets greatly restricted in salt or continous diuretic therapy have correlated the fall in blood pressure with a reduction in ECV.

The hypothesis put forward to explain the effect of salt may be summarized as follows: an increased salt intake leads to an increased ECV, which in turn, via circulatory and hormonal mechanisms, leads to increased excretion of salt and water by the kidneys. The individual's kidneys probably have a limited excretory capacity at a given blood pressure, however. For certain individuals the capacity is adequate whereas for others it is inadequate, to a greater or lesser extent. One way to increase the excretion and achieve balance with the intake is to increase the blood pressure and thus the filtration. The tendency for the blood pressure to increase with time might be due to the kidneys' excretory capacity or the efficiency of the adaptive mechanisms declining with increasing age, so that the blood pressure must be successively increased to maintain the same level of salt excretion.

On the global level, there is an association between salt intake, measured as salt excretion, and the prevalence of hypertension in the population. Table 5 summarizes data given by Freis[39]. In populations with, from the Western point of view, an extremely low salt intake hypertension does not occur and there is no blood-pressure increase with age. With increasing salt intake the pressure begins to increase with age and the prevalence of hypertension increases. A large number of analyses of salt excretion and blood pressure *within* different populations have been published. In most cases no correlation has been found and this has been interpreted as evidence that salt intake is not as important as has been claimed. However, no correlation is to be expected, for two reasons.

Table 5. Blood pressure behaviour in different populations according to the salt intake (summar of data given by Freis[39])

Salt intake	Blood pressure behavior in the population
< 10 mEq/day	No blood pressure increase with age. Hypertension is absent
10–70 mEq/day	"A few cases of hypertension will appear"
70–350 mEq/day	The blood pressure increases with age. About 15 % of the adult population will exhibit hypertension
> 350 mEq/day	Hypertension in about 30 % of the population

Let us assume that the global relationship has the form shown in figure 9, where the ellipse symbolized a hypothetical cluster of points in a global sample. When the relationship within a Western population is analyzed, only the points within the narrow range indicated are used. In other words, the span along the x axis is too small. The other reason is that in situations where the salt intake is about the same in all individuals the decisive factor for the blood-pressure level is perhaps not the salt intake as such but rather the ability of the organism to deal with the salt – the excretory capacity of the kidneys at a given pressure, the efficiency of the adaptive mechanisms etc.

Blood pressure and heredity

A third possibility is that the blood pressure is genetically determined. There is no doubt that there is a hereditary component. This is shown indirectly in study II through parental mortality from hypertension-related diseases. A large number of studies have been carried out in attempt to determine how much of the blood-pressure variation is genetically determined and how much is due to environmental factors. The ultimate object of these studies is to assess the possibilities of prevention. This approach is misleading, however, since it is not a question of heredity *or* environment but of an interaction between the two. The salt hypothesis may serve as an illustration.

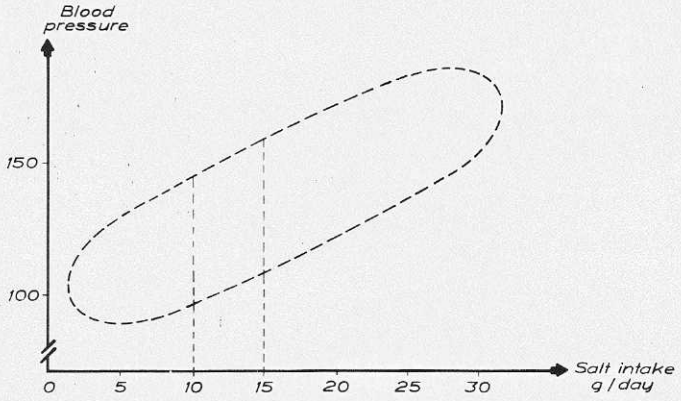

Figure 9. The relationship between salt intake and blood pressure in a hypothetical global sample. Effect of restriction of one of the variables under study.

The hypothesis assumes that the excretory capacity of the kidneys for salt and water is genetically determined and that the genetic component of the blood pressure is located here. If this hypothesis is correct, the blood-pressure level in Western societies, with their high and, in most individuals, fairly uniform salt intake, is mainly determined by the capacity of the kidneys to handle salt. This situation would imply that hypertensive disease is primarily genetically determined. But in situations of very low salt intake, for example in the primitive populations mentioned in the introduction, most kidneys would presumably cope with salt excretion without needing to increase the blood pressure. In other words, even if a disorder appears to be mainly genetically determined, manipulation of the environment may result in great changes in its prevalence.

Summarizing aspects concerning the aetiology of hypertension

In discussions on the aetiology of essential hypertension, Page's mosaic theory[87], according to which the aetiology is multifactorial, is often put forward. The theory does not necessarily assume, however, that all the suggested aetiological factors are equally important. The factors analyzed in study II explain together only a small part of the blood-pressure change and none of them seems to be a major cause of the blood-pressure increase. According to the model for blood-pressure change with time, it may be assumed that one or more main factors increase the blood pressure at a certain individual rate. Such a factor must exert an influence over a long period of time, perhaps throughout the individual's life, and will therefore probably vary little, if at all, in the same individual. This would lead to a completely stable blood-pressure ranking unless there were other factors which modified the blood-pressure change. The influence of a factor which does not vary in an individual or which varies in a uniform manner in all individuals cannot be measured in a longitudinal non-intervention study. There is therefore little likelihood of finding the essential blood-pressure increasing factors in a study of this type and the conclusions must be based on the overall results from different

types of studies. There is a good deal of evidence indicating that the high salt intake may be a factor of major importance, while obesity, consumption of alcohol, stress and other factors may modify the rate of blood-pressure rise.

Effect of pharmacological intervention

Study IV shows that the negative consequences of high blood pressure are not limited to the groups which would be regarded as "hypertensives" in a clinical context. It seems clear that high blood pressure is a graded disease even with regard to the prognosis. Although the disease is generally regarded as benign, and although most individuals in the highest blood-pressure groups receive treatment, the prognosis is poor and is comparable to that for a moderately malignant tumour. For patients who, in addition to high blood pressure, also have hypertensive vascular lesions the prognosis is even poorer. This probably reflects the time factor. A high blood pressure becomes increasingly injurious with time.

A beneficial effect of antihypertensive therapy on morbidity and mortality from cerebrovascular disease, congestive heart failure, accelerated hypertension and renal damage has been demonstrated in controlled studies[125, 126]. The influence on morbidity and mortality from coronary heart disease is more questionable, possibly owing to the fact that long observation periods are required in treatment trials[126]. In the Study of Men Born in 1913 a probable effect of treatment has been demonstrated in respect of mortality from coronary heart disease and a tendency towards reduced morbidity from coronary heart disease[115]. The same effects were observed in the Primary Preventive Trial in Gothenburg[6]. Since neither of these two studies was a controlled treatment trial in this respect, the results must be interpreted with caution. To summarize, antihypertensive treatment seems to be beneficial but does not eliminate the risk associated with high blood pressure.

Primary prevention

Possible effects: The prognostic data presented in study IV can be used to assess the effect of primary prevention, if it were fully effective. In table 6 the incidence of myocardial infarction and/or stroke during the period 1963–1976 is related to the systolic blood pressure in 1963. The table shows the number of individuals at risk in each blood-pressure interval at the start of the study, both in absolute numbers and as a cumulative percentage calculated from the upper end of the distribution. The incidence of infarction and stroke during the period is stated in per cent of cases and in absolute numbers. Although the highest blood-pressure groups have had the highest morbidity, they account for a rather modest part of the whole infarction and stroke population. The great majority of infarcts and strokes occur among groups with lower blood pressure.

The table also gives the theoretical effect on the incidence of infarction and/or stroke of intervention with five arbitrary levels of ambition. The calculations are based on the

Table 6. Incidence of myocardial infarction and/or stroke during 13.5 years of follow-up by systolic blood pressure. Possible effects of intervention

	Systolic blood pressure in 1963							
	100–115	120–135	140–155	160–175	180–195	⩾200	All	Proportion of events, %
Persons at risk	109	352	260	81	28	13	844	
Cumulative frequency, %	100	87	45	14	5	2		
Incidence, %	3.7	9.1	10.8	12.3	25.0	53.9		
Number of events	4	32	28	10	7	7	88	100
Number of prevented events								
by reducing SBP to < 160 mm Hg	0	0	0	1	4	6	11	13
by reducing SBP to ⩽135 mm Hg	0	0	4	3	4	6	17	19
by reducing SBP to ⩽115 mm Hg	0	19	18	7	6	7	57	65
by reducing SBP 10 mm Hg*	0	8	5	1	1	1	16	18
by reducing SBP 20 mm Hg*	0	19	4	1	4	4	32	36

* reduction in all individuals in all blood-pressure groups except the lowest. SBP = systolic blood pressure.

assumption that the intervention not only causes a reduction of blood pressure but reduces the risk accordingly. The two other main risk factors for myocardial infarction, smoking and serum cholesterol, are assumed to remain constant. This will result in a slight underestimation of the effect of intervention since the risk-factors potentiate one another.

If the two per cent of the population with the highest blood pressures had been treated so intensively that their risk was reduced to the same level as in the individuals with a systolic blood pressure of 140–155 mm Hg, 6 of the 7 cases in the group and 7 % of the total infarction and stroke morbidity could have been avoided. If the highest five per cent had been treated in the same way, 10 out of 14 events in the group and 11 % of all events would have been avoided. The efficiency of measures taken declines rapidly, however. In order to avoid 13 % of all events, 14 % of the population must be treated, and to reduce the number of events by 19 %, 45 % of the population would have to be treated. If 87 % were treated the incidence of infarction and stroke would be reduced by 65 %.

It would thus seem impossible to eliminate the myocardial infarction and stroke problem from the community by medical treatment. Even a massive effort, with drug treatment at a low level in the blood-pressure distribution, would not prevent more than 15 –20 % of all cases in this age-group. For comparison, table 6 shows that if a pressure reduction of 10 mm Hg could be achieved for the whole blood-pressure distribution except the lowest pressure group, the incidence of infarction and stroke would decline by 18 %. If a pressure reduction of 20 mm Hg could be achieved the incidence would fall by 36 %.

Possibilities of prevention: Treatment with antihypertensive drugs is at present the most widely used primary preventive measure. But the main effect is to reduce the risk in individuals at high risk. To solve the problem of infarction and stroke in the community, case-finding and drug treatment must be combined with other measures influencing the incidence in the low and middle risk interval. Such measures should be simple, cheap, harmless and applicable on a large scale in the entire population. They should also be self-generating i.e. it must be possible to incorporate the measures into a normal life pattern in order to avoid expensive "maintenance". No such ideal instrument is available at present. Tibblin and Eriksson[120] have suggested a primary preventive programme comprising weight control, physical activity, reduction of salt intake and meditation (to reduce sympathetic tone). The effect of weight reduction can be estimated from study II. A reduction of weight by 1 kg corresponded to a blood-pressure reduction of about 1 mm Hg. A shift in the systolic blood-pressure distribution of 10 mm Hg could thus be achieved by a weight reduction in the population of 10 kg.

If salt intake is as important for the blood-pressure level as there is reason to believe, restriction of the salt intake would be a natural preventive measure. Earlier attempts at prevention by restriction of salt intake in the diet have had a moderate effect of about

the same magnitude as treatment with diuretics[21, 77]. The reduction of salt intake has been moderate and interest has been concentrated on salt food and people who sprinkle extra salt on their food. The salt content of the diet can probably be further modified without greatly affecting the flavour of the food, for example by interesting the food industry in this problem.

There is thus reason to believe that the primary preventive measures at present available against hypertension and related diseases are beneficial. For adequate prevention, however, the measures must be extended and efforts concentrated on eliminating the cause or causes of high blood pressure.

SUMMARY AND CONCLUSIONS

A systematic sample of one-third of all men born in 1913 was drawn in 1963 from the general population of Göteborg, Sweden. The 973 men who were selected were invited to a survey. The sample was followed up with re-examinations in 1967 and 1973. Total mortality and morbidity from myocardial infarction and stroke was followed up until 1976. This thesis is a review of five papers from the study. The main findings and the conclusions were:

1. The hypothesis for change of blood pressure with time upon which this study was based assumes that the blood pressure in these men was relatively uniform when they were born in 1913 and that their pressures gradually diverged at individual rates. The hypothesis is supported by published individual blood-pressure observations over long periods, observations of the change in the blood-pressure distribution with time and stable ranking within the distribution, and by the correlation found in this study between the initial blood-pressure level and subsequent blood-pressure increase for systolic blood pressure.

2. Certain criteria were required for a factor to be regarded as a risk-factor for increase of blood-pressure. Increased weight, increased skinfold thickness, parental mortality from cardiovascular disease, a high blood-pressure during exercise and an increased serum-protein level fulfilled these criteria. The results from this and other studies show that weight is probably causally related to blood-pressure and that it is the amount of adipose tissue rather than body mass as such that is important. However, these factors together explain only a small part of the observed blood-pressure change. Among other proposed risk-factors, the influence of salt intake could not be measured in this series of studies. The results of other studies show that salt intake is of great importance for the blood-pressure level. An increased salt intake may be one of the main causes of increase of blood pressure with age, other factors modifying the rate of increase.

3. The blood-pressure level reached influenced the prognosis. The blood pressure measured at the start of the study was correlated to the mortality during the follow-up period, measured as death from any cause, death from myocardial infarction and death from cancer. There was also a strong correlation between blood pressure and morbidity from myocardial infarction, stroke and angina pectoris. The blood pressure was related to receipt of a disability pension during the period but not to sick leave. The prognosis for high blood pressure is probably even poorer in the population since a higher proportion of individuals in this sample have received antihypertensive treatment than in the general population.

4. Signs of hypertensive vascular lesions in the form of eyeground changes were associated with a poorer prognosis with respect to death from all causes, fatal coronary heart disease, fatal malignancy, non-cardiovascular death and stroke morbidity. This poorer prognosis remained when differences in blood pressure, cholesterol and smoking habits were corrected for. The eyeground changes were not of prognostic significance for infarction morbidity when the above risk-factors were taken into consideration, however.

5. Treatment with antihypertensive drugs has been shown to have a preventive effect against hypertension-related diseases. In this study, however, most cases of the two main complications of hypertension – myocardial infarction and stroke – occurred in the blood-pressure interval in which antihypertensive treatment is not possible today. The possible effect of intervention within the low and middle risk intervals was also calculated. A reduction in risk corresponding to a systolic blood-pressure reduction of 10 mm Hg in all but the lowest pressure group had the same effect as eliminating all risk over and above that for a systolic blood pressure of 135 mm Hg. A reduction of the risk corresponding to 20 mm Hg would be twice as effective and would reduce the morbidity from myocardial infarction and stroke by one-third. It is therefore important to combine case-finding and drug therapy with measures having a more general effect. The measures available today may be assumed to give some benefit but they need to be extended and further developed for adequate prevention.

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