

**SOME FACTORS AFFECTING MORBIDITY
AND MORTALITY IN HYPERTENSION**
The Framingham Study

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The natural history of essential hypertension is best discerned from a study of asymptomatic as well as symptomatic hypertension as a force of morbidity and mortality in a general population sample. Because essential hypertension is asymptomatic for some two decades before cardiovascular sequelae become manifest, it is important to study the disease prospectively as it evolves in the general population. If an undistorted picture of the manner in which it arises, evolves, becomes clinically manifest and terminates fatally is to be achieved routine periodic observations of blood pressure obtained in a representative sample of the general population must be examined in relation to subsequent morbidity and mortality from cardiovascular disease.

Such a study has been carried out in Framingham, where 5,209 men and women aged 30 to 62 years, classified by their blood pressure status and other related personal attributes and living habits, have been followed biennially for the development of a variety of cardiovascular disease outcomes, cerebrovascular disease and mortality. Various parameters of blood pressure have been examined in relation to these outcomes, including systolic versus diastolic pressure, and mean arterial pressure. The purpose of this report is to explore some factors that may affect the morbidity and mortality associated with the level of blood pressure. The methods employed, the criteria for disease outcomes, the sampling procedure and completeness of follow-up have been reported elsewhere in detail.^{1-4, 11, 14}

It is generally conceded that the first step in the evaluation of a "hypertensive" patient is the exclusion of a curable form of the disease. Essentially, this entails the identification of an etiology. The list of causes of "hypertension" grows each decade and includes such diverse etiologies as coarctation of the aorta, adrenal disorders, renal parenchymal disease and renovascular disease. In addition to certain history and physical examination items, detection of these requires a chest x-ray, intravenous pyelogram, catecholamine excretion, renin determination, serum potassium determination, urinalysis and a test of glucose tolerance. In as many as 90 per cent of persons encountered with "hypertension" these tests will be negative and no obvious cause will be discovered.

In proceeding from this point, the nature of the blood pressure elevation is usually considered next in deciding whether management is indicated. An evaluation concerned with estimation of prognosis is generally undertaken. In estimating prognosis a variety of factors is considered including the height of the pressure, the rate of progression of hypertension, the condition of the arterioles as revealed in the optic fundi, and the extent of organ damage including evidence of focal neurologic deficits, cardiac decompensation, myocardial ischemia or renal functional impairment.

Indications for management based on these criteria are unquestionably sound. Whether they are sensitive enough and provide opportunity for optimal control when hypertension is most manageable is moot. Most of the clinical data on which these judgments have been based are derived from experience with clinical hypertensive disease rather than early asymptomatic disease detected in the general population. Hypertension is for decades an asymptomatic condition that can be readily detected in the general population long in advance of organ damage. No guidelines exist based on clinical experience for this stage of hypertension, and factors that influence its impact as a force of morbidity and mortality are not well understood. The present report will attempt to identify within the general population factors that influence the prognosis in asymptomatic essential hypertension.

THE NATURE OF HYPERTENSION

The first consideration in evaluating a hypertensive is to ascertain whether or not "hypertension" is actually present. The diagnosis of "hypertension" is ultimately based on the determination of the blood

pressure. As such, it is really a physical finding rather than a disease, and is analogous to "fever," which also has a wide variety of causes. "Hypertension" is said to exist when the blood pressure exceeds some arbitrarily designated value. Over the years systolic pressures exceeding 160 millimeters of mercury and diastolic values in excess of 95 millimeters of mercury almost universally have come to be regarded as "abnormal" at any age.

An examination of the distribution of blood pressure in the general population fails to reveal any basis for selecting some critical value as the boundary between "normotension" and "hypertension." The distributions are reasonably smooth with no suggestion of bimodality and Gaussian in shape except for a long tail toward the higher values (Figure 1). Comparing the distribution of antecedent blood pressures among those who went on to develop coronary heart disease with those of their cohorts remaining free of the disease over 14 years reveals statistically significant differences in mean values. However, the overlapping of these distributions is considerable and no value, high or low, is clearly in the distribution of one group and not the other. Also, an examination of the incidence of the major cardiovascular

FIGURE 1. DISTRIBUTION OF ANTECEDENT BLOOD PRESSURES: CASES OF CORONARY HEART DISEASE VERSUS THOSE REMAINING FREE OVER 14 YEARS, MEN AGE 40-49 YEARS AT ENTRY

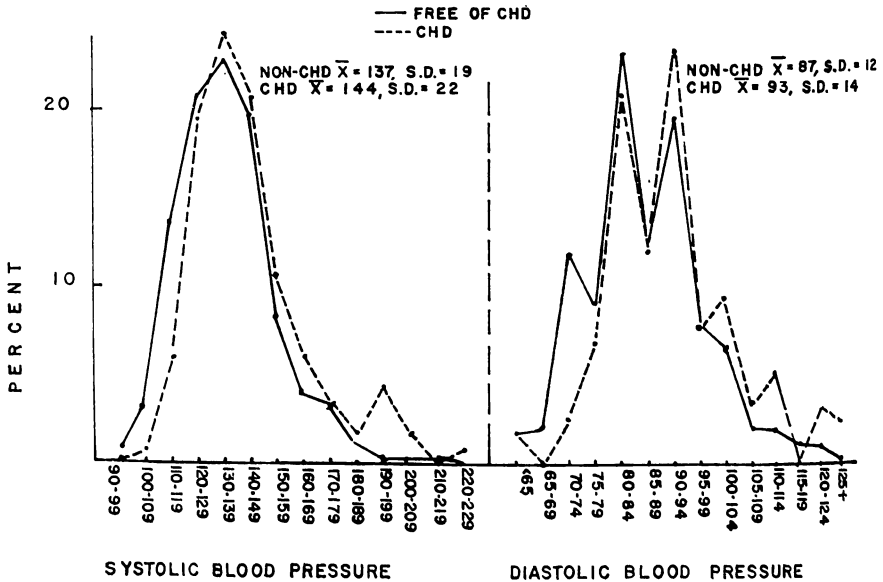
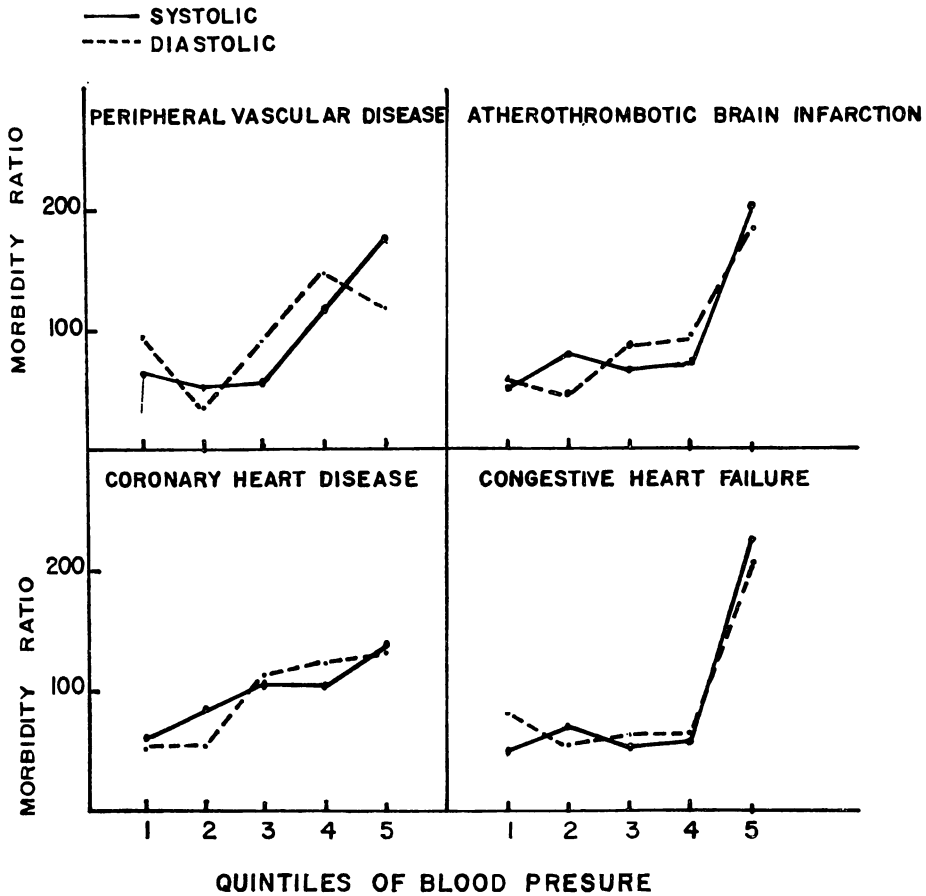
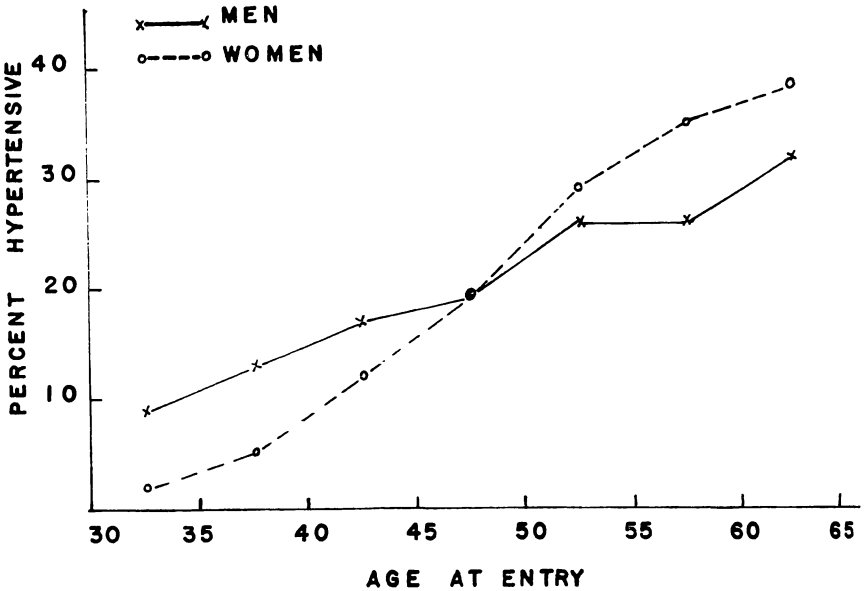


FIGURE 2. RISK OF CARDIOVASCULAR DISEASE OUTCOME ACCORDING TO SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, MEN AGE 30-62 YEARS AT ENTRY



sequelae of hypertension according to percentile of the distribution of blood pressure, except possibly for congestive failure, fails to show any clear-cut critical values where the incidence of disease outcomes takes a sharp turn upward (Figure 2). Consequently, the designation of some particular blood pressure value as "hypertension" must of necessity be somewhat arbitrary. Because no critical value can be identified, it seems more logical to pursue the objective of this report in relation to blood pressure *level* rather than "hypertensive" status. However, on occasion, purely as a matter of convenience for tabulation, blood pressure status will be used arbitrarily, defining "hyper-

FIGURE 3. PREVALENCE OF HYPERTENSION AT INITIAL EXAMINATION, MEN AND WOMEN AGE 30-62 YEARS AT ENTRY



tension” in familiar popular terms (i. e., two pressures ≥ 160 and/or 95 during an examination) and “normotension” at pressures below 140/90, with those in between designated as “borderline.”

Because of the lability of the phenomenon, variation in the criteria employed and observer bias, the prevalence and incidence of hypertension are not precisely known. Mean blood pressure increases with age, starting at a lower level in women than in men, but after age 45 ending up with advancing age progressively higher in women than in their male cohorts. If the popular definition of “hypertension” is used its prevalence follows suit (Figure 3). This makes it difficult to select a normal limit of blood pressure. It is difficult to decide whether the progressive elevation of pressure with age is a biologic consequence of aging or the increasing accumulation of “hypertensive” persons with advancing age. Also, the impact on the cardiovascular apparatus in the aged of this elevation of blood pressure is not well understood. Examination of the time-course of blood pressure in the Framingham cohort reveals that blood pressure tends to rise in individuals as they get older under observation. Sizeable generation or cohort effects evidently have not occurred over the past 30 years. The main deter-

minants of the rate of rise in blood pressure appear to be associated with the phenomenon of aging and not with the earlier blood pressure level. The increase in blood pressure in middle age is approximately equal for all earlier levels of blood pressure. One's future blood pressure history is by and large already determined by the level obtained by the fourth decade and the determinants of blood pressure level appear to operate before this age. The answer to the riddle of hypertension must be sought in youth and possibly in genetic factors operating early in life. However, no tendency can be demonstrated for the population to segregate into the bimodal distribution that would indicate a single gene determinant of a "hypertensive" trait. A polygenic inheritance would seem more likely. Slight secular trends in systolic blood pressure may exist for women, with those born more recently having lower pressures. On the other hand, younger men tend to have slightly higher diastolic pressures lately than formerly in this cohort.¹⁵

"Hypertension" by any definition is both a potent and a common contributor to cardiovascular morbidity and mortality. Few conditions so easily and early detected and so readily controlled have been discovered that are a more potent menace to health. Although the seriousness of an elevated blood pressure is largely a function of the level of the pressure (even within the "nonhypertensive" range) and of the duration of the "hypertension," other factors markedly influence the associated morbidity and mortality. Multiple factors are involved in the genesis of deterioration of the cardiovascular apparatus attributable to hypertension, and persons vary in their propensity to vascular degeneration and organ damage according to certain readily identified concomitants.

The type of hypertension. It is widely believed that some types of hypertension, based solely on the character of the elevation of blood pressure, are more pathologic than others. Clinically, an essential feature of the assessment of blood pressure status is believed to be the determination of whether the elevated blood pressure is labile or fixed and systolic or diastolic in nature. It is believed that casual blood pressure determinations are misleading and that a basal blood pressure assessment is essential to sound management.

Labile or casual blood pressure. Physiologically, the blood pressure is necessarily quite labile in response to the needs of the organism for perfusion of blood. Thus, blood pressure will rise precipitously during exercise and emotional stress. Labile blood pressure elevations are believed to often reflect a "prehypertensive" state in many persons

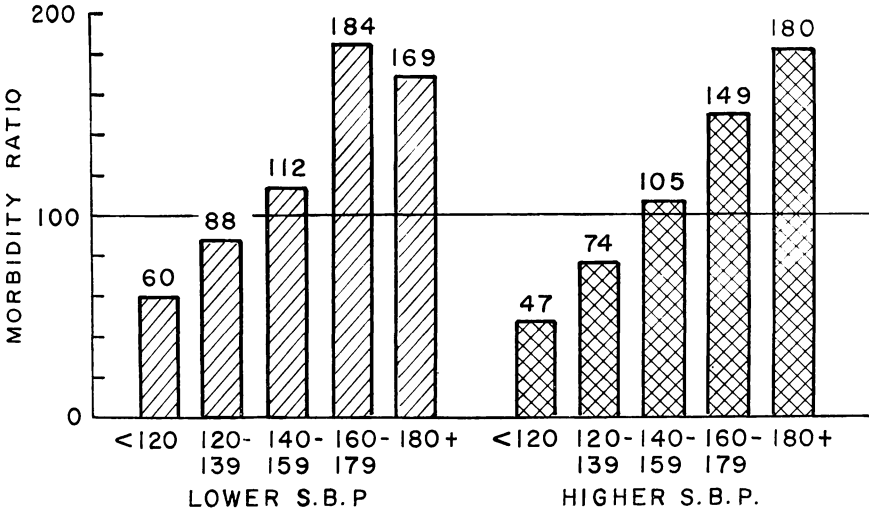
leading eventually to "fixed" hypertension. A small percentage of such persons have, instead, the episodic hypertension of pheochromocytoma. Sustained, fixed hypertension is associated with a high cardiovascular morbidity and mortality, but casual or labile elevations are also far from innocuous.

Dynamic assessments of function are beginning to replace static ones in medicine because they are more sensitive, detecting impaired function at an earlier, more easily correctable stage. Casual blood pressure levels may well reflect the operating pressures characteristic of the individual as he faces life's contingencies. Also, they correlate highly with the basal level of the individual. If one compares the incidence of coronary heart disease observed in persons classified according to the lowest versus the highest of three pressures obtained over one hour during a clinic visit it is quite apparent that each gives a comparable estimate of the risk of developing coronary heart disease (Figure 4). Casual pressures provide a valid assessment of the risk of all the major cardiovascular and cerebral sequelae of hypertension (Figure 2). Whether this provides an underestimate of the impact of hypertension on morbidity and mortality is uncertain, but risk is certainly proportional to the casual blood pressure level, and, except possibly for congestive failure, even within the nonhypertensive range (Figure 2). Some evidence indicates that at specified levels of pressure, lability adds further to risk. This deserves further investigation.

Systolic versus diastolic blood pressure. Another essential feature of the clinical assessment of blood pressure is to determine whether the pressure is elevated principally in its systolic or diastolic component. Systolic hypertension is generally conceded to be physiologically innocuous and important only insofar as it provides a clue to the existence of various conditions of high cardiac output including anemia, thyrotoxicosis, beri beri, arteriovenous fistula, complete heart block and aortic regurgitation, among others. In the elderly, it is generally attributed to inelastic large vessels made rigid by arteriosclerosis. Diastolic "hypertension" is universally accepted as physiologically dangerous and it is believed that the evil consequences of the hypertensive state derive principally from this component of the blood pressure. Despite its popularity, little acceptable clinical or epidemiologic evidence can be cited in support of this idea although the pathologic physiology of hypertension would suggest it to be true.

The major factors controlling the arterial pressure are the interplay of the cardiac output and the peripheral resistance. Most of the

FIGURE 4. RISK OF DEVELOPING CORONARY HEART DISEASE IN TEN YEARS ACCORDING TO LOWER AND HIGHER SYSTOLIC BLOOD PRESSURE ON INITIAL EXAMINATION: MEN AND WOMEN AGED 30-59 YEARS AT ENTRY



peripheral resistance is contributed by the arterioles. An increased peripheral resistance caused by widespread constriction or stenosis of the arterioles is believed to be the fundamental basis for essential hypertension. The cardiac output in most cases has been found to be normal. The viscosity of the blood has not been found to be significantly altered. Hypertension seems to set a vicious cycle into being in that the elevated pressure itself causes further increase in peripheral resistance as a direct consequence of increased stretching of arteriolar smooth muscle.

A comparison of the standardized mean deviations¹⁶ for systolic versus diastolic blood pressure between persons who have gone on to develop the major cardiovascular sequelae of "hypertension" versus those who have not provides a direct method for comparing the discriminatory power of the two components of the blood pressure. The greater this standardized difference the greater the discriminatory power of the blood pressure parameter. Such an analysis revealed no evidence of a stronger relation of diastolic blood pressure to any of the major cardiovascular disease outcomes including coronary heart disease, congestive heart failure, atherothrombotic brain infarction and intermittent claudication. The standardized differences are posi-

tive, indicating that risk is directly proportional to the level of the pressure. The differences tended to be greater for cerebrovascular accident and congestive heart failure than for coronary heart disease and intermittent claudication, suggesting a stronger relation to the former diseases. Also of note is the fact that in each instance the standardized differences were actually *larger* for *systolic* than diastolic blood pressure (Table 1). The data are averaged for all ages combined, but this was true virtually at all ages for each disease outcome. Also, development of left ventricular hypertrophy appeared as closely related to systolic as to diastolic pressure, whether judged by electrocardiogram, x-ray or heart weight at autopsy.

Examination of the incidence of cardiovascular outcomes in broad age groups of men classified by their systolic versus their diastolic blood pressure, and adjusting for differences in the age composition of these blood pressure categories, allows a visual comparison of the gradients of risk. Consistent with the foregoing, they show very similar gradients of risk for each blood pressure parameter, with nothing to suggest that diastolic is more potent (Figure 2). A more quantitative expression of these gradients is obtained by calculating the slopes of the average annual incidence on blood pressure for each disease and each blood pressure component. These reveal significant slopes for most age groups with most slopes exceeding twice the standard error. Slopes for systolic and diastolic pressure do not appear to be significantly or consistently different for the various cardiovascular disease outcomes (Table 2).

If the characteristic feature of essential hypertension is accepted as an increased peripheral resistance in the face of a normal cardiac output, "hypertension" should be expressed in terms of total peripheral resistance, which is the quotient of the mean arterial pressure divided by the cardiac output. This is not feasible under ordinary clinical circumstances because of the lack of an office procedure for measuring cardiac output. Measurement of blood pressure without taking into account the cardiac output should provide a poor estimate of the severity of essential hypertension. However, the work of the heart is roughly the product of the cardiac output and the mean arterial pressure. Inasmuch as the cardiac output is alleged to be normal, the work load imposed on the heart should be the mean arterial pressure. The heart is capable of maintaining a normal output against the increased peripheral resistance of essential hypertension, but after the passage of time it must hypertrophy and dilate to do so. Although

TABLE 1. AVERAGE OF STANDARDIZED MEAN DEVIATIONS* OF SYSTOLIC VERSUS DIASTOLIC BLOOD PRESSURE, THOSE DEVELOPING DISEASE VERSUS THOSE REMAINING FREE, MEN AND WOMEN 38-69

| | CHD \bar{x} Deviation | | I.C. \bar{x} Deviation | | CVA \bar{x} Deviation | | CHF \bar{x} Deviation | |
|-------|-------------------------|-----------|--------------------------|-----------|-------------------------|-----------|-------------------------|-----------|
| | No. | Diastolic | No. | Diastolic | No. | Diastolic | No. | Diastolic |
| Men | 252 | 0.41 | 58 | 0.60 | 53 | 0.61 | 44 | 0.92 |
| Women | 135 | 0.68 | 30 | 0.23 | 53 | 0.70 | 30 | 0.93 |

* Standardized mean deviation = $\frac{\text{mean pressure of cases} - \text{mean pressure of non-cases}}{\text{pop. S.D.}}$

TABLE 2. SLOPE OF AVERAGE ANNUAL INCIDENCE OF VASCULAR DISEASE ACCORDING TO SYSTOLIC VS. DIASTOLIC PRESSURE, MEN AND WOMEN 45-64

| | Men | | Women | |
|-----------|----------------|-----------------|----------------|-----------------|
| | Systolic Slope | Diastolic Slope | Systolic Slope | Diastolic Slope |
| Age 45-54 | | | | |
| CHD | 0.019 | 0.024 | 0.028 | 0.058 |
| CHF | 0.077 | 0.066 | 0.015 | 0.016 |
| B.I. | 0.047 | 0.053 | 0.038 | 0.071 |
| I.C. | 0.019 | 0.009 | 0.021 | 0.007 |
| Age 55-64 | | | | |
| CHD | 0.022 | 0.030 | 0.025 | 0.031 |
| CHF | 0.029 | 0.029 | 0.038 | 0.072 |
| B.I. | 0.045 | 0.069 | 0.054 | 0.085 |
| I.C. | 0.024 | 0.008 | 0.029 | 0.046 |

* Significant at $p = .05$ level.

** Significant at $p = .01$ level.

the output at rest may continue normal, under a load such as exercise a greater rise in pressure than is normal occurs and the rate of ejection is often lower than that observed in normotensive persons. Also, the net perfusion pressure would seem best expressed by the mean arterial pressure as regards atherogenesis.

Still more detailed analysis of the net contribution of systolic versus diastolic pressure is possible for coronary heart disease when a sufficient number of cases is available. If both systolic and diastolic blood pressures contribute to risk, discrimination of potential cases from those free of disease should be better if both systolic and diastolic measurements are used than if either alone were employed and risk would be a function primarily of the mean arterial pressure. Except possibly in younger men, use of both blood pressure parameters discriminated potential cases no better than either alone and systolic pressure alone discriminated, if anything, better than mean arterial pressure. The mean arterial pressure was, however, consistently better than the diastolic pressure alone although the difference was trivial (Table 3).

The influence of each blood pressure parameter on risk of coronary heart disease is apparently quite distinctive in young versus older men. For men under 45 years of age diastolic is clearly a better discriminator as revealed by the standardized mean deviations; for those aged 45 to 49 no distinction is seen; at ages over 49 systolic blood pressure tends to discriminate better (Table 4). Whether this age distinction applies to women and to other cardiovascular outcomes is uncertain owing to a shortage of information in this area.

These data provide little support for the clinical contention that diastolic blood pressure rather than systolic is primarily responsible for the major cardiovascular consequences of hypertension, except possibly in young men. One sees a strong suggestion of declining relative importance of diastolic pressure and a corresponding increase in the importance of systolic pressure with advancing age. Because in older persons the net contribution of systolic blood pressure is, if anything, greater than diastolic, the commonly held view that systolic elevation is innocuous in the elderly requires reevaluation. The common practice of discounting such elevations as inconsequential would seem premature until an assessment of risk associated with isolated systolic pressure elevation is undertaken. Meanwhile, the current practice of assessing the importance of hypertension at all ages solely on the level of diastolic pressure would seem unjustified.

TABLE 3. STANDARDIZED MEAN DEVIATION SYSTOLIC VERSUS DIASTOLIC VERSUS MEAN ARTERIAL PRESSURE CASES VERSUS THOSE FREE OF CHD, MEN AND WOMEN 38-69

| | <i>Men</i> | <i>Women</i> |
|------------------------|------------|--------------|
| No. of cases | 252 | 135 |
| Mean deviation* | | |
| Systolic | 0.41 | 0.68 |
| Diastolic | 0.28 | 0.39 |
| Mean arterial pressure | 0.37 | 0.57 |

* Average for all ages combined.

TABLE 4. MEAN BLOOD PRESSURES AND THEIR STANDARDIZED DIFFERENCES ACCORDING TO CHD STATUS, MEN 30-62

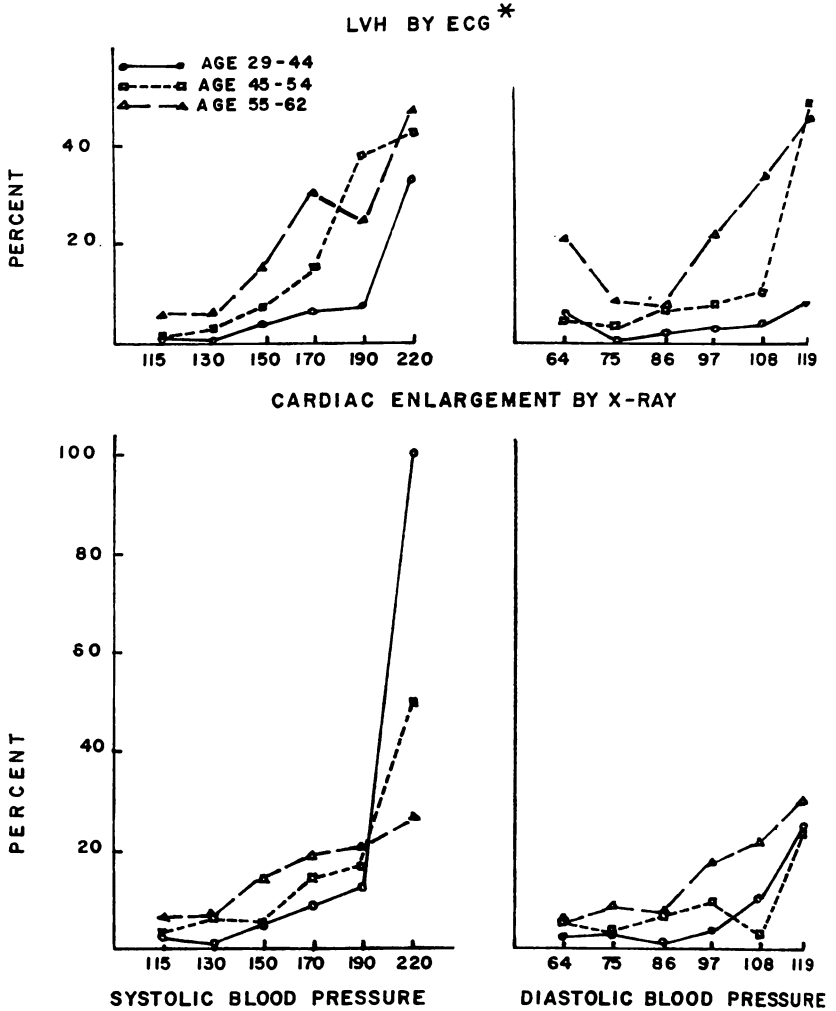
| <i>Age at Entry</i> | <i>\bar{x} Systolic Blood Pressure</i> | | | <i>\bar{x} Diastolic Blood Pressure</i> | | |
|---------------------|---|---------------|---------------------|--|---------------|------------|
| | <i>CHD</i> | <i>No CHD</i> | <i>Stand. Diff.</i> | <i>Stand. Diff.</i> | <i>No CHD</i> | <i>CHD</i> |
| 30-34 | 136.9 | 130.9 | 1.6 | 2.6 | 82.5 | 89.2 |
| 35-39 | 138.1 | 132.1 | 1.9 | 3.2 | 84.1 | 91.2 |
| 40-44 | 140.7 | 134.7 | 2.3 | 3.5 | 86.0 | 92.0 |
| 45-49 | 145.3 | 136.1 | 3.1 | 3.0 | 86.7 | 91.8 |
| 50-54 | 145.0 | 139.9 | 1.8 | 1.2 | 88.4 | 90.4 |
| 55-59 | 154.4 | 141.2 | 3.5 | 3.6 | 85.7 | 93.1 |
| 60-62 | 156.1 | 148.9 | 0.99 | 0.49 | 86.6 | 88.4 |

An examination of the risk of myocardial hypertrophy and failure in 5,209 men and women classified according to antecedent systolic and diastolic blood pressure status also reveals little to suggest a more important role for diastolic pressure. Classifying subjects according to levels of systolic versus diastolic blood pressure and examining the subsequent rate of development of overt congestive heart failure and cardiac hypertrophy or enlargement on x-ray or electrocardiogram revealed gradients of risk that were quite comparable for each component of the blood pressure (Figures 2, 5).

An examination of the relation of antecedent premorbid blood pressure to heart weight at death in 85 subjects who came to autopsy revealed a striking relation only in women. Comparing the regression of heart weight on systolic versus diastolic pressure revealed slopes with very similar gradients and the correlation with systolic (0.50) was, if anything, greater than that with diastolic (0.37) (Figure 6).

Comparing the discriminatory power of these two components of

FIGURE 5. PREVALENCE† OF LVH BY ECG OR CARDIAC ENLARGEMENT BY X-RAY ACCORDING TO INITIAL SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, MEN AGE 30-62 YEARS AT ENTRY

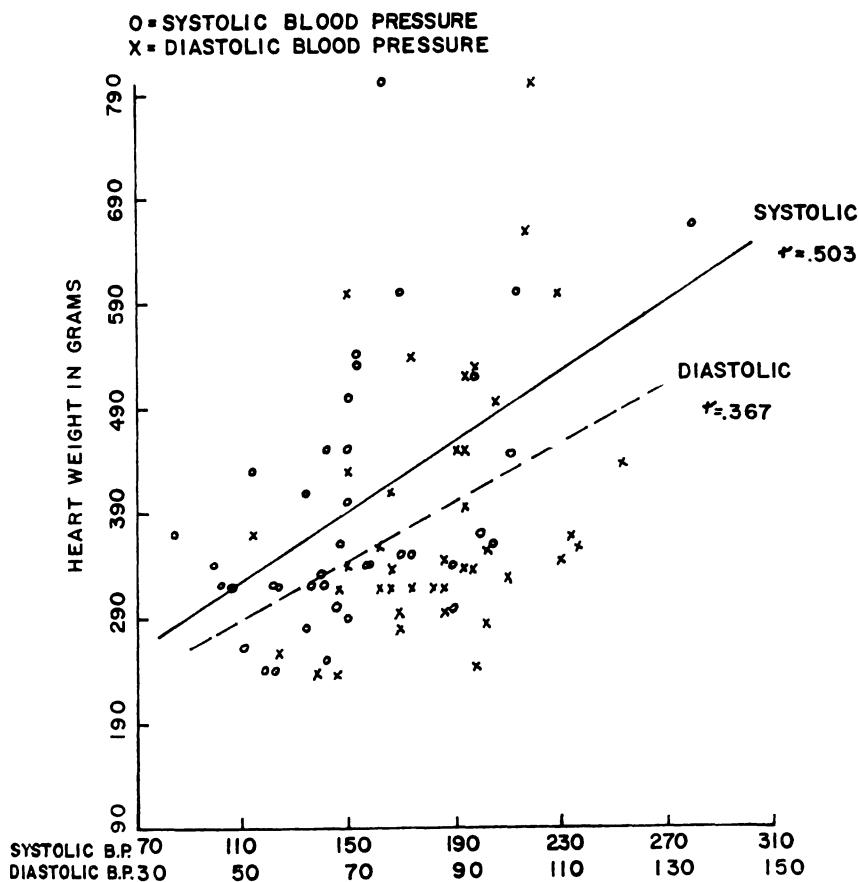


† Persons manifesting LVH by ECG on any of the first seven examinations, by blood pressure at the first examination.
 * Period prevalence.

the blood pressure using standardized mean deviations revealed no evidence of a stronger relation of diastolic pressure to cardiac hypertrophy or failure as evidenced on x-ray, electrocardiogram or clinical examination. Little evidence is available to show that both components

of the pressure contribute independently to cardiac hypertrophy and failure because both systolic and diastolic measurements discriminated potential hypertrophy and failure little better than systolic alone; nor did the mean arterial pressure. Also, no evidence was found of a declining influence of systolic pressure with advancing age to suggest that systolic pressure elevation in the elderly is innocuous. Evidently the popular notion that the diastolic component of the pressure is paramount in the pathogenesis of hypertensive myocardial hypertrophy and failure also requires reevaluation.

FIGURE 6. RELATION OF ANTECEDENT BLOOD PRESSURE TO HEART WEIGHT AT AUTOPSY, WOMEN AGE 30-62 YEARS AT ENTRY.



Scale of systolic blood pressure units is standardized to that of diastolic.

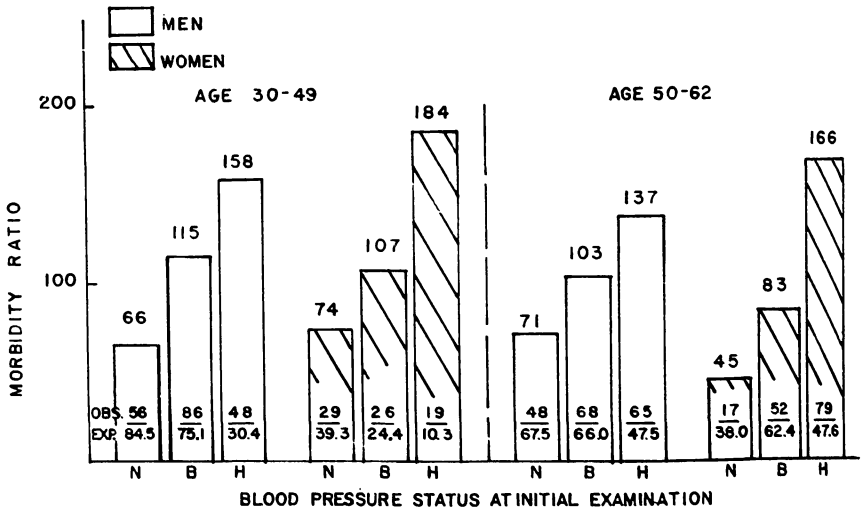
HOST FACTORS AND SUSCEPTIBILITY TO HYPERTENSIVE COMPLICATIONS

A number of host factors are believed to influence the impact of hypertension on the vascular apparatus including age, sex, race, menopause, blood lipids and impaired carbohydrate tolerance.

Age, Sex and Hypertension

For each major cardiovascular consequence of hypertension—intermittent claudication, coronary heart disease, cerebrovascular accident and congestive heart failure—little evidence is available to show that “hypertensive” levels of blood pressure are substantially less important in older persons than in their younger cohorts. Also, no evidence can be found to support the popular clinical notion that older women tolerate hypertension better than men. Although the absolute incidence of cardiovascular disease is greater in men than women the relative increase in incidence, comparing normotensives with hypertensives within each sex, is just as great in women as it is in men (Figure 7).

FIGURE 7. RISK OF CARDIOVASCULAR DISEASE* (14 YEARS) ACCORDING TO BLOOD PRESSURE AT INITIAL EXAMINATION, MEN AND WOMEN AGE 30-62 YEARS AT ENTRY.



* Cardiovascular disease: atherothrombotic brain infarction, coronary heart disease, congestive heart failure.

N = normotensive; B = borderline; H = hypertensive.

FIGURE 8A. DEATH RATES ACCORDING TO BLOOD PRESSURE BY AGE AT ENTRY, MEN AGED 29 TO 62 YEARS

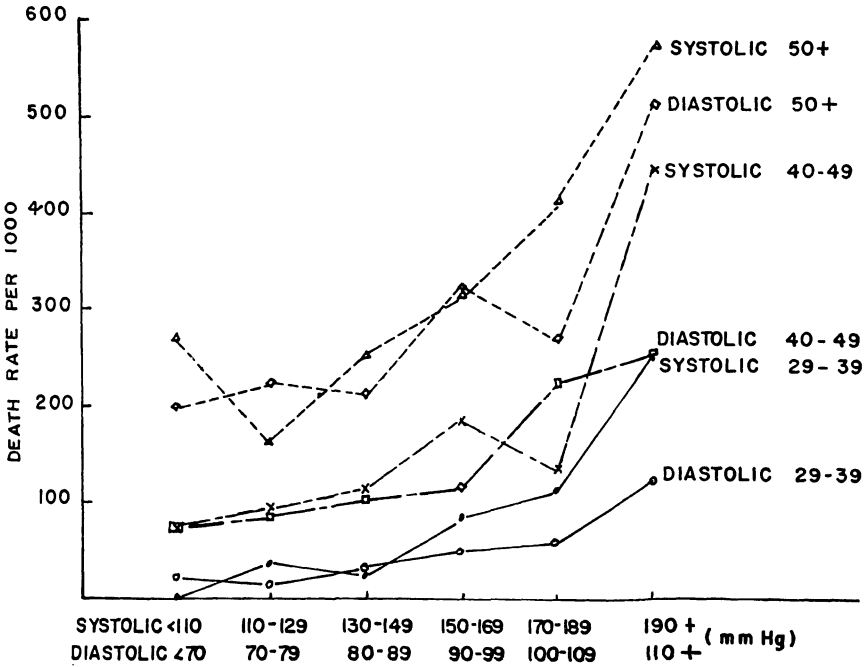
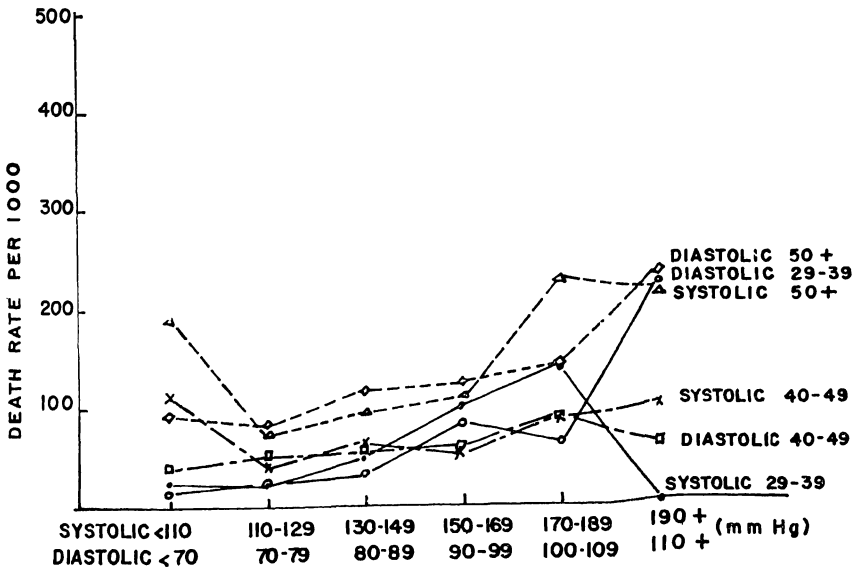


FIGURE 8B. DEATH RATES ACCORDING TO BLOOD PRESSURE BY AGE AT ENTRY, WOMEN AGED 29-62 YEARS



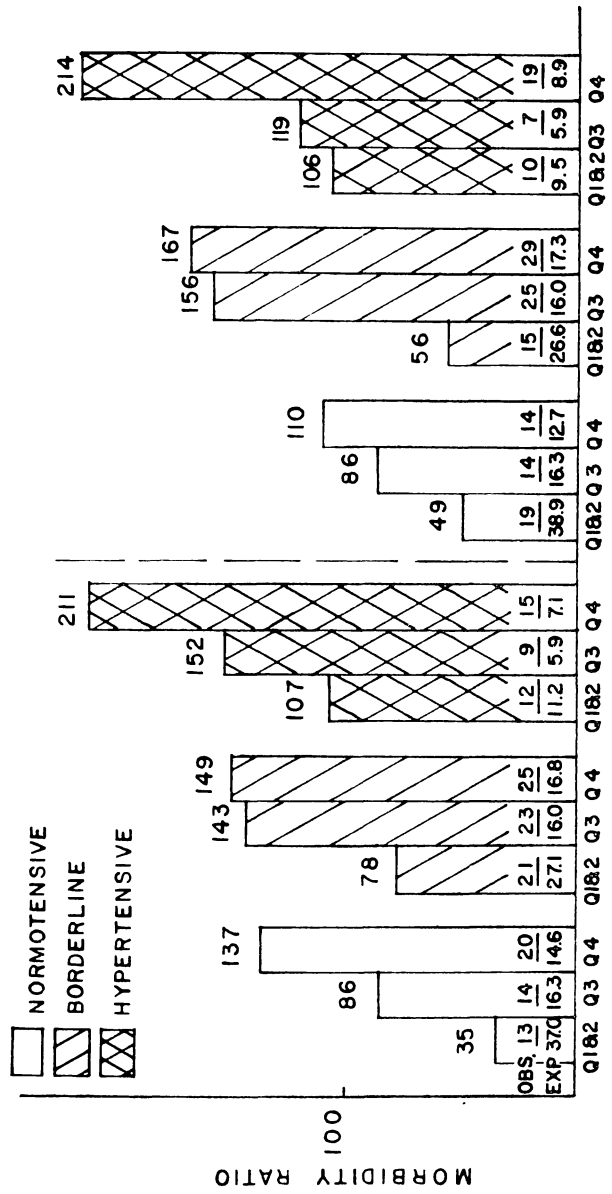
An examination of overall mortality according to blood pressure status reveals, in general, no steeper gradients with diastolic than with systolic pressure. Also, the slopes do not flatten with increasing age. The slopes in women do not appear as steep as in men. Mortality is, however, considerably greater at higher than lower pressures in both sexes, and in both the old as well as the young (Figures 8a and b).

The clinical tendency to regard hypertension in the postmenopausal woman over 50 as relatively innocuous deserves reevaluation. The impact of hypertension on the baseline rate of cardiovascular morbidity is quite comparable in the two sexes even though the women appear, according to absolute rates, to be the harder sex. Both the absolute and relative risks associated with hypertension in women are considerable and deserve attention. Also, the clinical tendency to regard blood pressure elevation in older persons, particularly the systolic component, as relatively innocuous, cannot be supported.

Influence of Blood Lipid

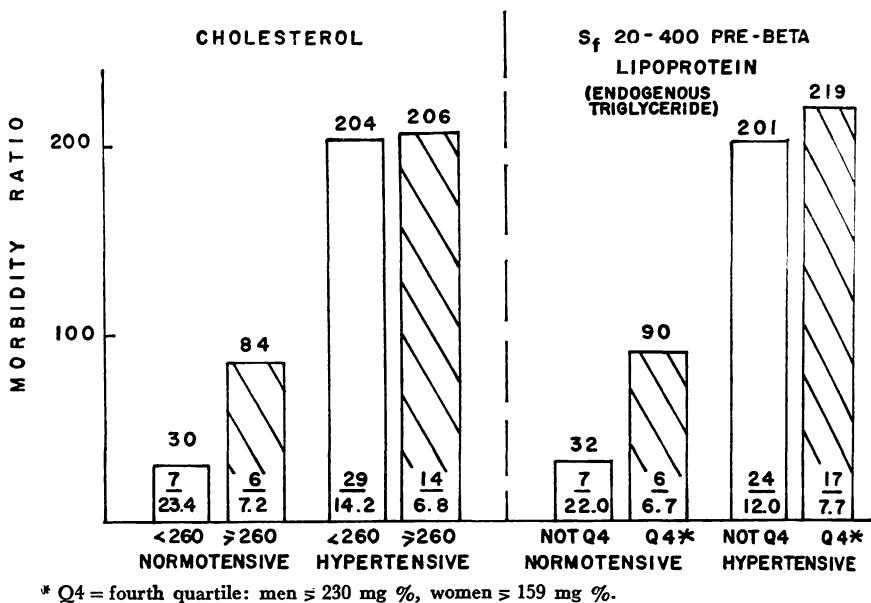
The preponderance of evidence points to a multifactorial causation of atherosclerosis and its clinical manifestations. If a common denominator does exist, some disorder of lipid metabolism or transport is very likely to be the one. Given enough time, everyone has enough blood lipid to manufacture atheromata; lipids probably have a contributory, if not essential, role in atherogenesis. Among those implicated, the single lipid that is most basic in atherogenesis is not yet established, if such does indeed exist. Risk of coronary heart disease has been shown to be strikingly related to the serum concentration of each of the major lipids and lipoproteins encountered in the blood.⁴⁻⁶ It is well established by animal experiments that hypertension accelerates lipid-induced atherogenesis.⁷⁻¹⁰ Also, a good deal of indirect evidence, based on clinical observations and autopsy studies, suggests that this also applies in humans. Prospective epidemiologic evidence is also entirely consistent with the perfusion hypothesis of atheroma formation. The blood pressure exerts a powerful influence on the risk of coronary heart disease associated either with the cholesterol-rich S₁ 0-20 beta lipoprotein or the triglyceride-rich S₁ 20-400 pre-beta lipoprotein concentration. Conversely, at any level of blood pressure the risk increases in proportion to the associated blood lipid concentration so that hypertension accompanied by high lipid values is much more ominous than that occurring in its absence, particularly in persons under 50 (Figure 9). The evidence linking atherothrombotic

FIGURE 9. RISK OF CORONARY HEART DISEASE (14 YEARS) ACCORDING TO LIPOPROTEIN CONCENTRATION AND BLOOD PRESSURE STATUS, MEN AGED 30 TO 49 YEARS AT ENTRY



Q1 = <419
 Q2 = 419-492
 Q3 = >493
 Q1 = <158
 Q2 = 158-229
 Q3 = >230

FIGURE 10. RISK OF ATHEROTHROMBOTIC BRAIN INFARCTION (14 YEARS) ACCORDING TO BLOOD LIPID AND BLOOD PRESSURE STATUS, MEN AND WOMEN AGED 30-62 YEARS AT ENTRY



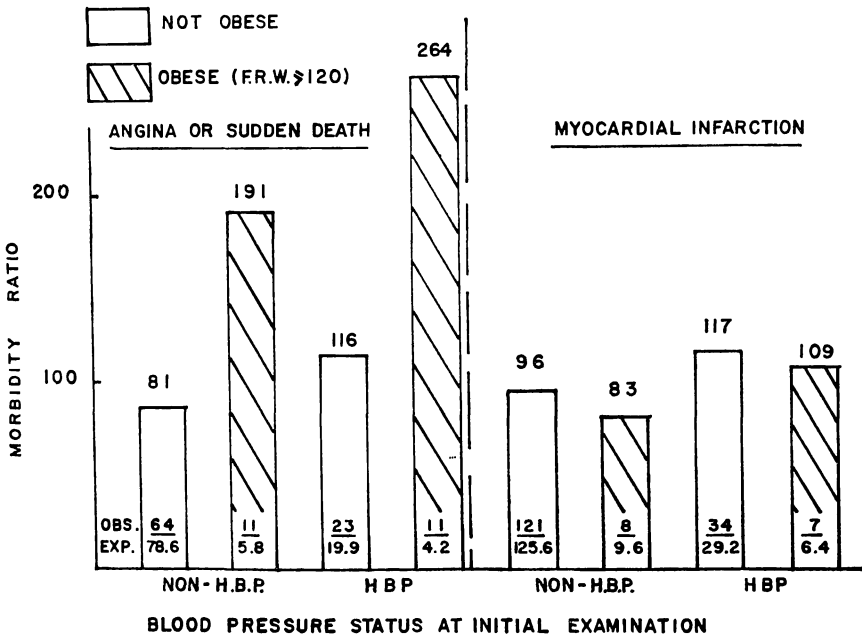
brain infarction to serum lipids is much less substantial, whereas evidence for a prominent role of hypertension in stroke is clear. Prospectively, cholesterol and endogenous triglyceride (as reflected by the S_f 20-400 pre-beta lipoprotein value) may be related to the subsequent rate of development of atherosclerotic brain infarction, but only when the lipid determination was obtained prior to age 50.¹² However, even in younger persons hypertension was a far more potent contributor to stroke than was lipid. When the associated blood pressure status is taken into account, very little additional contribution of lipid to risk can be discerned and this only in nonhypertensive victims of stroke. A shortage of numbers makes even this speculative at present (Figure 10).

In peripheral vascular disease, the other major manifestation of atherosclerosis, a modest contribution of both lipid and blood pressure to risk is noted with some augmentation of one by the other. In congestive heart failure blood pressure is the overriding feature.

Obesity

It has been claimed that obese hypertensives do as well or better than those of normal weight. This has been attributed to a fat arm artifact so that there is alleged to be an overestimate of the actual pressure. In point of fact, no sizeable consistent overestimate occurs of hypertension in obese subjects.¹¹ Obesity, by increasing the cardiac work load, appears to contribute slightly to the development of angina pectoris and sudden death independent of the blood pressure. But in persons so predisposed obesity had a greater impact (Figure 11). Whether predisposed or not, obesity contributed very little to myocardial infarction (or to atherothrombotic brain infarction or peripheral vascular disease). It also appeared to contribute to congestive heart failure, but largely and more potently in those predisposed by hypertension.

FIGURE 11. RISK OF ANGINA PECTORIS OR SUDDEN DEATH ACCORDING TO OBESITY AND BLOOD PRESSURE STATUS, MEN AGED 30-62 YEARS AT ENTRY

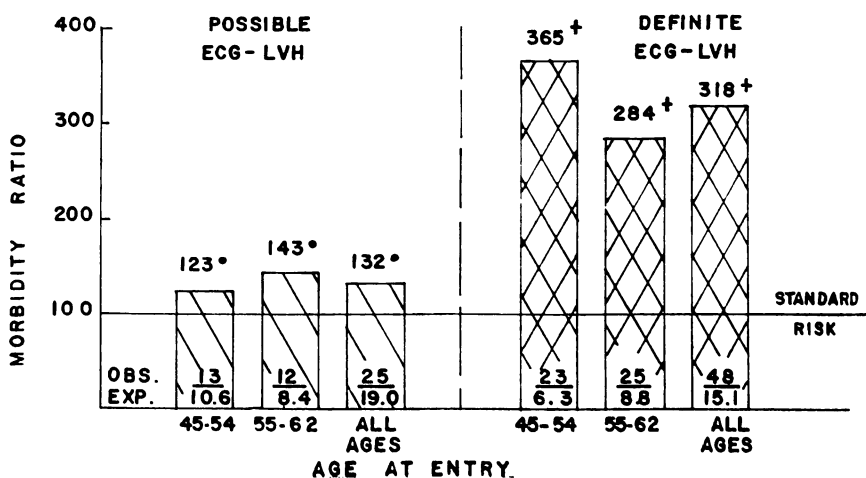


EVIDENCE OF OCCULT ORGAN DAMAGE

It has long been recognized that evidence of cardiac involvement in hypertensives is of serious importance. The risk of clinical overt cardiovascular and cerebral consequences of hypertension and of early mortality is markedly increased when evidence of cardiac involvement appears in the electrocardiogram or chest x-ray, even though this may be clinically silent.

Hypertensives who developed a pattern of left ventricular hypertrophy had a very serious prognosis indeed. Within 14 years, 60 per cent of the patients over the age of 45 died, a mortality three times greater than that among hypertensives without the electrocardiogram abnormality. Radiologic evidence of left ventricular hypertrophy was not nearly as serious a finding. Also, only 30 per cent of men and 50 per cent of women with left ventricular hypertrophy by electrocardiogram showed radiologic evidence of cardiac enlargement. This suggests the possibility that the appearance of ventricular hypertrophy on electrocardiogram may reflect something more than cardiac hypertrophy in response to the increased cardiac work load imposed by the increased peripheral resistance of hypertension. An examination of the

FIGURE 12. FACTOR OF INCREASED RISK OF CORONARY HEART DISEASE (14 YEARS) ACCORDING TO ECG-LVH STATUS, MEN AND WOMEN AGED 45-62 YEARS AT ENTRY*

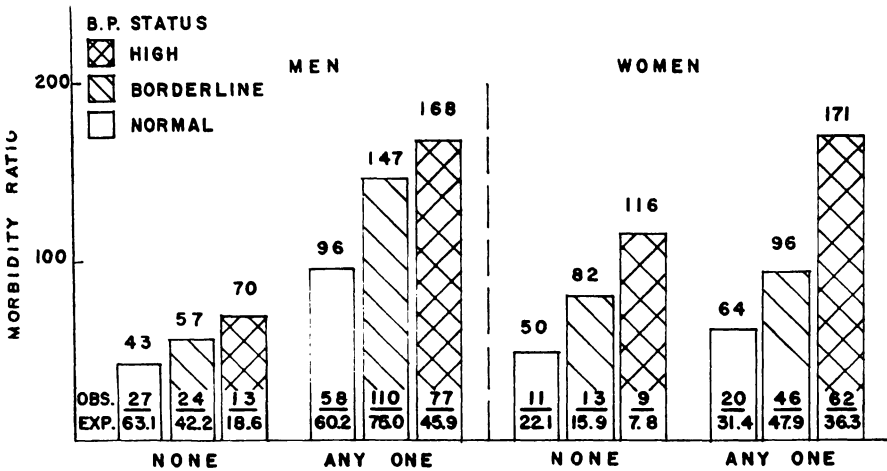


* Adjusted for blood pressure, age and sex. See section on methods for method of adjustment.

° Not statistically significant at $P < .05$ level.

† Excess over standard risk significant at $P < .05$ level.

FIGURE 13. RISK OF CORONARY HEART DISEASE (14 YEARS) ACCORDING TO BLOOD PRESSURE STATUS AND CONDITIONS PREDISPOSING TO CORONARY HEART DISEASE,* MEN AND WOMEN AGED 30-62 YEARS AT ENTRY



* Obesity, gout, abnormal lipid (cholesterol Q4, Sr 0-20 Q4, Sr 20-400 Q4) diabetes, electrocardiogram abnormality.

occurrence of coronary heart disease according to evidence of electrocardiographic left ventricular hypertrophy, adjusting for the effect of blood pressure, appears to bear this out. For "definite" (with S-T and T wave abnormality as well as voltage), but not "possible" (voltage only) electrocardiographic ventricular hypertrophy a residual threefold excess risk is still evident (Figure 12).

Hypertension makes a unique, independent contribution to risk of atherosclerotic disease because the risk with which it is associated in coronary heart disease is independent of factors believed related both to the development of coronary heart disease and to hypertension. Even after persons with these interrelated risk factors are excluded a distinct residual gradient of risk remains, increasing with the blood pressure. The impact of hypertension is, however, most pronounced in those with one or more of the other factors predisposing to coronary heart disease (Figure 13). Also, in discriminant analysis, blood pressure makes a potent contribution to risk of coronary heart disease taking some other variables into account as well. In women, the net contribution of blood pressure exceeds that of all other factors except age, and in older women potential coronary candidates can be discriminated practically as well on the basis of blood pressure alone as

TABLE 5. RISK FACTORS IN CHD LINEAR DISCRIMINANT FUNCTION COEFFICIENTS (STANDARD UNITS)

| <i>Men</i> <i>Risk Factors</i> | <i>Combined</i> <i>Ages</i> | <i>30-39</i> | <i>40-49</i> | <i>50-62</i> |
|-----------------------------------|--------------------------------|--------------|--------------|--------------|
| Age | .5934 | .2394 | .3334 | .2370 |
| Cholesterol | .4444 | .9613 | .3207 | .3790 |
| Systolic blood pressure | .3334 | .3427 | .1669 | .3809 |
| Relative weight | .1890 | .1941 | .3619 | .1036 |
| Hemoglobin | -.1050 | .0313 | -.0134 | -.2206 |
| Cigarettes smoked | .4192 | .6823 | .5084 | .3004 |
| ECG abnormality | .2626 | .2685 | .2556 | .2197 |
| | <i>Combined</i> <i>Ages</i> | <i>30-49</i> | | <i>50-62</i> |
| <i>Women</i> | | | | |
| Age | .6259 | .7325 | | .2600 |
| Cholesterol | .2844 | .7322 | | .1207 |
| Systolic blood pressure | .5556 | .1947 | | .4776 |
| Relative weight | .0975 | .0751 | | .1481 |
| Hemoglobin | .0392 | -.0304 | | .0734 |
| Cigarettes smoked | .0625 | -.0731 | | .1262 |
| ECG abnormality | .3048 | .2234 | | .2526 |

when lipids and relative weight are combined with blood pressure. In older age groups of men potential coronary heart disease can be discriminated equally well with systolic pressure and serum cholesterol level (Table 5).

CLINICAL IMPLICATIONS

Despite numerous clinical studies of "hypertensive" patients in clinical series, the course and prognosis of hypertensive disease as it occurs in the general population is poorly understood. Clinical series lack the asymptomatic and those dying too suddenly to reach medical attention. They also suffer from loss to follow-up. Prospective epidemiologic study of a reasonably representative sample under routine close medical surveillance can provide a less distorted appraisal of the impact of hypertension and blood pressure as a force of morbidity and mortality. Factors associated with increased morbidity and mortality have been identified from such a study in Framingham and the magnitude of their contribution estimated.

Objective evidence is increasing to support the clinical impression that reduction of an elevated blood pressure delays the onset and retards the progression of cardiovascular damage.¹³ A variety of

effective pharmacologic agents with acceptable side effects, as well as specific surgical procedures and general hygienic measures, are available to cope with and control most types of hypertension. Because the hypertensive state is for decades an asymptomatic condition, it must be systematically sought out periodically in apparently well persons if the condition is to be attacked in its earliest stage. The evidence presented indicates that this asymptomatic, mild hypertensive disease is not innocuous and is associated with a substantial morbidity and mortality. Now that "hypertension" is a more manageable condition evaluation of the hypertensive person has assumed greater importance than formerly. To implement effective prophylactic management of asymptomatic essential hypertension, for the purpose of avoiding and delaying the onset of cardiovascular sequelae, guidelines for when to treat and knowledge of factors that make a given pressure particularly dangerous are desirable. Also, this evaluation must be feasible at an office level if it is to be widely applied in asymptomatic persons.

The foregoing data can provide a basis for formulating such guidelines and certain implications seem inescapable. Hypertension is a potent force of morbidity and mortality and a major contributor to the development of cardiovascular and cerebrovascular disease. If it is effectively controlled early in its course it is reasonable to expect a substantial reduction in morbidity and mortality from these major contemporary health hazards to occur. In fact, no risk factor in these diseases is more readily detected and effectively controllable. More than any other factor, hypertension deserves the attention of those concerned with prophylaxis against the major cardiovascular killers. It would seem reasonable to monitor blood pressure periodically throughout life and to institute corrective measures promptly, early in the course of hypertension, before it becomes fixed at an elevated level and associated with occult evidence of organ damage.

Certain misconceptions appear to exist concerning the nature of essential hypertension that tend to impede most effective prophylaxis against the cardiovascular consequences of hypertension. Elevated blood pressure, whether predominantly systolic or diastolic, labile or fixed, casually or basally elevated, in either sex and at any age, deserves attention. It assumes increasingly grave significance when attended by abnormal blood lipids, impaired glucose tolerance, cardiac enlargement or left ventricular hypertrophy by electrocardiogram, the risk mounting precipitously when more of these are present.

Hypertension, however defined, is associated with a substantial excess morbidity and mortality from the major cardiovascular and cerebrovascular diseases. It is a common phenomenon, as well as a potent one, silently afflicting a large proportion of the population. The commonly accepted beliefs that systolic hypertension is unimportant, that postmenopausal women tolerate hypertension well, that elevated pressure can be a normal concomitant of aging and that labile hypertension is innocuous appear to require reevaluation. Attempting to determine where "hypertension" begins, except as a convenience, is pointless. The relation between arterial pressure and cardiovascular mortality is such that risk is simply proportional to the level with no critical "hypertensive" level and it is a mistake to treat "hypertension" based simply on some arbitrarily designated blood pressure value. Multiple factors are involved in the genesis of cardiovascular and cerebrovascular disease and blood pressure is only one such factor. Although the seriousness of an elevated pressure is largely a function of its level, the other identified factors that markedly influence morbidity and mortality must also be taken into account.

Blood pressure should be controlled initially by hygienic measures such as weight reduction, sedation, exercise and avoidance of rich, high-calorie and salty foods. If refractory to these measures or of severe and fixed degree or accompanied by factors that have been shown to adversely affect its course, effective antihypertensive agents are available, which if prudently used can effectively control hypertension with minimal hazard. To await the onset of symptoms before employing such agents would seem a disservice to the patient. All too often the first symptom is also the very last (i.e., sudden death from coronary heart disease), or an irreversible brain infarction may be the initial complaint.

Ideally, prevention of essential hypertension would seem the method of choice. In the present state of ignorance concerning the determinants of essential hypertension it can only be sought out methodically and once detected, controlled early in its course. Evidence is already available to indicate that a substantial reduction in cardiovascular mortality can be achieved by control of moderate to severe hypertension.¹³ Research is urgently needed to determine the efficacy and possibly the hazards associated with the control of milder and more labile degrees of hypertension. However, even milder degrees of hypertension are associated with a substantial morbidity and mortality, and because such hypertension is more easily and safely con-

trolled, prophylactic management of the early hypertensive as well as late disease would seem both rational and justifiable.

Whether isolated systolic pressure elevation in the elderly is a cause or effect of diseased vessels is moot. The responsiveness to therapy and efficacy of reducing such pressure elevations deserves investigation.

However, in all of these endeavors it is important to reckon the cost and hazards involved. Although the relative increase in mortality associated with hypertension is substantial, the absolute decrease in survival and life expectancy is more modest. The older one gets, however, the more precious these few years become.

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