ATHEROSCLEROTIC COMPLICATIONS OF HYPERTENSIVE DISEASE: RELATION TO THERAPEUTIC RESPONSE AND TO SERUM PROTEIN AND TO LIPOPROTEIN CONCENTRATIONS

Preliminary Report

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THE course and prognosis of severe essential hypertension have been profoundly modified, in the past five years, by the effective use of antihypertensive drugs in patients with advancing vascular disease.[1] Favorable responses to these agents can be anticipated in a majority. Such responses include lowering of arterial pressure, stabilization or remission of, or, in some patients, actual recovery from manifest cardiac, cerebral, or renal hypertensive vascular disease.[2]

Although the mechanisms and sites of action of the available antipressor agents are varied, the common denominator of their effectiveness is the lowering of arterial pressure. This is followed by improvement of the obvious aspects of renal or cerebral arteriolosclerosis or of cardiac failure. Such remissions are clinical confirmations of the experimental finding that high blood pressure, per se, is the primary cause of arteriolar damage and cardiac strain. While hypertensive vascular disease is primarily an affliction of the *arterioles*, its association with *arterial* disease, namely, atherosclerosis, is also well recognized. The purpose of this report is to describe the beneficial effects of antihypertensive therapy on the survival of patients with advancing vascular disease and to discuss the extent to which atherosclerotic complications are affected by treatment.

Some of the many glowing reports on the use of antihypertensive drugs overlook the axiom that new solutions resolve old problems, but they inevitably create new ones. Unfortunately not all the old problems have been solved, for there still are a few patients in whom blood pressure is not controlled by the present therapeutic regimens; in these arteriolar disease continues[3]. The new problem of major and increasing concern is the occurrence of complications of atherosclerosis in treated patients, including some who respond well in terms of cardiac and arteriolar status, blood pressure, and general well-being. Some aspects of this problem have been discussed elsewhere[4,5]; and others[6] have noted "the unpleasant fact . . . that despite improvements in other respects, many patients after being restored to comfort and to living productive lives, die

unexpectedly of a stroke." But, as we shall show, strokes are only one aspect of the problem. The basic issue is that of arterial disease, namely, atherosclerosis.

Clinical material. Our report is based on a five-year survey of results of treatment of 106 hypertensive patients, nearly all of whom had been under treatment with antihypertensive drugs. Before treatment was begun, all were observed in the ward of the Research Division. There, during several weeks of study and evaluation,[7] the hypertension was categorized as malignant in 61 and as essential (nonmalignant) in 45. The severity of the hypertensive disease was scored according to a Severity Index[2,7] that covers a range from 1 (minimal hypertension) to 16. The index is the sum of the points that four panels rate on a scale from 0 to 4. The panels are (a) diastolic arterial pressure, the functional status (b) of the heart, and of the (c) cerebral, and (d) renal circulations.

Seventy per cent of the patients were between 40 and 59 years of age. In this age group, hypertension generally is more common in women than in men. The fact that two thirds of the patients were men reflects the greater severity of hypertensive disease in the male sex.

Survival and severity. Experience in this series clearly demonstrated the prognostic value of the severity index. In the group of 61 patients having malignant hypertension the mean index of severity was 9 and the mortality was 44 per cent. In the group of 45 patients having essential hypertension, the mean index of severity was 6 and the mortality was 27 per cent. Furthermore, in the 'malignant' group, mortality was 70 per cent for the subgroup having severity indexes of 10 or higher, and only 25 per cent for the subgroup having severity indexes from 6 to 9.9. Among survivors of the 'essential' group the mean index of severity was 5.4 and among those who died it was 7.3.

The cumulative survival in the 'malignant' group is graphically presented in Figure 1. This is a dramatic demonstration of the efficacy of modern methods of treatment in comparison with previous experience. In 1939, Keith, Wagener, and Barker[8] reported a four-year survival rate of 2 per cent in relatively untreated patients who had been classified as having grade IV hypertension; whereas, experience to date shows a 25 per cent four-year survival rate in our clinically comparable group. Since one fourth of the deaths in our patients were due to pulmonary fibrosis associated with the use of hexamethonium—a complication that has not occurred during the past three years—it is likely that the four-year survival rate of patients who now are beginning to receive treatment will be of the order of 40 per cent.

The causes of death in this series are listed by major subgroups in the Table, together with the incidence of nonfatal atherosclerotic complications. The high frequency (37 per cent) of renal failure as the cause of death in patients with malignant hypertension is to be expected. Most of the patients who died of renal failure had shown evidence of renal damage at the time that treatment was begun. Since a minority with initially severe renal damage have survived for several years, we believe that renal failure does not contraindicate vigorous treatment of malignant hypertension although it lessens the prospect of success and increases the difficulties. The one death from renal failure in the 'essential' group occurred in a patient who evidently had developed terminal malignant

Table. *—Causes of death, and incidence of nonfatal atherosclerotic complications (106 patients)*

Group	Cause of death	No. of patients	Nonfatal atherosclerotic complications	No. of patients
Malignant (61 patients)	Renal failure	10	Cerebrovascular accidents (among 34 survivors)	7
	Pulmonary fibrosis	7		
	Atherosclerosis	10		
	Myocardial infarct . . 5			
	Cerebral hemorrhage . 4			
	Aortic aneurysm . . . 1			
	Total	27		7
Essential (45 patients)	Renal failure	1	Cerebrovascular accident	1
	Atherosclerosis	11	Angina pectoris	2
	Myocardial infarct . . 5			
	Cerebral hemorrhage . 5		(among 33 survivors)	
	Aortic aneurysm . . . 1			
	Total	12		3
	TOTAL	39		10
	Total number of deaths resulting from atherosclerosis. . . . 21*			

**After this list had been compiled and the manuscript completed, one man in the 'malignant' group (response fair) died of dissecting aneurysm of the aorta, and another (response fair) died of cerebral hemorrhage, bringing the total number of deaths resulting from atherosclerosis to 23.*

hypertension (without the characteristic retinopathy), since at autopsy the kidneys showed typical malignant nephrosclerosis.

Atherosclerotic disease. The incidence of atherosclerotic complications, such as cerebrovascular accident, myocardial infarct, angina pectoris, and aortic aneurysm, is also shown in the Table. In this report patients who had those complications were classified as *atherosclerotic*, and the remainder of the patients, without prejudice to their presumed latent atherosclerosis, were provisionally classified as *nonatherosclerotic*.

In these terms, atherosclerosis accounted for somewhat more than half of the deaths in the entire group (Fig. 2); it was as frequent a cause of death as renal failure in the 'malignant' group and it was the cause of nearly all of the deaths in the group having essential hypertension. The dotted line in the figure suggests that atherosclerosis would have accounted for as large a proportion of deaths in the 'malignant' group if renal failure and pulmonary fibrosis had not supervened. It is probable that as more patients with malignant hypertension receive treatment before they have sustained severe renal damage, a larger proportion will survive only to die from atherosclerosis.

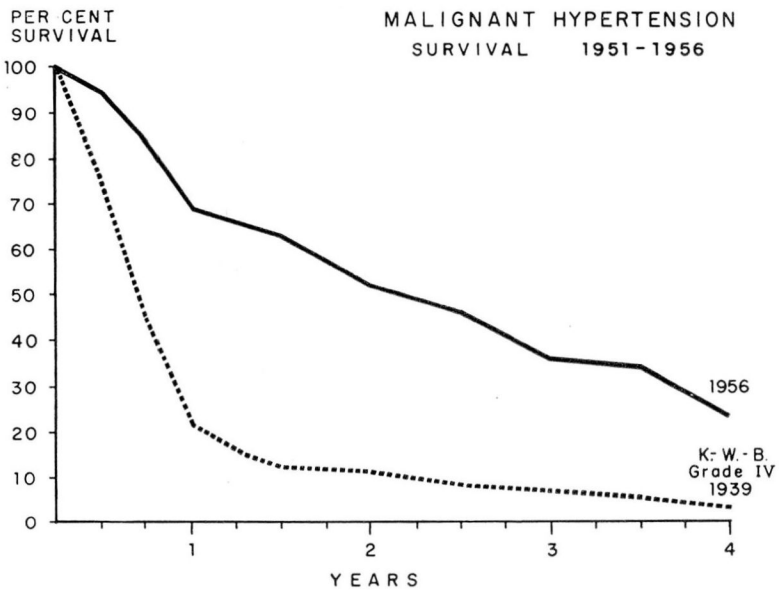

Fig. 1. Cumulative survival rates in the grade IV group of Keith, Wagener, and Barker,[8] as reported in 1939 (dotted line), and in our patients with malignant hypertension (continuous line) as of March 1956.

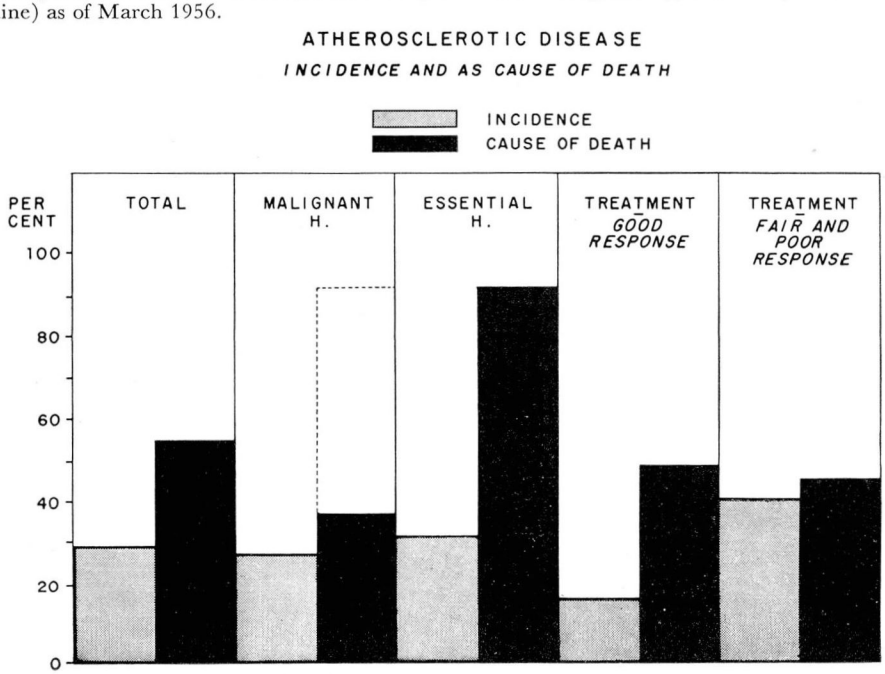

Fig. 2. Incidence of atherosclerotic complications, fatal and nonfatal, in entire group and in subgroups (shaded areas), and incidence of atherosclerotic complications as causes of death (black areas).

The patients also were classified according to an estimate of therapeutic response. The *good-response* group comprises those patients who maintained averages of resting, supine, diastolic pressures of less than 110 mm. Hg; those in the *fair-response* group had averages ranging from 110 to 120; and those in the *poor-response* group had averages of more than 120 mm. Hg. However, even the patients in the poor-response group showed at least temporary remission of the signs of malignant hypertension. For the discussion that follows, the fair- and the poor-response groups have been combined into one group (fair-poor response group).

The percentages of deaths caused by atherosclerosis were approximately equal in the two response groups. It is significant that the incidence of atherosclerotic complications, fatal or not, is much less (16 per cent, 8 of 49 patients) in those patients with good responses than it is in those with fair-poor responses (40 per cent, 23 of 57 patients). The major common characteristic of the fair-poor response group is persistence of diastolic hypertension, which indicates that in man diastolic hypertension per se contributes greatly to atherogenesis. This also is true in rabbits[9] and in dogs.[10] The corollary should be that early, effective control of diastolic hypertension is a primary means of preventing the development of atherosclerotic complications.

Serum protein and lipoprotein analyses. Serum protein concentrations were measured electrophoretically by the Longsworth modification of the method of Tiselius, and lipoprotein concentrations by the Green, Lewis, and Page[11] modification of the Gofman procedure. Serum cholesterol was determined by the method of Abell, Levy, Brodie, and Kendall.[12]* Since these data have not yet been completely analyzed, this presentation is, in part, preliminary.

Inspection disclosed no consistent abnormalities in concentrations of the electrophoretically separated serum protein fractions other than those of beta-globulin, so that data concerning this fraction were studied first. In regard to lipoproteins, current interest in the light, lipid-rich fractions of the beta-lipoproteins and in the ratio of these to the concentration of relatively dense, lipid-poor alpha-lipoproteins prompted us to select for initial review data concerning the $-S_{1.21}$ fractions 2-8 (corresponding to alpha-protein) and the fractions 40-70 (corresponding to the S_f 12-100 material in Gofman's unmodified procedure).

Figure 3 summarizes the data concerning beta-globulin and serum cholesterol. The mean normal concentration of beta-globulin by this method is 13 per cent and the upper limit of normal is about 17 per cent. Hence, the mean concentration of beta-globulin is increased in the entire hypertensive group; it is somewhat greater in the malignant than in the essential subgroup and in those who had atherosclerotic complications than in those who did not have them. Except in the good-response group, the means of concentration of serum cholesterol show some association with the averages of beta-globulin. The lipoprotein data are not shown, since the means of concentrations of the two fractions studied and of their ratios one to another are nearly the same in all the groups.

**Determinations were made with the assistance of Helen Brown, Ph.D., of the Division of Research.*

The observed differences in mean concentrations of beta-globulin and of cholesterol between the subgroups of Figure 3 are not statistically significant. However, the differences between the means may indicate trends that, in a much larger series, might prove statistically significant. This is suggested by the fact that the incidences of abnormal concentrations of cholesterol follow the trend of the means of the concentrations. Thus, the concentrations of beta-globulin were 17 per cent or more in two thirds of the entire group and in about the same proportion of each of the subgroups; concentrations of serum cholesterol were increased (greater than concentrations found in 80 per cent of normal subjects of matched age and sex) in one fourth of the entire group, in one third of the malignant, in one seventh of the essential, in one third of the atherosclerotic, and in one fifth of the nonatherosclerotic groups. Abnormal concentrations of the lipoprotein fractions were uncommon. Thus, the $-S_{1.21}$ 2-8 fraction was high in 5, and low in 14 of 77 patients; and the fraction 40-70 was high in 8, with no trend toward higher incidences in any of the subgroups. The conclusion from this is that hypercholesteremia or abnormalities of the lipoprotein fractions studied are not major determinants of atherogenesis in hypertensive disease, although study of a larger series might reveal some minor contributory influence.

Serum beta-globulin in hypertensive disease. Increased concentration of serum beta-globulin was found to be associated with the presence of hypertensive vascular disease in patients with malignant hypertension, and in dogs with experimental renal hypertension[13] (Fig. 4). More recently, this increased concentration was observed in rats made hypertensive by treatment with desoxy-

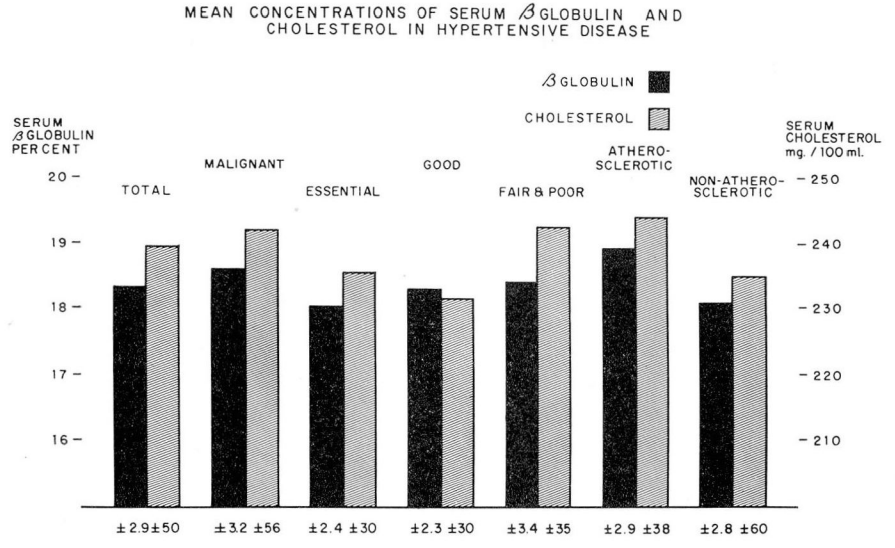

Fig. 3. Means of concentrations of serum beta-globulin (black areas) and cholesterol (shaded areas) in entire group and in subgroups. The numerals below each column indicate standard deviations of the means. Data compiled from analyses made simultaneously in 78 patients, prior to use of antihypertensive drugs.

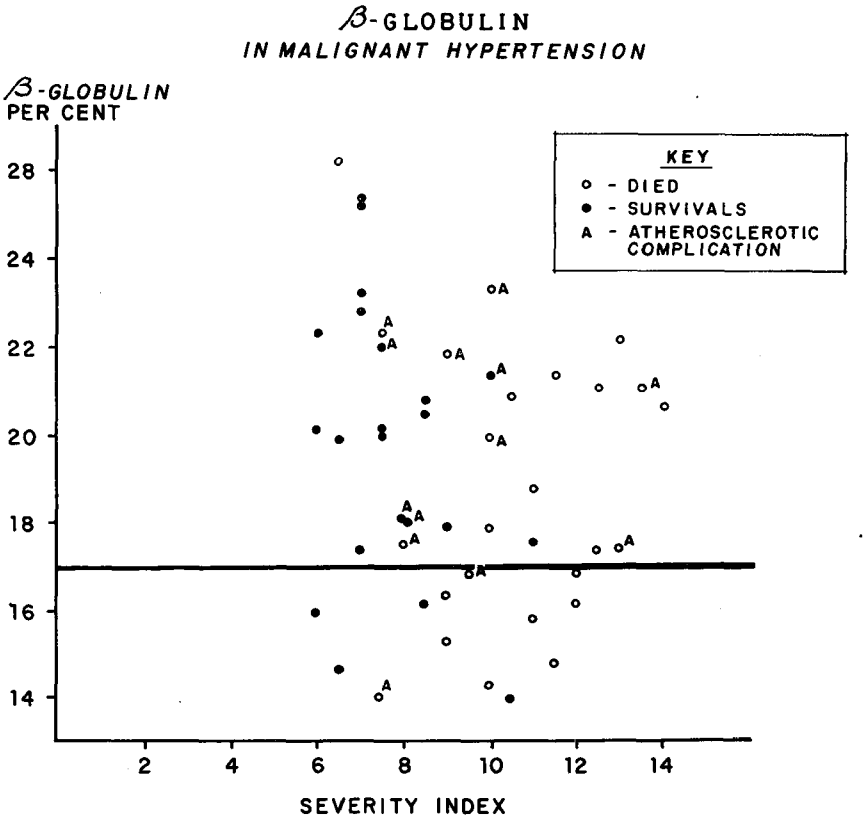

Fig. 4. Scatter of serum beta-globulin concentrations in our patients with malignant hypertension, and lack of correlation with severity indexes, mortality, and atherosclerotic disease.

corticosterone acetate (DCA) and sodium chloride; in these the abnormality was increased by injections of renin; the increased concentration did not appear in rats treated with cortisone and sodium chloride or with sodium chloride alone, but it was elicited in rats treated with cortisone and sodium chloride and then renin injection.[14] The positive correlation of increased concentration of beta-globulin with hypertensive disease was again evident in these experiments; severe vascular damage is present in rats given DCA and NaCl, and may assume a hyperacute form in rats given DCA, NaCl and renin, or in rats given cortisone, or NaCl and renin; whereas, under these conditions, neither NaCl alone nor cortisone and NaCl elicit more than minor hypertension and do not provoke lesions with the characteristics of hypertensive vascular disease.

Hence, there is clinical as well as experimental evidence of an association of increased concentration of serum beta-globulin and hypertensive vascular disease. This association is further borne out in the lowering of the concentration

of serum beta-globulin which occurs during treatment, and by the finding that the decrease is greater in patients with good responses than in those with fair or poor responses.[5] But, since the nature of the abnormality of beta-globulin is not characterized, the significance of this association is purely speculative. The data do indicate some correlation between changes in beta-globulin and changes in serum cholesterol. This, in turn, suggests that the increment in concentration of beta-globulin may be due to a cholesterol-containing lipoprotein that migrates electrophoretically as a beta-globulin. On the basis of present data, this fraction does not correspond either to the relatively dense or to the relatively light lipoprotein fractions. Further study of the available data may determine where this material is distributed in the ultracentrifugally measured fractions.

Here, for the moment, the problem rests. However, the association of increased concentrations of serum beta-globulin with hypertensive vascular disease as such and, to a minor degree, with inadequate responses to treatment and with predisposition to atherosclerotic complications, indicates that definition of the nature and mechanism of this abnormality may be of considerable value. To our knowledge, increased beta-globulinemia represents one of the few, if not the only aspect of the chemistry of the blood that can be considered an abnormal characteristic of hypertensive vascular disease.

Summary and Conclusions

1. The prognosis in severe hypertension has been greatly improved by the advent of effective antihypertensive drugs. Today, patients with malignant hypertension have a four-year survival rate of 25 per cent, as compared with about 2 per cent in 1939; it is likely that patients coming under treatment at this time will have a four-year survival rate of about 40 per cent.

2. A numerical index of the severity of hypertensive disease is useful in assessing prognosis as well as in therapeutic evaluation.

3. The present status of hypertensive disease involves two major problems. One is that of patients who are partially resistant to drug treatment. The other is that of atherosclerotic complications.

4. Atherosclerotic disease is a major cause of death and disability in patients under treatment for hypertensive disease, including some with good therapeutic responses. These complications are two to three times more common in patients whose resting diastolic pressures average 110 mm. Hg or more, than in patients with good responses (diastolic average less than 110 mm. Hg).

5. The concentration of serum beta-globulin is increased in a majority of patients with severe hypertensive disease. Concentration of serum cholesterol is increased in a minority of patients. Means of the concentrations of serum beta-globulin and cholesterol in subgroups show some correlation. Neither the relatively dense ($-S_{1.21}$ 2-8) nor the relatively light (40-70) serum lipoprotein fractions show differential changes between these malignant and essential, atherosclerotic and nonatherosclerotic subgroups of patients. From these findings it seems that abnormalities of serum cholesterol or of these serum lipoprotein

fractions are not major factors in atherogenesis in hypertensive disease.

6. Rather, the primary factor is arterial hypertension, and the prevention of atherosclerotic complications is best accomplished by prompt, effective, and persistent control of hypertensive disease.

7. Attention is directed to the association of increased concentration of serum beta-globulin with clinical and experimental hypertensive disease, the possibility that the abnormality may be due to a lipoprotein, and that this is the only abnormality of blood chemistry that seems to be characteristic of hypertensive disease.

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