The Effectiveness of Long-Term Treatment of Malignant Hypertension

By Harriet P. Dustan, M.D., Roland E. Schneckloth, M.D., A. C. Corcoran, M.D., and Irvine H. Page, M.D.

HYPERTENSION even of mild degree shortens life span. Thus Dublin, Lotka and Spiegelman in 1940 stated, ‘‘mortality rises steadily and markedly with increasing elevations of both the systolic and diastolic pressures’’ and, ‘‘In the group with the highest blood pressures included in this [insurance] experience—and these are not considered seriously high by many clinicians—the mortality from cardiovascular renal disease was nearly 41/2 times the average for all standard risks.’’

This actuarial experience has been supplemented by Bechgaard, Kopp, and Nielson, who have followed the clinical courses of 1,038 out-patients with hypertension over periods of from 16 to 22 years. As compared with a normotensive group, the patients with hypertension, especially the men, showed decreased survival with increasing levels of pressure and, at the end of an average follow-up of 19 years, there survived only one fifth of the men and about half the women.

These impressive data on prognosis in hypertension should not obscure the fact that the outcome in individual cases of essential hypertension is highly unpredictable. Some patients, most of them women, may go through a normal or nearly normal span of life. However, a majority will die prematurely, not from hypertension or hypertensive vascular disease as such, but from complications of hypertensive and coronary heart disease, cerebrovascular damage or some other arterial (not arteriolar) catastrophe. Potent antihypertensive drugs have been in use for 7 to 8 years but with such a variable course and a lack of association between the cause of death and the extent of arteriolar damage it is impossible to assess therapeutic gains in such terms as prolongation of life or prevention of complications. To be convincing, such an evaluation must await a survey of very large numbers of patients over long periods of time.

The situation is quite different when we deal with the malignant (accelerated) phase of essential hypertension. The course of this hypertensive syndrome is well characterized, predictable and relatively brief, with survival of only 10 to 20 per cent of patients for 1 year. Death is caused primarily by hypertensive arteriolar vascular damage. This is commonly expressed by malignant nephrosclerosis with rapidly progressive renal failure, by intracerebral hematoma, and not infrequently by uncontrollable cardiac failure. A survey of survival and causes of death among a group of patients suffering from this condition who have been under intensive treatment with potent antihypertensive agents available during the past 7 years, should establish the beneficial effects of these agents in terms of prolongation of life. Further, these drugs act in various ways to effect their common denominator of decreased arterial pressure. Hence, such a survey might also delineate those aspects of the vascular disease

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of malignant hypertension that are pressure-dependent and indicate some that may have no direct association with arterial pressure level as such.

This report therefore has a 2-fold aim: (1) to show the effect of treatment with potent antihypertensive drugs on survival in a group of patients with malignant hypertension, and (2) to evaluate the extent to which the height of the blood pressure is a factor in the complications supervening during its treatment.

**EVALUATION OF THE SEVERITY OF VASCULAR DISEASE**

Comparative or critical study of the value of treatment in hypertensive disease demands careful, systematic assessment of the severity and extent of that disease prior to treatment, followed by sequential, similar estimates during treatment. While this applies to the individual patient, averages of these estimates—if they fall within a fairly narrow range—can then apply to comparisons between groups. It is not enough to describe a patient or patient group as suffering from malignant hypertension. It would be misleading to compare results of treatment between patients in whom vascular disease had just begun and those in whom vascular damage was extensive. Further, it is desirable to have some systematic way of associating observed blood pressure levels with the other manifestations of this hypertensive syndrome. Lastly, a means of expressing the course of the disease in simple numerical terms is particularly useful at the present time. Although it is well recognized that antihypertensive treatment can control some of the more acute aspects of severe hypertensive disease effectively and promptly, we know little of the "natural history" of treated malignant hypertension.

To serve these purposes we have used a numerical Severity Index based on objective estimates made in the more accessible vascular beds. The mode of calculation of this index is indicated in Table 1 (table modified from reference 7). A maximum of 4 points is allotted to each of 4 panels of cardiovascular status; these are, respectively, average of supine diastolic pressure, and estimates of circulatory status in the cardiac, renal, and cerebral vascular beds. The sum of the grades from the 4 panels considered constitutes the Total Severity Index. For example, a patient with a supine diastolic average between 95 and 110 mm. Hg but no objective indication of vascular changes in the other panels would be graded as having a Total Severity Index of 1, while a patient with a diastolic average greater than 140 mm. Hg severe cardiac failure, retinal hemorrhages, exudates and papilledema, hypertensive encephalopathy, and severe azotemia, would have a total score of 16. This index is used in the description of clinical courses and mortality that follows. The diastolic blood pressure averages used in the sequential estimates during treatment for the most part were obtained from daily meas-

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**Table 1.—Calculation of the Severity Index**

<table>
<thead>
<tr>
<th>Datum</th>
<th>Units Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic pressure, average</td>
<td></td>
</tr>
<tr>
<td>95 or&lt;</td>
<td>0</td>
</tr>
<tr>
<td>96-110</td>
<td>1</td>
</tr>
<tr>
<td>111-125</td>
<td>2</td>
</tr>
<tr>
<td>126-140</td>
<td>3</td>
</tr>
<tr>
<td>&gt;140</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac (American Heart Association grades)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>I</td>
</tr>
<tr>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (Gm./24 hr.)</td>
<td></td>
</tr>
<tr>
<td>0.2 or&lt;</td>
<td>II</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>III</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>IV</td>
</tr>
<tr>
<td>Serum creatinine (mg./100 ml.)</td>
<td></td>
</tr>
<tr>
<td>0.2-0.5</td>
<td></td>
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<tr>
<td>&gt;3.0</td>
<td></td>
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<tr>
<td>Cerebral Fundi (Keith-Wagener)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>I</td>
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<tr>
<td>0</td>
<td>II</td>
</tr>
<tr>
<td>Severe</td>
<td>Old</td>
</tr>
<tr>
<td>Encephalopathy or fresh stroke</td>
<td></td>
</tr>
</tbody>
</table>

*Where a panel is graded by 2 components the sum of the estimated units is divided by 2 to establish the value for that panel.*
urements taken at home by the patient or a member of his family.

**Patient Group**

The group under consideration consists of 84 patients, 56 men and 28 women of an average age of 46 years, who presented the syndrome of malignant hypertension. The period of the study was from January 1, 1951, to January 1, 1958. We have included only those who survived for a minimum of 3 months from the time the diagnosis was established. The period of observation extends from this minimum to nearly 7 years. In 75 of the 84 the disease process was considered to be the malignant phase of essential hypertension, in 5 it was associated with chronic pyelonephritis and in 4 with occlusive lesions of major renal arteries. These last 4 were treated by nephrectomy, and in 3 hypertension and vascular disease remitted. Eighty-one patients, including the 1 patient in whom nephrectomy was of no benefit, were treated with 1 or more of the available potent antihypertensive drugs, singly or in combination.

**Survival**

During this period of 7 years, 52 of the 84 patients died. This over-all mortality (62 per cent) is at first glance discouraging. However, the obverse is that 32 per cent survived. This datum is encouraging indeed to all acquainted with the course of untreated or ineffectively treated malignant hypertension, whether from personal experience or from the reports of Keith, Wagener, and Barker, Page, Schottstaedt and Sokolow, Kincaid-Smith, MacMichael and Murphy, and others. Among these reports, the later ones bear out in general the experience of Keith, Wagener and Barker, and their earlier estimates of survival will be used for simplicity’s sake as indicative of the course of malignant hypertension prior to the use of potent antihypertensive drugs.

Keith, Wagener and Barker reviewed clinical courses of 146 patients who presented themselves with severe hypertension, retinal hemorrhages, exudates and papilledema, and usually other symptoms of diffuse, rapidly advancing arteriolar disease. Some 20 per cent of the these patients survived for 1 year and, very significantly as concerns the present survey, only 1 survived 5 years or more; in general, experience has been that most such patients are dead or wholly disabled by the end of 1 or 2 years and that all—with rare exceptions—are dead at the end of 4 or 5 years.

Figure 1 shows a comparison of survival rates in the Keith, Wagener and Barker group with the experience in our group of patients treated for malignant hypertension. The figure indicates that treatment causes a significant prolongation of life in many patients with malignant hypertension, although it does not prevent premature death in the majority. Certain reservations should be made as to the comparability of our data with those of Keith, Wagener and Barker. Their study covered a period of 5 years and followed the courses of 146 patients during this time. In contrast, not all of our treated group have been followed for 7 years, since we are dealing with patients who started treatment between January 1, 1951 and January 1, 1957. Thus we have followed 84 patients from 3 months to 1 year, but as the period of observation became longer the numbers of patients became progressively smaller, as indicated in figure 1. Our final estimate of survival is made from
about 7 years' experience with 19 patients. Secondly, as will be noted below, nearly a third of the first-year mortality in the total group was attributable to a complication of treatment (hexamethonium pneumonitis) which we have not witnessed in recent years. Other factors than antihypertensive drugs, such as sodium restriction in congestive heart failure, the use of mercurials and of other supportive measures, may have altered the course of malignant hypertension in our patient group as compared with the group of Keith, Wagener and Barker. However, our former experience had shown us that these measures were nearly always ineffective and that even major procedures, such as sympathectomy or treatment with kidney extracts of pyrogens, usually evoked no more than a few months remission in the course of the disease. Hence we believe that the 2 groups of patients are initially roughly comparable and that the major difference between them is the use of antihypertensive agents in our group.

Analysis of Causes of Death

Previous reports by our group and by many others abundantly show that the syndrome of malignant hypertension is reversible by any procedure that results in prolonged lowering of diastolic pressure toward normal levels. This result has been accomplished largely by appropriate and intensive use of antihypertensive drugs, by restriction of dietary sodium by nephrectomy or other surgical procedures in patients with remediable renal hypertension, and by extensive lumbodorsal or dorsal sympathectomy. However, most such reports provide little information on prognosis over long periods, as concerns either survival or disability. In this regard, the data of figure 1 indicate that reversal of the syndrome of malignant hypertension—accomplished in practically all of the 84 patients—does not protect them against premature death from cardiovascular causes or, by inference, restore them to abundant health.

Of the 52 deaths, 8 were attributable primarily to interstitial pneumonia complicating treatment with hexamethonium. Median survival in this group of 8 was 5 months and all had died at the end of 8 months. While these patients as a group presented evidences of very severe disease prior to treatment, this complication of treatment probably distorts the survival data of the first year, since it accounts for one third of the first-year mortality. The influence of this unfortunate complication can be estimated by comparing mortality (24 of the 84 patients) among the total first-year group with mortality in 33 patients observed after January 1, 1954, when the use of hexamethonium had been discontinued. Among these 33 only 6 (18 per cent) died during the first year, whereas 9 or 10 deaths would have been anticipated. Hence, avoidance of pneumonitis seems to yield a definite gain in prognosis. We have no indication of the mechanism or pathogenesis of this complication.

It is exemplified by the course of a 44-year-old man who came with advanced malignant hypertension, heart failure and azotemia (serum creatinine 5.6 mg./100 ml.). With hexamethonium, lying diastolic pressures were maintained at about 110 mm. Hg, papilledema regressed, proteinuria decreased, and congestive failure was easily controlled. At the end of 3 months, he developed severe dyspnea, which decreased on lying down. This symptom was progressive, and during the course of 2 weeks he developed pulmonary consolidation and died of diffuse pneumonitis.

The most common (42 per cent) single cause of death was renal failure. This occurred in 22 patients and was present in severe degree in 2 patients whose proximate cause of death was myocardial infarction. Renal failure in the 22 patients followed two courses.

Nine patients showed rapidly progressive loss of renal function; of these 5 died within 6 months and all in less than 12. For example, a 28-year-old Negro woman had a diastolic pressure average of 165 mm. Hg, other signs of severe malignant hypertension, and adequate renal function (urea clearance of 40 per cent of normal and serum creatinine 1.7 mg./100 ml.). She was given chlorisondamine and mecamylamine. Blood pressure response was poor, with supine diastolic average
of 130 mm. Hg and modest decrease in standing blood pressure. Retinopathy diminished but renal function progressively deteriorated and the patient died at the end of 3 months in uremia.

In contrast to those who went rapidly into renal failure, the lives of 13 patients who died of slowly progressive renal failure seemed definitely to have been prolonged by treatment. These survived from 14 to 60 months and the median survival was 27 months. In all, treatment was begun when renal function was definitely impaired. In contrast with the former group, however, excretory function stabilized for long periods during treatment and only deteriorated during several months prior to death. For example, the blood pressure of a man of 51 years with malignant hypertension responded very well to treatment with hydralazine, which was started in April 1951. At that time urea clearance was 28 per cent of normal and blood urea 84 mg./100 ml. In September 1954, 3½ years later, blood urea was the same and creatinine was 2.7 mg./100 ml. However, in March 1955, 6 months later, azotemia had increased and serum creatinine had risen to 5.7, and in August 1955 to 11.5 mg./100 ml. He died in uremia 5 years after beginning treatment.

The remaining 22 deaths were attributable to complications of arteriosclerosis, presumably atherosclerotic. Among these were 13 instances of cerebral hemorrhage, 7 of myocardial infarction and 2 of ruptured aortic aneurysm. These catastrophes occurred at intervals of from 5 to 66 months of treatment. They showed no pattern of occurring early during treatment, as in patients succumbing to hexamethonium pneumonitis or rapidly progressive renal failure, or later in the course as in those with delayed or slowly progressive renal failure. By way of example we cite the case of a white woman of 49 years, whose intense malignant hypertension responded well to treatment with ganglion-blocking agents and was later controlled with reserpine. During the first 3 years of treatment supine diastolic was persistently less than 110 mm. Hg, but during the fourth year it rose to an average of 112 mm. Hg. At the end of the fourth year of treatment she died from a massive cerebral hemorrhage, having maintained fair health and productivity in the interval.

Considering the deaths associated with hexamethonium pneumonitis as accidental and not representative of present experience, we summarize by noting that 9 patients died of rapidly progressive renal failure, 13 of delayed or slowly progressive renal failure and 22 of complications of atherosclerosis. Death from rapidly progressive renal failure is the usual course of untreated malignant hypertension, and the clinical data in this group of 9 patients indicate that treatment caused no more than some attenuation of the progress of the disease. However, neither delayed or slowly progressive renal failure nor complications of atherosclerosis are characteristic of the untreated disease. Since these causes of death in the majority of patients differ substantially from the usual course of malignant hypertension, we conclude that treatment has significantly altered the evolution of this condition.

**INITIAL SEVERITY OF VASCULAR DISEASE AND SURVIVAL**

It would be anticipated that treatment would be more successful in prolonging life and preventing complications in patients with recent malignant hypertension and minor evidences of diffuse vascular damage as compared with those in whom the process has been active for long periods and had resulted in extensive destruction of the circulation. This anticipation is supported by our data. The Total Severity Index in nonsurvivors averaged 10.4, whereas the average was 8.0 in the survivors. Grades of scoring in each panel of the Severity Index were higher among nonsurvivors with one exception. Averages of these panel grades respectively as between nonsurvivors and survivors were as follows: blood pressure 3.1 and 2.6; cardiac 2.3 and 1.7; renal 2.3 and 1.2; and cerebral 2.7 and 2.5. The exception in the cerebral panel suggests that this means of estimate may be defective. Apparently retinopathy, which enters into this datum, is
not a valid index of the presence or extent of latent cerebrovascular damage. Among the differences, the greatest and most significant is the initial estimate of renal damage. This was definitely higher in nonsurvivors than in survivors. Thus, the data support the belief that prolonged survival during treatment is a function of the over-all initial severity of the disease and especially of the degree of initial renal damage. However, some azotemic patients—such as the one noted above who died of slowly progressive renal failure—have surprised us by surviving for months and years. During this time they have maintained their social and economic positions much to their own and their families’ advantage. Hence, contrary to some physicians, who seem to advocate withholding treatment in patients with severe hypertension and azotemia, we believe that there is little to lose and much to gain by undertaking treatment in all but the desperate circumstances.

**Arterial Pressure and Survival**

The control of blood pressure during treatment was considered “good” if the supine diastolic average was persistently less than 110 mm. Hg. Some patients whose responses were good at first later became resistant to treatment, so that control was “poor” during a large part of the treatment period. For simplicity’s sake, these latter are considered here to have shown poor responses throughout.

First, we could establish no association between the occurrence of hexamethonium pneumonitis, the doses of drug used and the estimate of blood pressure control; this complication occurred, however, in patients with severe disease who showed some azotemia.

Among the 9 patients with rapidly progressive renal failure there were only 2 whose blood pressure control was considered good while poor responses were observed in the other 7, who also showed no more than a modest blood pressure fall when standing. However, even this slight degree of blood pressure control may be significant, since none of those with rapidly progressive renal failure who came to autopsy showed the florid and diffuse necrotizing renal arteriolar lesions characteristic of untreated malignant hypertension. Rather, the lesions were discrete and attenuated, being more productive than inflammatory in appearance.

Among the 13 patients with slowly progressive renal failure as a primary cause of death, there were 7 whose control was considered good and 6 in whom it was listed as poor. Apparently, in this group, the adequacy of blood pressure control is a less significant determinant of course than in those with rapidly progressive renal disease. Rather, the significant factors in this condition seem to be the extent and severity of the disease at the time treatment started and in particular the initial severity of renal disease.

The next major cause of death was cerebral hemorrhage. Among 13 patients who died of this complication 10 showed poor control and 3 good control. Control of supine diastolic pressure at levels under 110 mm. Hg therefore significantly reduces the risk of this complication. There were 7 patients who died of myocardial infarction, 2 of whom had slowly progressive renal failure. In this small group myocardial infarction did not show an association with blood pressure control; it occurred in 5 with good and 2 with poor responses to treatment.

In brief, rapidly progressive renal failure and cerebral hemorrhage in treated malignant hypertension show an association in their incidence with poor control of blood pressure. Clinical and pathologic evidence suggests that the modest fall in standing blood pressure provoked by treatment in patients with poor control did attenuate the severity of vascular disease. In contrast, the occurrence of 2 other major complications, slowly progressive or delayed renal failure and myocardial infarction, showed no close association with levels of supine diastolic pressure during treatment, which were often classed as good.

This last observation suggests that there may be some unusual characteristic of the renal and coronary vasculature of patients with treated, even well-treated, malignant hypertension. The coronary vascular lesions
have not been reviewed in detail. However, the renal vessels have been studied carefully, and these show remission of all or most aspects of the necrotizing arteriolar lesions of malignant hypertension in patients with apparently good control. However, the larger arteries—major branches, arcuates and interlobar arteries—exhibit a diffuse fibrous intimal hyperplasia that is sometimes occlusive. It is this productive, arteriosclerotic lesion that seems to be the cause of the syndrome of slowly progressive renal failure. This arteriosclerotic renal lesion, like myocardial infarction, apparently can develop in spite of good blood pressure control. Hence it may be that the fatal myocardial infarcts that occurred during treatment are attributable to similar diffuse intimal lesions developing in the coronary vessels.

This demonstration of an unusual type of arteriosclerotic lesion in the large renal vessels of patients with treated malignant hypertension poses several problems as to its nature. First, it might be supposed that this is a delayed reaction to damage done mechanically to larger arteries or done by lipid “infiltration” during the course of the malignant hypertension prior to treatment. However, there is no convincingly direct evidence that this is the case. Alternatively, this process may represent mitigation of a basic process, which in the absence of control of blood pressure is expressed primarily in arteriolar damage and necrosis, and with control of blood pressure, by intimal fibroplasia in larger vessels. On the latter assumption, it would seem that toxic, humoral factors may contribute to this lesion, which shows little association with ambient blood pressure levels. However, this problem has yet to be solved.

Summary

A survey is reported of the courses of 84 patients who presented the syndrome of malignant hypertension and who have been under treatment with potent antihypertensive drugs.

Among these, 70 per cent survived 1 year of observation, 50 per cent 3 years, 33 per cent 5 years, and 26 per cent 6 years. These survival rates represent substantial therapeutic gains over survival rates in the untreated series of Keith, Wagener, and Barker.

The reported first-year survival rate is weighted by the untoward complication of hexamethonium pneumonitis, and current survival is greater than in the estimate presented.

Other causes of death are (1) rapidly or (2) delayed or slowly progressive renal failure and (3) complications of atherosclerosis. The first is usually associated with poor control of blood pressure. It seems merely an attenuation of the usual course of malignant hypertension. The syndrome of delayed or slowly progressive renal failure is associated with diffuse occlusive fibrous intimal hyperplasia of major renal arteries. Among the complications of atherosclerosis, cerebral hemorrhage was the most common and was associated with poor control of blood pressure level, while myocardial infarction, the next most common, was not. It may be that the coronary arteries, like the renal, are subject to progressive occlusive disease in some patients with treated malignant hypertension. It is not clear whether this process represents a continuation in vessels larger than arterioles, of a basic vascular disease or a delayed response on the part of the arteries to pre-existing severe hypertension.

Survival is improved in patients who undertake treatment before malignant hypertension has caused extensive vascular damage. Patients who present themselves for treatment with evidences of severe renal damage generally do not survive for long periods. However, several such have maintained active lives for many months and years. Hence treatment should be withheld only in the most desperate circumstances.

Summario in Interlingua

Es reportate un studio del curso clinic de 84 patientes con le syndrome de hypertension maligne, tractate perdurativamente con potent drogas antihypertensive.

Ex le total de 84 patientes, 70 pro cento superviveva 1 anno de observation, 50 pro cento superviveva 3 annos, 33 pro cento superviveva 5 annos, e 25 pro cento superviveva 6
LONTE-TERM TREATMENT OF MALIGNANT HYPERTENSION

annos. Iste cifras de supervivencia representan un considerabile avantiamento terapeutico in comparison con le cifras de supervivencia in le serie de casos non tractate que esseva reportate per Keith, Wagener, e Barker.

Le supra-notate cifra de supervivencia al fin del prime anno es deprimita per le adverse complication de pneumonitis a hexamethonium. Al tempore presente iste cifra esserea plus favorabile.

Causas de morte—altere que pneumonitis—es (1) insufficientia renal a progresso rapide, (2) insufficientia renal a progresso tardive o lente e (3) complicationes de atherosclerosis. Le prime occurre usualmente in association con grados insufficiente de control del pression sanguine. Illo pare esser simplemente un forma attenuate del curso usual de hypertension maligne. Le syndrome de insufficientia renal a progresso tardive o lente es associate con diffuse hyperplasia fibrose occlusive del intima de major arterias renal. Inter le complicationes de atherosclerosis, hemorrhagia cerebral esseva le plus commun e se trovava associate con inadequate control del pression de sanguine, durante que infarcimento myocardial—le proxime in le ordine de frequentia—occurriva sin ille association. Il es possibile que le arterias coronari (como le arterias renal) es susceptibile de disveloppar un progressive morbo occlusive in certe patientes con tractate hypertension maligne. Il non es clar si iste processo representa un continuation—in vasos plus grande que le arteriolas—de un morbo vascular fundamental o si illo representan un responsa tardive, del parte de le arterias, al pre-existente grados sever de hypertension.

Le supervivencia es meliorate in patientes qui recipe tractamento ante que le hypertension maligne ha causate extense damnos vasculare. In general, patientes qui se presentia al tractamento con signos de sever grados de danno renal non supervive longemente. Ta- men, in plus que un tal caso, le patiente ha mantenite un vita active durante multe menses e annos. Per consequente, le non-initiation del tractamento es justificate solmente sub le conditiones le plus desperate.

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