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Discriminant functions in predicting death from renal failure in two hospital populations of primary hypertensives

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by

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To my

Parents

for their love and devotion

and to

Doctor William M. O'Brien

for his inspiration and enthusiasm

I am deeply indebted to many individuals without whose generous assistance this thesis would not exist. Doctors J. Edwin Wood and Carlos R. Ayers provided helpful criticism and patient guidance throughout many long months of toil. Doctor Larry Z. Goss shared with me the trials of investigation and helped make possible the joys of resolution. Doctor William M. O'Brien saved me from despair on so many occasions with his unflagging enthusiasm and continually motivated me with his boundless inspiration. My last debt, however, is to Dr. Roy Acheson whose acumen and vision enabled me to place all in its proper perspective.

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INTRODUCTION

INTRODUCTION

The purpose of this investigation is to establish a method which will enable the physician to predict which individuals afflicted with primary hypertension are likely to die of renal failure with the belief that this knowledge will be of assistance not only in the classification of individuals with hypertension but also in the intelligent choice of therapy. The hypothesis is that primary hypertension destined to terminate in fatal uremia presents a clinical picture sufficiently distinct from primary hypertension terminating in other forms of death to be identified at the time the diagnosis of hypertension is first made.

In order to test this hypothesis, it was first necessary to examine thoroughly the clinical and post-mortem records of a population which suffered from primary hypertension to determine which clinical criteria provided the best means of identifying those individuals who died of renal failure. A discriminant equation, the parameters of which represented the age, systolic blood pressure, heart size, and blood urea of each individual at the time the diagnosis of hypertension was initially made, was derived from one population and proved to be a good means of achieving this identification. It was essential, however, that the prognostic accuracy of this equation be assessed by applying it on a different population of individuals with primary hypertension, and this was done with encouraging results.

REVIEW

REVIEW OF THE LITERATURE

I. Classification of Hypertension:

The classification of hypertension began well over a century ago when Bright first observed the occurrence of contracted kidneys and cardiac hypertrophy in patients with a clinical history of albuminuria and an elevated blood urea:

> I do not...by any means assert, that all the lesions...flow as a consequence from the kidneys alone; but that they are such derangements as generally co-exist with this peculiar disease of that organ....(p. 395)
>
> ...the chemical qualities of the blood are so far changed, that urea is to be detected in that fluid....(p. 395)
>
> ...either the altered quality of the blood affords irregular and unwonted stimulus to the organ [heart] ...or, that it so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant sub-divisions of the vascular system. (pp. 396-7)[1]

Bright concluded that:

> ...the hypertrophy of the heart seems, in some degree, to have kept pace with the advance of the disease in the kidneys.... the hardness and contraction of the kidney bespoke...of a long continuance of the disease...(p. 397)[1]

In the years following Bright's work, Gull and Sutton[2] broadened our knowledge of the pathologic changes

associated with hypertension by describing the vascular alterations seen in Bright's disease, while Mahomed, in 1879, actually implicated high blood pressure as the etiological culprit: "high arterial pressure, and the subsequent cardio-vascular changes are the primary and most important conditions to recognize, while the kidney symptoms are only secondary."[3] As Pickering[4] notes, however, the concept that a form of hypertension might occur independently of nephritis truly became well established with the writings of Huchard[5] and Allbutt[6], among others.

The current classification of hypertension has much of its foundation in the work of Volhard and Fahr who, in 1914, divided renal disease into three categories: nephrosis; nephritides; and arteriosclerotic disease.[7] They noted the association between pure sclerosis of the renal vessels and benign hypertension and also described a sclerotic kidney with necrotic changes compatible with the current concept of the kidney in malignant hypertension. It remained, though, for Klemperer and Otani[8] to stress that the kidneys in this form of hypertension are generally not contracted, for Keith, Wagener, and Kernohan,[9] as well as Ellis,[10] to emphasize the importance of papilledema in the diagnosis of this condition, and for Derow and Altschule[11] to note that malignant hypertension might occur in a variable context: with no evidence

of previously existing hypertension; as the end stage of essential hypertension, with or without uremia; or as the end stage of a miscellaneous group of conditions which might cause secondary hypertension.

Since the work of Volhard and Fahr, progress in the classification of hypertension has involved, for the most part, the discovery of other causes of secondary hypertension, which is defined as hypertension occurring as the manifestation of a known disease.[4] Nevertheless, despite the discovery of causes such as Cushing's syndrome, renal artery stenosis, and primary aldosteronism, the vast majority of cases of hypertension remain of unknown etiology and, hence, are designated as primary, or essential, hypertension.

II. Prognosis of Hypertension:

One of the earliest investigations into the prognosis of hypertension was published in 1913 by Janeway[12] who studied a population of patients, referred to him or his father, over a 9-year period. Janeway concluded that "the most prominent symptoms associated with high blood pressure are circulatory rather than renal" and that the disease underlying high arterial pressure was predominantly a disease of the circulatory system "best designated hypertensive cardiovascular disease."

A. Symptoms:

For Janeway, symptoms played a prominent role in the prognosis of hypertensive cardiovascular disease.

He reported[12] that among his population dyspnea indicated a greater than 50% probability of death by cardiac insufficiency, while "anginoid" pain indicated about a one-third probability of death in an anginal paroxysm. Polyuria, especially nocturnal, and headache, particularly early morning, each indicated about a 50% probability of a uremic death. One of the major difficulties, however, with Janeway's study was that essentially no autopsies were performed, and he, himself, notes that the incidence of uremic deaths is almost certainly too high, with apoplexy being the terminal event in many of these cases. Also, one is uncertain as to how many of his uremic deaths were secondary to nephritis rather than to primary hypertension with severe nephrosclerosis.

In fact, with the possible exception of malignant hypertension, the development of which is frequently heralded by visual impairment[13,14], and severe headaches,[9,13,14] clinical symptoms alone have not generally been found to be very useful for the prognosis of hypertension. Thus, Rasmussen and Bøe[15] concluded that myocardial infarction and uremia were difficult to prognosticate in hypertension as they showed no distinct relation to earlier symptoms in the cardiovascular or renal systems, and Griep *et al*[16] felt that the most significant prognostic factor was the initial presence of vascular disease as manifested by signs and laboratory

tests, rather than symptoms. Nevertheless, Sokolow and Perloff[17] were able to demonstrate some correlation between symptoms such as headaches, nervous tension, and dizziness and overall mortality, though this was felt to be a factor of the associated vascular complications rather than of the symptoms alone. Further, their most impressive correlations were between signs and laboratory tests and overall mortality.

B. Ophthalmologic Findings:

As noted earlier, Keith, Wagener, and Kernohan[9] stressed the importance of papilledema in the diagnosis of the malignant form of hypertension. Somewhat later, in 1939, Keith, Wagener, and Barker[18] devised a classic system for grading the severity of essential hypertension based primarily on the findings on fundoscopic examination which ranged from minimal changes in retinal vessels through compression at arterio-venous junctions to severe sclerosis, hemorrhages, and plaques, and, finally, to edema of the discs. They were able to demonstrate four different survival curves, one for each grade of severity, and the validity of their prognostic system has been reaffirmed by Simpson and Gilchrist[19], by Sokolow and Perloff[17] and, most recently, by Breslin et al[20] who showed that ten and twenty-year survival rates of patients with essential hypertension were both lower than those for the normal population at the same age and correlated well with the Keith-

Wagener-Barker ophthalmologic grouping. They also found this grouping to correlate well with the diastolic blood pressure of their hypertensive patients.

C. Sex:

Another extremely significant contribution to the prognosis of hypertension was the large study of Bechgaard,[21] published in 1946, of over one thousand untreated patients with hypertension seen at a polyclinic in Copenhagen. The vast majority of these patients was in the fifth through the seventh decade of life and was followed initially for up to eleven years. Bechgaard demonstrated unquestionably that men tolerated elevations of blood pressure, both systolic and diastolic, less well than did women. The overall mortality for men was 41% compared to only 22% for women, and the proportion of men dying was greater than women in all age groups. Further, while the mortality for both sexes increased with elevation of the blood pressure, men displayed a large increase in mortality at systolic pressures equal to or greater than 200 mm Hg, but women displayed a similar increase only when systolic pressures equal to or greater than 220 mm Hg were reached. Men also displayed a very high mortality rate at diastolic pressures equal to or greater than 130 mm Hg in contrast to women who had a much lower mortality rate at this level. It is assumed that this decreased tolerance of

men for elevated blood pressures is the reason why the mean blood pressure in old men is somewhat lower than in old women.[22]

This decreased male tolerance for elevated blood pressures is also consistent with Janeway's[12] finding of an average survival time after the onset of symptoms of only 4 years for men and 5 years for women. Moreover, it is in agreement with a greater percentage of male than female deaths among hypertensive patients reported by investigators such as Blackford et al[23] and Rasmussen and Bøe.[15] This sex intolerance has more recently been confirmed by Breslin et al[20] who demonstrated that women survived longer than men in each ophthalmologic grade, though there is some evidence to suggest that the mortality rates for the sexes tend to equal each other in the more severe grades.[17,24,25] A general male intolerance to elevated blood pressure greater than the female intolerance has, of course, been reported by numerous other investigators[16,19,26,27] since Bechgaard and may, in part, be attributable to the increased incidence of the malignant phase of hypertension[9,13,17,28,29] as well as coronary artery disease in men.[30]

D. Age:

As Pickering[4] notes, almost all investigators are agreed that essential hypertension is a disease of middle age or later. It would be expected, therefore, that hypertension presenting at a relatively young age might have a

poorer prognosis[21,25,26] than hypertension appearing later in life for several reasons. First, hypertension in a young person has a relatively greater likelihood of being secondary hypertension with either primary renal disease or hormonal secreting tumors, for example, as the etiology. Also, one might expect that a young person presenting with symptoms referrable to hypertension already has a rather serious degree of systemic involvement. A third factor, however, which worsens the prognosis of hypertension appearing at an early age is that it might be malignant hypertension which has an earlier age of onset than does benign hypertension, a fact reported by virtually every investigator in this field.[8,9,10,13,18,21,28,31] An additional explanation for findings such as Bechgaard's[21] that while the excess mortality rate for patients with hypertension, compared to the Dutch population as a whole, was 143% for women and 288% for men, the mortality was highest in the younger age groups and diminished with advancing age is Pickering's[4] suggestion that this is a consequence of the tendency for arterial pressure to increase with age in the population at large.

E. Height of Blood Pressure:

Janeway[12] concluded that systolic blood pressures above 160 mm Hg were always pathological, though he suspected that some day 150 mm Hg would be considered the

upper limit of normal. Nonetheless, the relationship between the height of the blood pressure and the prognosis remained doubtful to him though, in his population, a systolic pressure well above 200mm Hg tended to augur death from uremia or apoplexy. Rasmussen and Bøe,[15] recording pressures obtained after eight to fourteen days of rest, found that nearly one-third of their patients with systolic pressures greater than 200mm Hg and more than one-third with diastolic pressures greater than 125mm Hg died of apoplexy. Bechgaard,[21] reported an increase in the overall mortality rate with elevations of both the systolic and diastolic blood pressure, with the aforementioned sexual differences, and Leishman[27] concluded that an elevated diastolic pressure was an unfavorable prognostic sign. Also, Sokolow and Perloff[17] demonstrated an increase in mortality rate with increasing levels of both systolic and diastolic blood pressure, though Griep *et al*[16] felt that an elevated blood pressure, *per se*, without evidence of hypertensive complications, had little effect on the prognosis. The latter group of investigators were also unable to correlate elevations of blood pressure with apoplexy. In general, then, it is fair to say that severe elevation of blood pressure is associated with decreased survival time but has a questionable relationship to the actual cause of death.

F. Cardiac and Renal Status:

1. Cardiac Enlargement and Left Ventricular Hypertrophy: The estimation of the prognosis of hypertension on the basis of clinical signs and laboratory findings pertaining to cardiac and renal status has, in general, been more fruitful than has the application of clinical symptoms, such as dyspnea or polyuria, for this purpose. Thus, Janeway[12] noted that a very high percentage of his deceased patients had evidence of cardiac enlargement on physical examination, and Rasmussen and Bøe[15] found that mortality, especially from cardiac insufficiency and to a lesser extent from myocardial infarction, rose considerably with increased heart size, as demonstrated by roentgenology. Mortality rates from cardiac insufficiency also seemed related to the degree of left ventricular hypertrophy, by electrocardiographic criteria, in their study. Bechgaard[21] employed roentgenologic evaluation of cardiac size and electrocardiographic evidence of cardiac damage in a very general manner in estimating prognosis in his study. Griep et al[16] found a higher mortality among patients with roentgenologic evidence of cardiac enlargement and among patients with either left axis deviation or T-wave inversions on the electrocardiogram but was unable to correlate these findings with any particular cause of death. Leishman,[27] however, concluded that strain patterns on the electrocardiogram did not appear to influence the

prognosis. Simpson and Gilchrist[19] reported that T-wave abnormalities indicated a worse prognosis.

One of the best studies of the effect of cardiac status on the prognosis of hypertension, however, was that of Sokolow and Perloff.[17] They placed cardiac enlargement, on the basis of roentgenology, into four grades according to the percent enlargement and found the difference in mortality between successive grades of enlargement to be highly significant ($p < 0.001$), with a greater mortality for men than women only in the first grade of enlargement. There was no significant sex difference in mortality rates for the higher grades of enlargement though the mortality rate for both sexes increased with each grade of enlargement. Electrocardiographic evidence of left ventricular hypertrophy was also placed into four grades of increasing severity with significant differences in mortality rates observed between the normal electrocardiogram and grades I and II, combined, and grades III and IV, combined. Again, lower mortality rates for women were observed only for the mildest degrees of hypertrophy. These investigators did not correlate a particular cause of death with cardiac status alone, however.

2. Abnormal Renal Function: Abnormal renal function is generally considered to be an ominous sign in the prognosis of hypertension since it may herald the arrival

of malignant hypertension, may represent primary renal disease, or may bespeak the severity of nephrosclerosis or the presence of cardiac failure. Several investigators[8,14,32] have documented the almost universal presence of persistent or moderate proteinuria with malignant hypertension. Rasmussen and Bøe[15] reported that those patients with persistent proteinuria showed a considerably increased mortality rate, especially from apoplexy and cardiac insufficiency, while those with only transient proteinuria and those without proteinuria had virtually identical mortality rates. Interestingly, though, they found no significant increase in mortality rate for those patients with a decrease in urea clearance. Leishman[27] found that persistent and/or moderate proteinuria foreshadowed death from uremia or cerebrovascular accident, and Griep et al[16] and Simpson and Gilchrist[19] concluded that proteinuria was an ominous sign. The latter group also demonstrated that a decrease in the urine urea concentration indicated a poor prognosis for women, while Sokolow and Perloff[17] found that impaired renal function secondary to arteriolar disease was associated with a very high mortality rate.

G. Multiple Parameters:

In an attempt to improve the accuracy of prognosis in hypertension, some investigators have employed systems in which patients are grouped into different categories

on the basis of the severity of involvement of more than one organ system. Thus, Palmer et al[31] grouped patients into four categories according to clinically recognizable changes in the fundi, heart, and kidneys, with placement determined by the most severe changes whether in one or more systems. They found that the mortality rose significantly with the different categories of severity over an eight-year period.

More recently, Sokolow and Perloff[17] employed degrees of elevation of both systolic and diastolic pressure, fundal changes, electrocardiographic changes, and cardiac enlargement, as evidenced by roentgenologic examination, with the most severe degree of involvement in any system determining the ultimate grade, to classify their patients for the purpose of prognosis. A progressive rise in 5-year mortality was observed between each successive grade of severity. The only association between grade of severity and cause of death, however, was that those patients in the two lowest grades of severity seemed more prone to "atherosclerotic" causes of death, by which term they were evidently referring to lesions such as coronary thrombosis, cerebrovascular accident, and dissecting aneurysm, as well as to non-cardiovascular causes of death. Those patients in the two highest grades of severity seemed prone to both "atherosclerotic" and "hypertensive-related" causes of death. The latter term evidently referred to conditions such as uremia, cardiac failure, and malignant

hypertension. Unfortunately, the precise definition of terms is unclear. Also, most of their information regarding causes of death was derived from death certificates and reports from physicians, casting the validity of some of their conclusions in this area into doubt.

H. Treatment:

One of the finest studies of the effect of medical treatment on the prognosis of hypertension is that of Smirk[33] who discovered that the 5-year mortality among adequately treated hypertensive patients with either grade I or II (Keith-Wagener-Barker) fundal changes was reduced considerably below that of hypertensive patients with either comparable or milder degrees of involvement who remained untreated. Further, the degree of reduction in the mortality was greater when the basal blood pressure was high than when it was only moderately elevated. Another study attesting to the efficacy of treatment in improving the prognosis of hypertension is that of Leishman[27] who found that in benign hypertension the mortality rate among treated patients was in no instance appreciably more than one-third that of the untreated cases.

Treatment has also been found to alter the relative frequency of the causes of death in hypertension. Leishman[27] reported a notable decrease in death due to cerebrovascular

accident and uremia in treated patients compared to his control group, though the average duration of therapy for the group receiving medical treatment was only 3 years and 9 months. Hood et al[34] reported that congestive failure as a cause of death dropped to an insignificant position among treated patients while the case fatality rate from myocardial infarction and cerebrovascular accident remained essentially unchanged. Finally, Smirk and Hodge[35] reported a very sharp decline in mortality from congestive heart failure and almost a three-fold increase in mortality from coronary artery disease and sudden cardiac death in their treated group of hypertensive patients compared to their untreated group. Also, death from cerebrovascular accident showed a modest decline among the treated patients. Interestingly, the mortality from uremia showed a slight decline in the group under treatment from 1959 to 1961 compared to the control group (1950-1958). When the data for the treated group from 1950 to 1958 are analyzed, however, the mortality from uremia is actually increased compared to the control group for the same years. Since the group of treated patients from 1959 to 1961 included several hundred patients who were also in the treated group from 1950 to 1958, it is possible that the mortality from uremia is lower in this later group because many of the patients died in the years from 1950 to 1958 of this disease.

In all of these studies, especially that of Smirk and Hodge, the percentage of deceased patients actually coming to autopsy was relatively low which creates certain difficulties in interpreting the results of these studies. For example, while it is true that a necropsy properly done provides a catalogue of the diseases with which a person dies rather than an indictment of the actual cause of death, it is often extremely difficult to determine, solely from clinical evidence, whether or not a uremic death has been hastened by a cerebrovascular accident. It is also rather difficult, at times, to determine whether or not severe cardiac failure is the result of myocardial infarction or results solely from the effects of prolonged or severe hypertension. In general, however, the consensus seems to be that medical treatment not only has increased the survival time of patients with hypertension but also has lowered the proportion of deaths due to congestive heart failure. It has either increased or left unchanged the proportion of deaths due to coronary artery disease.

I. Race:

Finally, some comments are in order concerning the relationship between the Negro and hypertension. It is a fairly well established fact that Negroes in the United States have higher blood pressures, both systolic and

diastolic, than do whites.[36,37,38] It has also been established that the prevalence of hypertension is twice as great in the Negro as the white population[39] and that the likelihood of finding hypertensive heart disease associated with definite hypertension is greater for Negro than for white persons.[39] Also, the Negro death rate from hypertension, with or without mention of heart disease, is higher than it is for whites for every age group between 20 and 84.[40]

METHODS

METHODS

I. Derivation of Discriminant Equation:

A. Selection of Population:

1. Comparison Group:

Postmortem records from the University of Virginia Hospital of 250 patients dying consecutively in the years 1960 through 1967 who had the clinical diagnosis of primary hypertension, defined as a persistent elevation of the systemic blood pressure without evident cause[4] and without papilledema, attached to their necropsy reports were carefully studied. Each record was examined for information concerning the age at death, cause of death, the weight and appearance of the kidneys and the heart (including the proximal 2 cm. of the ascending aorta), and the left ventricular thickness. Review of these records revealed that 7 patients had lesions suggestive of inflammatory kidney diseases (e.g. pyelonephritis or glomerulonephritis). Since it was felt that these diseases represented clinically diagnosable causes of secondary hypertension, all 7 patients were removed from the study, leaving 243 patients (see Table 1). Further, none of these remaining patients had evidence of

fibrinoid necrosis on renal section.

Of the 243 remaining patients, the clinical records of 85 patients were either lost or incomplete to the extent that it was impossible to verify the diagnosis of hypertension.These 85 patients were, therefore, removed from the study, leaving 158 patients, 20 of whom died of renal failure. The 138 patients with primary hypertension who died of other causes form the comparison group for this study (see Table 1).

2. Case Group:

The postmortem records of an additional 20 patients dying consecutively in the years 1960 through 1967 who had only the clinical diagnosis of uremia, not primary hypertension or any other renal disease, attached to their necropsy reports were also carefully studied in the manner described above. None of these 20 patients had lesions suggestive of inflammatory kidney disease or of any other causes of secondary hypertension or renal failure on review of these records, nor was there any evidence of fibrinoid necrosis. Review of their clinical records revealed that 16 of these 20 patients had a history of hypertension without papilledema. These 16 patients were combined with the 20 patients dying of renal failure described above to form the case group of 36 patients with primary hypertension who died of renal failure (see Table 1).

B. Clinical Observations:

Clinical histories taken at the time when the diagnosis of hypertension was made at the University of Virginia Hospital were carefully examined for information concerning systemic blood pressure, heart size, blood urea, and blood creatinine levels, body bulk, and age. Age, when recorded, represented the age of only those patients who had no known previous history of hypertension prior to evaluation at this hospital. It was, therefore, the patient's age when his hypertension was initially discovered. This age is referred to in this study as the age at onset.

Hypertension was considered present when a diastolic pressure equal to or greater than 90 mm Hg was recorded on at least two occasions or a diastolic blood pressure equal to or greater than 95 mm Hg was recorded on one occasion. Multiple readings, when recorded at the time of diagnosis, were averaged.Heights and weights were used as a basis for calculating the ponderal index (height in inches/cube root of weight in pounds). Blood urea and blood creatinine were determined by the methods of Skeggs[41] and Chasson et al,[42] respectively. Cardiac-thoracic ratio (widest transverse diameter of the heart/widest transverse diameter of the thoracic cavity taken just above the level of the dome of

the diaphragm), a fair estimate of heart size, was measured only from large upright chest films taken during full inspiration.

It should be noted that virtually all the patients in this study, both those dying of renal failure and those dying of other causes, received various forms of medical therapy, often quite vigorous, for their hypertension. Treatment was, of course, prescribed on an individual basis and ranged from dietary control, salt restriction, and mild sedation to the use of diuretics, Rauwolfia alkaloids, and ganglionic-blocking drugs. Specific antihypertensive medication was administered to the great majority of the patients with only a few patients being treated solely by dietary control and salt restrictions.

C. Discriminant and Regression Analysis:

For all the variables measured, means and standard deviations were calculated. The significance of differences between means was tested by the student's t-test. An analysis of the clinical variables collected on the 2 groups was performed to determine which combination of clinical variables best separated those patients dying from renal failure from those dying of other causes, leading to the development of a discriminant equation[43] which described the manner in which this separation was achieved. Simple regression analyses[44]

were calculated using heart weight and kidney weight respectively as dependent variables and several clinical variables as independent variables to determine which of these clinical variables were the most effective predictors of cardiomegaly and renal atrophy. Since the techniques of both discriminant and regression analysis require that all the data on each variable be present, cases with any missing observations were discarded for that particular analysis. The numbers of patients actually used in the analyses are indicated in the appropriate tables. The occurrence of missing data in the patients' charts had no obvious pattern, so it is hoped that the omission of patients with incomplete data in these analyses will not introduce any bias.

II. Application of Discriminant Equation to a Second Population:

A. Selection of Population:

1. Comparison Group:

Subsequent to the derivation of a discriminant equation based on the population at the University of Virginia Hospital, an attempt was made to apply this equation to the clinical variables derived from a different population of patients, all of whom suffered from primary hypertension, in order to determine how accurately it would predict those patients destined to die of renal failure and those destined to die of other causes.

The clinical records of 300 patients consecutively admitted to, dying in, and autopsied at the Yale-New Haven Hospital from 1956 to 1966 who had a clinical diagnosis of primary hypertension were carefully examined to determine which patients actually had the diagnosis of hypertension made for the first time at this hoepital, or were referred to it untreated within 2 weeks after their own physician initially made this diagnosis. Only 52 patients actually satisfied this criterion (see Table 2). The other 248 patients had a history of hypertension prior to evaluation at this hospital and, because this made them incomparable with the series from the University of Virginia Hospital, they were excluded from the study. The hospital records were carefully reviewed for these remaining 52 patients for information regarding cardiac-thoracic ratio, blood urea level, systolic pressure, and age all at the time the diagnosis of hypertension was initially made.

Of these 52 patients, chest x-rays were not available for 12 patients and not taken for another 6 patients at the time the diagnosis was made. Of the remaining 34 patients, 6 did not have blood drawn for urea estimation at the time the diagnosis was made, and autopsy reports were not available for another 4 patients.

Postmortem records of each of the 24 remaining patients

were carefully studied with the intention of excluding any patients with evidence of inflammatory kidney disease, any other lesion capable of causing secondary hypertension, or fibrinoid necrosis. No such evidence was found for any of these 24 patients. Further, none had a clinical history of papilledema.

Of these 24 patients, 5 died of renal failure. The remaining 19 patients with primary hypertension first diagnosed at this hospital and with all of the above mentioned clinical data recorded at the time of the diagnosis died of other causes and form the comparison group for application of the discriminant equation. (see Table 2)

2. Case Group:

The clinical records of 58 patients consecutively admitted to, dying in, and autopsied at the Yale-New Haven Hospital from 1956 to 1966 who had a clinical diagnosis of uremia but who had no mention of the diagnosis of hypertension on the headsheet of their hospital chart were also carefully studied to determine which of these patients fit all of the previously mentioned criteria for the comparison group, save that they died of renal failure. Of these 58 patients, 14 had no previous history of hypertension while 36 had either a history of hypertension prior to evaluation at this hospital or a clinical history of inflammatory renal disease. The remaining 8 patients had a clinical history of hypertension which was first evaluated at this hospital and

had no clinical history of either inflammatory renal disease or papilledema. Chest x-rays taken at the time hypertension was initially discovered were obtained for 6 of these 8 patients. The films of 2 patients were unavailable, as were the autopsy reports of 2 other patients. The remaining 4 patients had all of the clinical variables which were recorded for the comparison group available, and all were recorded at the time hypertension was first discovered.

The postmortem records of each of these 4 patients were then carefully studied for further evidence of inflammatory renal disease, causes of secondary hypertension, and fibrinoid necrosis. No such evidence was found. These 4 patients were combined, therefore, with the 5 patients who died of renal failure mentioned under the selection of the comparison group. These 9 patients, all of whom had primary hypertension first discovered at this hospital, had all of the pertinent data recorded at the time this hypertension was discovered, and died of renal failure, form the case group for application of the discriminant equation. (see Table 2)

B. Clinical Observations:

As previously noted, information regarding systolic blood pressure, blood urea level, cardiac-thoracic ratio, and age, all recorded at the time hypertension was initially discovered in each of the 19 patients in the comparison group and the 9 patients in the case group, was obtained for each of the 28 patients. The same criteria for defining hyper-

tension in the study performed at the University of Virginia Hospital were employed in this study, as well. Multiple readings at the time the hypertension was discovered, when recorded, were averaged, and the cardiac-thoracic ratio was derived in the manner previously described. Prior to April, 1959, the non-protein nitrogen level was measured at the Yale-New Haven Hospital.[45] This value was converted to the blood urea by multiplying it by a factor of 0.9.[46] After April, 1959, the blood urea nitrogen level was measured,[47] and this value was converted to the blood urea by multiplying it by a factor of 2.1.[46] Means and standard deviations were calculated for each of the clinical variables.

C. Application of the Discriminant Function Equation:

The systolic blood pressure, age, blood urea, and cardiac-thoracic ratio, all at the time the diagnosis of hypertension was initially made, were then entered into the discriminant equation derived from the population at the University of Virginia Hospital for each of the 28 patients in the population at the Yale-New Haven Hospital. A discriminant score for each patient was then calculated, and its effectiveness in predicting those patients who were to die of renal failure examined.

RESULTS

RESULTS

I. Derivation of Discriminant Equation - University of Virginia Hospital:

A. Population:

The entire population in the study performed at the University of Virginia Hospital consisted of 174 patients, all of whom suffered from primary hypertension. Classification by race and sex is found in Table 3. Negroes, both male and female, constituted the largest segment of the 36 patients who died of renal failure (72.2%), while white females comprised the smallest segment of those dying of renal failure (8.3%). Among those patients who died of other causes, there was a slight predominance of whites (53.6%), though white females again constituted the smallest segment(18.8%).

B. Causes of Death:

The causes of death in the comparison group are listed in Table 4. The major cause of death in this group was cerebrovascular accident (73). Fifty-three patients died of cerebral hemorrhage and 20 succumbed to cerebral infarction. Only a slightly greater proportion of Negro than white deaths were associated with a cerebrovascular accident. Myocardial infarction was the second most common cause, accounting for 29 deaths, 20 of which were of white patients. Congestive

heart failure and very severe diabetes mellitus (with gangrene and sepsis,or ketoacidosis) each accounted for 16 deaths, though 13 other patients had mild diabetes; aortic aneurysms were responsible for 13 deaths. Interestingly, 11 of these 13 deaths were of white patients. Chief among the other causes of death were pulmonary emboli (4), septicemia (3), cardiac arrhythmia (3), and mesenteric artery thrombosis (2). In addition to these, 12 other causes of death were discovered and are listed in Table 4. In several cases, multiple causes of death were listed for patients in this comparison group.

Renal failure was unquestionably the cause of death in each of the 36 patients in the case group. In several cases, however, other conditions were associated with death from renal failure, and these are listed in Table 5. The most commonly associated conditions, especially among Negroes, were congestive heart failure and diabetes mellitus. Nonetheless, in each case congestive heart failure developed subsequent to the onset of uremia; none of the patients in the case group with diabetes mellitus had evidence of Kimmelstiel-Wilson lesions on renal section.

C. Pathologic Data:

Examination of the pathologic data for those patients dying of renal failure revealed striking and significant dif-

ferences with regard to age at death, heart weight, and kidney weight when compared to the comparison group (see Table 6). Those persons dying of renal failure died 10 years younger than did those dying of other causes. The mean age at death for the renal failure group was 52 years, while for the comparison group it was 62 years ($t=4.35$, $p<0.001$). An analysis of the age at death according to decades for both groups is presented in Table 7. While the youngest age at death was in the comparison group, 24 years old compared to 31 years old in the case group, 27 patients (75%) of the case group had died of renal failure by the age of 59 contrasted to only 60 patients (43%) of the comparison group who had died of other causes by this age. The oldest age at death in the case group was 72 (2 persons), while in the comparison group one patient lived to 90 and 7 died in the ninth decade.

While both groups demonstrated substantial cardiac hypertrophy (the mean heart weight of the entire population was 524 Grams), those dying of renal failure had a much greater degree of hypertrophy (see Table 6). The mean heart weight of the renal failure group was 607 Grams, while of the comparison group it was 503 Grams ($t= 3.96$, $p<0.001$). The lightest heart in the renal failure group weighed 350 Grams compared to 275 Grams among those patients dying of other

causes. Further, while 79% of those dying of renal failure had hearts weighing 500 Grams or more, only 51% of the comparison group had hearts weighing 500 Grams or more (see Table 8). The heaviest heart in each group weighed 900 Grams.

The last substantial difference between these 2 groups was the weight of the kidneys which averaged 112 Grams for the renal failure group and 150 Grams for those dying of other causes ($t = 4.24$, $p < 0.001$; see Table 6). The kidneys of those patients dying of renal failure were generally contracted and shrunken grossly with a granular appearance. Microscopic examination revealed evidence of arteriolar nephrosclerosis in all cases, but in none was there evidence of fibrinoid necrosis.

The thickness of the left ventricle was also measured in both groups. The mean was 19mm for the renal group and 17 mm for the comparison group. Because of the possibility of slight inconsistencies in measurement, however, it was felt that not too much importance could be attached to this difference.

D. Clinical Data:

An examination of the clinical variables (see Table 9) also reveals important differences, especially with regard to the age at onset, initial systolic blood pressure, initial cardiac-thoracic ratio, and initial blood urea level

between the group dying of renal failure and the group dying of other causes. An analysis of some of these clinical variables within the entire population, according to race and sex, is also provided in Table 10.

The mean age at onset of hypertension, that is, when the diagnosis was first made, was 46 years for the renal failure group and 54 years for the comparison group ($t = 3.20$, $p < 0.001$). Of the renal failure group, 54% had the diagnosis of hypertension first made prior to age 50 as contrasted to only 34% of the comparison group (see Table 7). The youngest age at which the diagnosis was made was 26 years among those dying of renal failure; the oldest age was 63 years. Among those dying of other causes, the youngest age at which the diagnosis was made was 23 years; the oldest was 84 years.

The mean initial systolic blood pressure for the renal failure group was 212 mm Hg, while for the comparison group dying of other causes it was 190 mm Hg ($t = 2.80$, $p < 0.003$). White patients dying of renal failure had a somewhat higher mean initial systolic blood pressure (223 mm Hg) than did Negroes (208 mm Hg), though in the group dying of other causes the mean values of the 2 racial groups were virtually identical. Also, the mean initial systolic blood pressures of white and Negro patients in the entire population were virtually identical, though females, as a whole, had a

somewhat higher mean value than did males (see Table 10).

The mean initial cardiac-thoracic ratio was 58% for the renal failure group but only 53% for the comparison group ($t = 2.51$, $p < 0.008$). Negroes, in both the case and comparison groups had a greater mean value for this variable than did whites. In the entire population, females had a greater mean initial cardiac-thoracic ratio than did males (see Table 10).

The mean initial blood urea for the renal failure group was 135 mg/100 ml, while for the comparison group it was 45 mg/100 ml ($t = 5.95$, $p < 0.001$). White patients had a higher mean initial blood urea than did Negroes in the renal failure group, though in the comparison group the difference was quite small. Also, the mean initial blood urea was higher for males than for females (see Table 10). The mean of the highest recorded blood urea in each patient at any time since the initial diagnosis of hypertension and the mean of the last recorded blood urea were 489 mg/100 ml and 465 mg/100 ml, respectively, for the renal failure group, as contrasted to 94 mg/100 ml and 72 mg/100 ml, respectively, for the group dying of other causes.

Blood creatinine was also recorded, but the number of people with this information was much smaller in the comparison group since this test was generally performed only when renal

malfunction was suspected. Ponderal indices were calculated whenever both height and weight were recorded in the charts, but no substantial difference between the two groups was observed (see Table 9).

There was also no substantial difference between the mean initial diastolic blood pressure of the renal failure group, which was 119 mm Hg, and the comparison group, which was 113 mm Hg. This statement holds true when both these groups were separated by race, as well (see Table 9). Further, there was no difference between the sexes in the population as a whole for this value (see Table 10).

Finally, duration of the illness from the time the diagnosis of hypertension was first made was calculated. It was shown that the renal failure group, though at a younger mean age at the time of diagnosis, lived for an average of only 5.0 years after the diagnosis was made, while, on average, the comparison group succumbed 7.5 years ($t = 2.07$, $p < 0.03$) after the diagnosis. Interestingly, white patients who died of renal failure survived for an average of only 2.3 years, while Negro patients survived for 5.8 years. Among the comparison group, however, the average duration after the time of diagnosis of hypertension for white and Negro patients was essentially identical, 7.4 and 7.6 years, respectively (see Table 9). Also, in the population as a whole males and females had essentially identical average durations of 7.0 and 6.8 years, respectively.

E. Derivation of Discriminant Equation from Clinical Data:

No single clinical variable clearly separated those who died of renal failure from the rest of the population. For example, although the blood urea was much higher in the renal failure group, it was also quite elevated in many of the patients in the comparison group. Since many of the variables are intercorrelated, the impact of all the variables taken together is difficult to assess. Discriminant analyses using several different combinations of the clinical variables were, therefore, performed on those patients on whom complete data was available to determine whether the 2 groups could be more clearly differentiated on the basis of optimally weighting the clinical variables obtained at the time the diagnosis was first made.

In discriminant analysis a single score is given to each patient and this score is a measure, in terms of the factors studied (the clinical variables in this instance), of the likelihood that a given patient will die of renal failure rather than of some other cause. The different factors are weighted in such a manner as to produce as small a range of scores as possible within each of the 2 groups and as little overlap as possible between the 2 groups. The efficiency of the discriminant score for selecting those who will die of renal failure from those who will die of other

causes diminishes, therefore, the more the scores for the 2 groups overlap.[48] The best discriminant analysis is shown in Table 11. Although only 49 cases (14 from the group dying of renal failure and 35 from the group dying of other causes) with complete data for all of the variables used in this analysis were available, the results were highly significant.

Each of the 4 clinical variables (initial blood urea, age at onset, initial cardiac-thoracic ratio, and initial systolic blood pressure) contributed in varying degree to the differentiation of the renal failure group from the comparison group, but it can be seen that the greatest discrimination was made by the blood urea. The F ratio for the discriminant function was 12.02 ($p < 0.001$), indicating the differences in the discriminant scores could hardly have occurred by chance.

This discriminant equation was then applied to the original data for the purpose of determining how well it could actually discriminate the renal from the comparison group. As is the usual custom, the discriminant co-efficients (see Table 11) were multiplied by a constant (in this case, 1000) to avoid using cumbersome decimals, and the simplified equation actually employed was:

D= -1.5 (age at onset) + 3 (initial cardiac-thoracic ratio) + 0.5 (initial systolic blood pressure) + 1 (initial blood urea)

Note that age at onset has a negative coefficient since

older people tended to die of other causes. The other three variables have positive coefficients since they tended to favor death from renal failure. The coefficients, then, are essentially an optimal mathematical estimate of how much each piece of initial clinical information should be weighed, and the advantage of using a discriminant score is that several clinical variables and their complex interrelations are reduced to a single number.

The discriminant scores for the renal failure group ranged from 221 to 471 (mean, 325; S.D. = 75.6), while the comparison group scores ranged from 134 to 287 (mean, 216; S.D. = 32.1). Thus, in these patients if the score was less than 221, the patient was certain to die of other causes, and if the score was greater than 287, the patient was certain to die of renal failure.

With scores in the range of 221 to 287, a definite prognosis could not be made, but the clinician could clearly indicate the uncertainty of his prediction. At a score of 230, one-third of the patients would die of causes other than renal failure, while at a score of 250 this would be true of only 14%, and at a score of 275 of only 3%. The minimum misclassification was at a cutoff point of 249, where 15% of those patients with scores above 249 died of other causes, and 15% with scores below 249 died of renal failure. (This point is usually obtained by bisecting the Mahalanobis distance

between populations,[49] but in this case, since the variances of the 2 groups were different, the point was obtained by working directly with the standard deviations of the 2 groups).

F. Regression Analysis:

Regression analysis was also performed, using the initial systolic and diastolic blood pressure, systemic pulse pressure, mean arterial pressure, blood urea, cardiac-thoracic ratio, and the duration of the hypertension from the time of the initial diagnosis in attempts to predict the final kidney weights and heart weights. The best fit for a single independent variable was found to be an inverse relation between the initial systolic blood pressure and the mean kidney weight at autopsy, although a wide initial pulse pressure also tended to indicate that the terminal kidney weight would be low (see Table 12). A summary of the other regression results is provided in Tables 13 and 14.

II. Application of Discriminant Equation - Yale-New Haven Hospital:

A. Population:

The entire population collected from Yale-New Haven Hospital consisted of 28 patients, all of whom suffered from primary hypertension. Of this population, 9 patients diedof renal failure and 19 died of other causes. Classification by race and sex is provided in Table 15. White females and Negro males constituted the larges segment (77.7%) of those patients ultimately dying of renal failure, while whites,

both male and female, comprised the largest segment (84.2%) of those patients ultimately dying of other causes.

B. Causes of Death:

The causes of death among those patients not dying of renal failure are listed in Table 16. Again, cerebrovascular accidents were the most frequent cause of death though only 5 patients died from this. Four patients died of myocardial infarction, and pneumonia and pulmonary embolus each claimed 2 lives.

Renal failure was the cause of death in 9 patients. Postmortem examination again revealed kidneys which were generally contracted and shrunken with granular appearance on gross inspection. Microscopic inspection revealed evidence of arteriolar nephrosclerosis in each case, but no evidence of fibrinoid necrosis. The mean weight of the kidneys of those dying of renal failure was 86 Grams as contrasted to 131 Grams for those dying of other causes.

C. Clinical Data:

A summary of the clinical data used in the discriminant equation for the group dying of renal failure and the group dying of other causes is presented in Table 17. The mean systolic blood pressure at the time the diagnosis of hypertension was first made was 212 mm Hg for those patients who ultimately died of renal failure and only 183 mm Hg for

those who eventually died of other causes. The average age at which the diagnosis of hypertension was first made was only 45 years for those dying of renal failure, but was 66 years for those dying of other causes. The initial blood urea was 100 mg/100 ml for those dying of renal failure and 35 mg/100 ml for those dying of other causes. The initial cardiac-thoracic ratio was 53% for patients dying of renal failure, and 51% for those dying of other causes. Finally, the average age at the time of death was 46 years among those dying of renal failure and 71 years among those dying of other causes.

D. Discriminant Scores and Accuracy of Prediction:

The discriminant equation derived from the clinical data of the patients at the University of Virginia Hospital was then applied to the above mentioned clinical data obtained from the population of patients with primary hypertension at the Yale-New Haven Hospital. The discriminant scores calculated both for those patients dying of renal failure and those dying of other causes are listed in Table 18. The discriminant scores for those dying of renal failure ranged form 176.5 to 456.0 (mean, 297.6; S.D.= 89.9). The discriminant scores for those dying of other causes ranged from 144.2 to 273.0 (mean, 181.4; S.D.= 27.7).

Of the 9 patients who ultimately died of renal failure,

2 had discriminant scores less than 249 (176.5, 224.0) and would, therefore, have been predicted incorrectly to die of other causes. Of the 19 patients who ultimately died of causes other than renal failure, only 1 had a discriminant score greater than 249 (273.0) and would, therefore, have been predicted incorrectly to die of renal failure. The expected number of misclassifications (based on the 15% misclassification observed in the population at the University of Virginia Hospital at the cutoff of 249) in the group dying of causes other than renal failure was 3. The expected number of misclassifications in the group dying of renal failure was 1. The false negative ratio for those predicted to die of renal failure was 2/9 or 22%, whereas the false positive ratio was 1/19 or 5.3% (see Table 19). Another manner of expressing the prognostic accuracy of the discriminant equation is depicted in Table 20. When the patients were ranked into tertiles of discriminant score, it was found that 8 of the 9 patients in the lowest tertile died of other causes while all 10 of the patients in the middle tertile died of other causes. In the highest tertile, 8 of the 9 patients died of renal failure.

DISCUSSION

DISCUSSION

I. Discussion of Methods:

The basic goal in choosing the populations, both for the study at the University of Virginia Hospital and at the Yale-New Haven Hospital, was to select those patients who suffered from primary hypertension and whose cause of death could be documented as accurately as possible. In order to avoid including any patient with a lesion capable of causing secondary hypertension, the post mortem record of each patient in the study had to be carefully reviewed. It is quite possible, however, that the kidneys of a patient with either chronic glomerolonephritis or chronic pyelonephritis might be very difficult to distinguish from those of a patient with only primary hypertension and renal failure. Therefore, the clinical record of each patient was also carefully reviewed to avoid including any patient in the study with a history of inflammatory kidney disease. Nevertheless, it is still possible that a patient with chronic asymptomatic urinary tract infection would have escaped such scrutiny and have been included in the study.

With regard to the measurement of the clinical variables which made up the parameters used in the discriminant analysis,

a few words are in order. While it is probably true that the cardiac-thoracic ratio is a rough and often inaccurate estimate of the presence of cardiac enlargement,[50] it is a simpler, more reproducible measurement than many of the other methods available. Also, there appeared to be a rather good association between the cardiac-thoracic ratio and the degree of cardiac enlargement found at postmortem examination, since the renal failure group had both a significantly greater mean heart weight ($p < 0.001$) and a significantly greater mean cardiac-thoracic ratio ($p < 0.008$) than did the comparison group. Nonetheless, it is true that regression analysis failed to demonstrate a very close fit between heart weight and initial cardiac-thoracic ratio (see Table 14). Similarly, the blood creatinine would have been a more specific and a more sensitive index of renal function than the blood urea,[51] but the fact that the blood creatinine was initially measured in only 9 patients in the comparison group at the University of Virginia Hospital precluded its use. Further, the blood urea did provide the greatest discrimination among the variables used in the discriminant equation (see Table 11).

The majority of the blood pressures recorded in this study were taken only once during the initial examination, though multiple readings were averaged when they were recorded.

In the light of recent information suggesting that Negroes demonstrate a greater decline on subsequent readings of blood pressure than do whites[36], it is possible that the mean blood pressures in this study, especially of Negroes, are biased toward higher values.

With regard to the actual age at onset of hypertension, it is, of course, quite impossible to determine this with any great accuracy retrospectively. Hypertension is initially discovered either when it becomes symptomatic or fortuitously on physical examination. The term "age at onset" has been arbitrarily defined as the patient's age when the diagnosis of hypertension was initially made, and it is a necessary concept in this study to insure that the other clinical parameters are all measured at a comparable time in each patient's course. This is not to say by any means that all of the patients presented for evaluation at the same stage in the course of their disease. The majority of the patients from both hospitals had their hypertension discovered when they became symptomatic and sought medical aid, but presumably both the threshold for, and the tolerance of, symptoms varies from one patient to another. Also, by choosing only those patients evaluated for the first time for hypertension at either hospital for inclusion into discriminant analysis, the effect of medical treatment on the parameters being

measured was excluded. Patients being hospitalized in the terminal stages of hypertensive cardiovascular disease were excluded, for the most part as well, by this method, for it would be of questionable validity to derive a means for predicting those patients destined to die of renal failure predominantly by analyzing patients already in florid uremia.

What has been attempted, then, is to predict who such patients will be on the basis of their clinical findings at a time when their ultimate fate is not so apparent, and also at a time which is most useful in terms of mode of treatment - that is, when the disorder is first discovered by their physician. The major disadvantage of this requirement is apparent on examining Tables 1, 2, and 9. Out of a final total population of 174, only 110 (26 in the renal failure group and 84 in the comparison group - see "Age at Onset" in Table 9) had their hypertension first diagnosed at the University of Virginia Hospital. Out of an initial total population of 358 patients, over 250 had a previous known history of hypertension in the study at the Yale-New Haven Hospital. A possible explanation for the greater number of patients with a known history of hypertension at the Yale-New Haven Hospital may be that, at least in the years studied, it served the function of primary physician to a smaller proportion of the population than did the University of Virginia Hospital,

though this is only speculation.[52]

The number of patients actually employed in deriving the discriminant equation was even smaller than the 110 patients noted above because only 49 patients (14 in the renal failure group and 35 in the comparison group) had all of the data recorded for each clinical variable (see Table 11). Nonetheless, the differences between the variables of each group were very similar to those observed in the larger population (see Table 9), and the F ratio was clearly significant ($p < 0.001$).

Finally it should be noted that this study, of necessity, utilized information gathered from patients who were all hospitalized at least once in the course of their illness and who all died. The likelihood, therefore, that the population in this study is one of patients suffering from fairly severe hypertension is strong, a conclusion which is supported, moreover, by the mean blood pressures of all the groups in this population (see Tables 9, 10, and 17). Unfortunately, any study which relies on postmortem findings and hospital case records must suffer both from the problems of missing data and the bias of hospital selection.

II. Discussion of Results:

A. Pathological and Clinical Findings:

Given the relatively young age at onset of hyper-

tension, the apparent severity, and the predominance of Negroes in the groups of patients dying of renal failure, the question naturally arises as to whether or not this simply represents a group of patients with malignant hypertension. Several important facts argue against such a conclusion, however.

First, none of the patients in either the study at the University of Virginia Hopsital or at the Yale-New Haven Hospital had a history of papilledema,[9,10] or evidence of fibrinoid necrosis on renal section.[10] Second, descriptions of kidneys removed during post mortem examination of patients with malignant hypertension have shown that these kidneys vary from slightly below normal weight[10] (130 Grams,[14] 139 Grams[9]) to normal or slightly greater than normal weight.[21] In contrast, the kidneys from the group dying of renal failure at the University of Virginia Hospital were markedly contracted and decreased in weight (112 Grams, see Table 6). Third, cardiomegaly, while an extremely common finding in malignant hypertension, has rarely been recorded at the level observed in the renal failure group (607 Grams, see Table 6).[8,9,13,14] In fact, 79% of those patients dying of renal failure at the University of Virginia Hospital had hearts weighing 500 Grams or more (see Table 8). Kidney and heart weights were not specifically analyzed in the population selected from the Yale-New Haven Hospital since this population was chosen solely for application of the discriminant

equation. Fourth, the mean duration or survival time from the initial diagnosis of hypertension until death from renal failure in the University of Virginia Hospital group was 5 years (see Table 9), in contrast to durations in malignant hypertension ranging generally from 1 month to 2 years.[8,9,10,14] Admittedly, the mean survival time was shorter for white patients and for both white and Negro patients in the renal failure group at the Yale-New Haven Hospital, and the reason for this difference is not clear since in no case was there any evidence of papilledema or fibrinoid necrosis. Finally, the renal failure group from both hospitals had only a slight predominance of males over females which contrasts with the male predominance found in most studies of malignant hypertension and reported variously as 3:2,[9,13] 2:1,[28] and greater.[29]

Despite all of these facts, the mean age at which the diagnosis of hypertension was made was 46 years in the renal failure group at the University of Virginia Hospital and 45 years at the Yale-New Haven Hospital (see Tables 9 and 17). Further, more than 50% of the patients in this group for whom the diagnosis was made at the University of Virginia Hospital were less than 50 years old when the diagnosis was made. (see Table 7). This is very similar to the age at which malignant hypertension has been discovered, reported variously as less than 50 years old,[8,21] between 40 and 50,[10] between 33 and 55,[9] and between 30 and 50,[13] with an average ranging from

39 to 47.[8,9,13,17,28] The systolic blood pressure of the renal failure group at both hospitals was quite elevated at 212 mm Hg (see Tables 9 and 17), though still slightly less than the systolic levels most frequently reported in malignant hypertension which range from 220 mm Hg to 280 mm Hg.[8,9,13,28] It is entirely possible, however, that by excluding patients with papilledema from either study, a population of patients in a premalignant phase of severe primary hypertension were selected. Since these patients all received medical therapy, usually quite vigorous, after the diagnosis was made, it is conceivable that this treatment prevented them from ever acquiring many of the usual characteristics of malignant hypertension.

A precedent for this point of view is to be found in the work of Dustan et al[53] who studied the effect of medical treatment on the course of malignant hypertension. Out of a total of 81 patients receiving vigorous medical therapy for malignant hypertension, they observed a 38% 7-year survival rate. Among these patients, the most common single cause of death was renal failure, accounting for 22 deaths. Interestingly enough, renal failure followed 2 different courses. The first was characterized by the rapidly progressive loss of renal function with death within 5 months to 1 year for 9 patients. The second, however, was characterized by death

from slowly progressive renal failure for 13 patients. These patients survived from 14 to 60 months with a median survival time of 27 months, and their excretory function stabilized for long periods of time, deteriorating only several months prior to death. Equally significant from the point of view of the present study was the fact that renal sections of these patients with slowly progressive renal failure who came to autopsy showed remission of all or most aspects of the necrotizing arteriolar lesions of malignant hypertension, though the major branches of the renal artery, arcuate and interlobular, showed a diffuse fibrous intimal hyperplasia which was sometimes occlusive. Increased survival time[54-57] and remission of necrotizing arteriolar[54-56] lesions have been reported in medically treated patients with malignant hypertension by other investigators, as well. Unfortunately, no mention was made of either the cardiac or renal weight of the patients in these studies.

The group of renal failure patients at the University of Virginia Hospital were probably less severely ill than Dustan's group of patients with slowly progressive renal failure for none had papilledema and their mean survival time was longer. Their hypertension, however, was of a more severe form than their respective comparison group which lived longer and had lower levels of blood pressure (see

Table 9); it was virtually premalignant. The fact that their hearts were larger than those usually reported in malignant hypertension might, in part, be explained by the fact that they lived much longer than most patients with untreated malignant hypertneion.[8-10,14] But their hearts were even larger than those of the comparison group which had a longer mean survival time. One reason for this might be that their hypertension was more severe, but the regression analysis failed to support this view because it did not demonstrate a very close fit between initial systolic blood pressure and cardiac weight at death (see Table 14).

Perhaps a more feasible explanation is that the renal failure group of patients had a greater fluid volume than did those patients dying of other causes, and this served as an additional stimulus for cardiac hypertrophy, since it has been shown that increased cardiac wall tension, as might be produced from the increasing radius of a dilating heart in a patient with excess fluid volume, will affect cardiac hypertrophy.[58] In fact, initial dilatation with subsequent hypertrophy would also explain why the renal failure group had a significantly greater cardiac-thoracic ratio ($p < 0.008$) than did the comparison group early in the course of their disease.

A final explanation for the degree of cardiac hypertrophy observed in the renal failure group might well be that the status of their coronary circulation was better than that of the comparison group both because they were younger and

because patients with severe coronary artery disease who died of myocardial infarction were excluded from this group. To date, however, there have been no studies which document an actual association between coronary blood flow and myocardial hypertrophy, but it certainly seems reasonable that the increased metabolism of hypertrophy might require more nutrition from the vascular system.

The markedly diminished weight of the kidneys of the renal failure group contrasted to those of patients with malignant hypertension,[9,10,14,21] again, could be explained by the prolonged course of their illness, though regression analysis failed to show a close fit between kidney weight and duration of hypertension (see Table 13). The reason for this may be that values for the entire population, both renal failure and comparison groups, were employed in the regression analysis. The comparison group, on the other hand, would be expected to have kidneys closer to normal weight simply because they were not afflicted with severe renal impairment. Interestingly, though, regression analysis did show a close association between kidney weight and both initial systolic blood pressure and pulse pressure (see Table 12).

As previously noted, the case group of patients dying of renal failure at the University of Virginia Hospital had a predominance of Negroes in it (26 Negroes and 10 whites in a hospital whose population is 45% Negro). At the Yale-New Haven Hospital there was only a slight predominence of Negroes in the renal failure group though the comparison group had

a much higher proportion of whites than Negroes (16 whites and 3 Negroes). All of this suggests that death from renal failure was more common among Negroes than whites in the present study. While the renal failure groups in both hospitals had a much higher systolic blood pressure than did the comparison groups (see Tables 9 and 17), Negroes at the University of Virginia Hospital dying of renal failure had somewhat lower systolic blood pressures than did whites. The clinical data obtained at the Yale-New Haven Hospital was not analyzed by race as the number of patients was smaller. Furthermore, in the comparison group and in the population as a whole at the University of Virginia Hospital, the blood pressure, both systolic and diastolic, of Negroes and whites were essentially identical. The findings, therefore, of investigators such as McDonough,[37] Comstock,[38] and others[36] that Negroes have higher blood pressures than whites were not consistent with those in this study, especially in view of the previously mentioned possibility of a bias toward slightly higher levels of blood pressure for Negroes in this study.

In fact, despite the measurement of 16 clinical and pathological variables, significant ($p < 0.05$) racial differences within each of the 2 groups from the University of Virginia Hospital study were found in only 4 variables - heart weight, kidney weight, and cardiac-thoracic ratio in the comparison group and duration of the disease in the renal

failure group (see Tables 6 and 9). These small differences, however, cannot account for the much larger differences observed between the 2 groups.

The relative predominance of Negroes dying of renal failure in the case groups from both hospitals does suggest, however, that there may be a racial difference in the susceptibility of the renal vascular bed to sclerosis. This increased susceptibility for Negroes could well be related to a relatively early onset of hypertension (see Table 9) destined to terminate in about 5 years in death from renal failure with severely contracted, shrunken kidneys. There are, of course, other possible explanations for this racial predominance. In particular, one might speculate that Negroes in this study had a greater prevalence than whites of chronic asymptomatic urinary tract infection from the outset with subsequent renal failure and secondary hypertension. It is impossible to refute such an hypothesis, though the preponderance of Negroes dying of renal failure makes it unlikely that this alone could explain the racial difference.

The major racial differences among the causes of death in the comparison group at the University of Virginia Hospital were that a smaller percentage of Negro than white deaths were associated with aortic aneurysm or myocardial infarction, while a slightly higher percentage were associated with

cerebrovascular accidents (see Table 4). The number of Negro patients in the comparison group at the Yale-New Haven Hospital was too small to make any comment regarding racial differences (see Table 16).

The entire comparison group at the University of Virginia Hospital, both Negroes and whites, had a greater percentage of deaths associated with cerebrovascular accidents than did either the series of treated hypertensive patients reported by Smirk and Hodge[35] or by Leishman,[27] though the percentage of deaths associated with cerebrovascular accidents in the comparison group at the Yale-New Haven Hospital was essentially identical to the series of Smirk and Hodge. The percentage of deaths associated with myocardial infarction in both comparison groups in the present study was similar to that reported by Hood et al[34] in their series of treated hypertensive patients but lower than that reported by Smirk and Hodge. Death associated with congestive heart failure was infrequent in both the comparison groups in this study and in the series reported by Smirk and Hodge and Hood et al.

Differences and even similarities in causes of death between the comparison groups of the present study and those of other investigators are, of course, notoriously difficult to interpret. Processes of selection and modes of therapy

both undoubtedly differ from one study to another. Since death was a primary requisite for inclusion into the present study, it is reasonable to assume that the patients in this study were on the average more severely ill than the patients in the aforementioned studies. In addition, since postmortem examination was also a requisite in the present study, it is likely that a greater proportion of lesions such as cerebrovascular accident and myocardial infarction were discovered. Further, causes of death in the comparison groups in this study were occasionally multiple so it is difficult to compute case fatality rates accurately. In this context, then, it would be questionable at best to attempt to employ the findings of this study regarding cause of death in the comparison groups to either support or refute the findings of other investigators in this area.

B. Discriminant Analysis:

The value of the discriminant equation as a tool in the prognosis of disease has been admirably demonstrated by Morris et al[48] in their study of ischemic heart disease in London busmen. The present study demonstrates its usefulness in predicting which patients with primary hypertension will ultimately die of renal failure on the basis of easily measured clinical parameters obtained rather early in the course of the disease.

While the initial discriminant equation was derived from the analysis of only 49 patients out of the total population at the University of Virginia Hospital, the mean values of the clinical variables of these patients were quite representative of the population as a whole (see Tables 9 and 11). Further, application of this equation onto the population from which it was derived revealed a misclassification rate of only 15% at scores below or above 249. To evaluate truly the accuracy of this prognostic tool, however, it was necessary to apply the equation onto a new population of patients.

The mean values of the clinical variables of the population at the Yale- New Haven Hospital on which the discriminant equation was applied, except for somewhat smaller cardiac-thoracic ratios in both case and comparison groups and an older age at onset for the comparison group, were very similar to those at the University of Virginia Hospital (see Tables 11 and 17). Discriminant analysis of this population revealed a very good separation of discriminant scores with little overlap. The mean value of the discriminant score for the group dying of renal failure was 297.6 ± 89.9, while for the comparison group, it was 181.4 ± 27.7 (see Table 18). Indeed, if the discriminant scores are grouped by tertiles it can be seen that 18 of the 19 patients (95%) who ultimately died of causes other than renal failure fell into the lower two-thirds of the discriminant scores, while only 1 of the 9 patients (11%) who ultimately died of renal failure fell into the lower two-thirds.

On the other hand, 8 of the 9 patients (89%) who ultimately died of renal failure fell into the upper one-third of discriminant scores, while only 1 of the 19 patients (5%) who ultimately died of causes other than renal failure fell into this one-third (see Table 20). Another possible manner of viewing these results is presented in Table 19. Using the cutoff point of 249 derived from the study at the University of Virginia Hospital, a false negative ratio of 22% and a false positive ratio of 5% were obtained.

To demonstrate the usefulness of the discriminant equation, a typical patient has been selected from the case group and the comparison group for sample calculations:

> Case No. 7 is that of a Negro male who was diagnosed as hypertensive when he was 45 years old. At this time, his systolic blood pressure was 225 mm Hg. A chest film revealed a cardiac-thoracic ratio 57%, and his blood urea was found to be 48.3 mg/100 ml. Therefore, D= -1.5 (45) + 3 (57) + 0.5 (225) + 1 (48.3) = 264.3. Since D is greater than 249, the prediction is that he would die of renal failure, which he did at age 48.
>
> Case No. 14 is that of a white male who was diagnosed as hypertensive at the age of 59. His systolic blood pressure was 170 mm Hg, his cardiac-thoracic ratio was 50%, and his blood urea was 33.3 mg/100ml. Therefore, D = -1.5 (59) + 3 (50) + 0.5 (170) + 1 (33.3) = 179.8. Since D is less than 249, the prediction is that he would die of some cause other than renal failure. The cause of death was a massive cerebral hemorrhage at age 67.

In conclusion, then, it would seem from the present study that the individual with severe primary hypertension who is likely to die of renal failure presents to the clinician initially as a man or woman of either race, though most probably a Negro, about 45 or 46 years old, with a high blood pressure, especially systolic, fairly marked cardiac enlargement, and an elevated blood urea. Such a person may be suffering from premalignant hypertension and, if untreated, might go on to develop papilledema and expire within a year's time. When treated vigorously, survival may be prolonged for several years with death ultimately coming in the form of renal failure accompanied by extreme cardiomegaly and markedly contracted, sclerotic kidneys.

SUMMARY

SUMMARY

In a study of 174 patients who died with severe primary hypertension, it was found that those patients dying of renal failure could be identified with reasonable accuracy on the basis of the initial measurement of the systolic blood pressure, the cardiac-thoracic ratio, the blood urea, and the age of the patient at the time when the diagnosis of hypertension was first made. Such patients had higher initial systolic blood pressures and blood ureas, greater cardiac-thoracic ratios, and were of a younger age when the diagnosis of hypertension was initially made than were those patients with severe primary hypertension who died of other causes. The patients dying of renal failure also had a shorter survival time, a much greater degree of cardiomegaly, and more markedly contracted kidneys than did those dying of other causes.

When the initial clinical observations were substituted in the discriminant equation: D = -1.5 (age at onset) + 3 (cardiac-thoracic ratio) + 0.5 (systolic blood pressure) + 1 (blood urea), it was found that 85% of the patients with a discriminant score (D) greater than 249 died of renal failure while 85% of the patients with a discriminant score

less than 249 died of other causes. This discriminant equation was then applied to a second population consisting of 28 patients who died with severe primary hypertension to determine its prognostic accuracy. A false negative ratio of 22% and a false positive ratio of 5% were obtained in this second population using 249 as the cutoff point for the discriminant scores. Further, when the patients in this second population were grouped by tertiles of their discriminant scores, 89% of the patients who died of renal failure fell into the upper one-third of discriminant scores while 95% of the patients who died of causes other than renal failure fell into the lower two-thirds of the discriminant scores.

While no convincing evidence was found that the natural history of primary hypertension varied between the white and Negro races, a majority of all those patients dying of renal failure were Negroes. It is suggested that the susceptibility to sclerosis of the renal vascular bed may be greater for Negroes than for whites. It is also postulated that the population dying of renal failure in this study may have been suffering from a form of premalignant hypertension when first evaluated and their survival time and postmortem findings may reflect the effect of vigorous medical therapy.

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TABLES

Table 1. Selection of Comparison and Case Groups from the Population at the University of Virginia Hospital.

Comparison Group		Case Group	
1. Patients with a clinical diagnosis of primary hypertension on portmortem records	250	1. Patients with a clinical diagnosis of uremia on postmortem records but of these	20
but of these		a. patients without a history of primary hypertension in clinical records	4
a. patients having inflammatory kidney diseases	7	2. Remaining:	
b. patients with lost or incomplete records	85	patients with clinical and postmortem records consistent with the diagnosis of primary hypertension who died of renal failure	16
2. Remaining:		plus 20 (see 2a in opposite column) (Case Group)	36
patients with post-mortem and clinical records consistent with the diagnosis of primary hyper-tension	158		
a. those patients dying of renal failure	20		
b. those patients dying of other causes (Comparison Group)	138		

Final Total Population (Comparison and Case Groups)

174 patients

Table 2. Selection of Comparison and Case Groups from the Population at the Yale-New Haven Hospital.

Comparison Group		Case Group	
1. Patients with a clinical diagnosis of primary hypertension	300	1. Patients with a clinical diagnosis of uremia	58
but of these		but of these	
a. patients with a history of hypertension prior to evaluation at this hospital	248	a. patients without a previous history of hypertension	14
b. patients for whom chest x-rays were unavailable	12	b. patients with either a history of hypertension prior to evaluation at this hospital or a history of inflammatory kidney diseases	36
c. patients for whom chest x-rays were not taken	6	c. patients for whom chest x-rays were unavailable	2
d. patients for whom blood urea levels were not drawn	6	d. patients whose postmortem records were unavailable	2
e. patients whose postmortem records were unavailable	4		
2. Remaining: patients with primary hypertension first diagnosed at this hospital with all necessary clinical data available	24	2. Remaining: patients dying of renal failure with a clinical history of primary hypertension first diagnosed at this hospital with all necessary clinical data available	4
a. those patients dying of renal failure	5	plus 5 (see 2a in opposite column) (Case Group)	9
b. those patients dying of other causes (Comparison Group)	19		

Final Total Population (Comparison and Case Groups) 28 patients

Table 3. Characteristics of the Hypertensive Population at the University of Virginia Hospital - Those who died from Renal Failure (36) and Those who died from other Causes (138).

Race	Sex	Death from Renal Failure	Death from Other Causes
White	Male	7	48
	Female	3	26
Negro	Male	13	31
	Female	13	33

Table 4. Causes of Death among the 138 Patients of the Comparison Group at the University of Virginia Hospital.*

Causes of Death	Total		Race	
	No.	%	White	Negro
Cerebrovascular Accident	73	52.9	36	37
cerebral hemorrhage	53		26	27
cerebral infarction	20		10	10
Myocardial Infarction	29	21.0	20	9
Congestive Heart Failure	16	11.6	8	8
Diabetes Mellitus	16	11.6	6	10
Aortic Aneurysm	13	9.4	11	2
Pulmonary Embolus	4	2.9	2	2
Cancer	4	2.9	3	1
Septicemia	3	2.2	1	2
Cardiac Arrhythmia	3	2.2	2	1
Mesenteric Artery Thrombosis	2	1.4	1	1
Other	12	8.7		

Other includes one case each of ruptured berry aneurysm, pancreatitis, splenic infarction, terminal renal infarction, aspiration, pneumonia, brain abscess, myocardial fibrosis, asthma, ulcerative colitis, meningitis, and pulmonary artery thrombosis.

* In several cases, multiple causes of death were recorded for this comparison group so that the total number of causes of death is greater than 138 and the total percentage is greater than 100%.

Table 5. Associated Conditions among the 36 Patients dying of Renal Failure at the University of Virginia Hospital.

Associated Conditions	Total		Race	
	No.	%	White	Negro
Diabetes Mellitus	7	19.4	1	6
Congestive Heart Failure	7	19.4	2	5
Pneumonia	2	5.5	1	1
G.I. Bleeding	1	2.8	0	1
Pulmonary Embolus	1	2.8	0	1

Table 6. Means ± Standard Deviations of Pathologic Data for the Entire Population at the University of Virginia Hospital.

	Death from Renal Failure				Death from Other Causes			
	Entire Group		10* Whites	26* Negroes	Entire Group		74* Whites	64* Negroes
	Means ± SD	(Sample Size)	Means	Means	Means ± S.D.	(Sample Size)	Means	Means
Age at Death	52.1 ± 10.0	(36)	55.5	50.7	61.7 ±12.2	(138)	61.0	62.4
Heart Weight (gms.)	607.1 ± 136.4	(34)	620.0	601.7	503.2 ±137.3	(138)	487.8	521.1
Left Ventricular Thick.(m.m.)	19.2 ± 3.5	(33)	19.8	18.9	16.8 ± 4.1	(129)	16.2	17.4
Mean Kidney Weight (gms.)	111.6 ± 34.7	(33)	117.0	109.5	149.9 ±49.0	(136)	154.8	143.4

*Sample sizes for individual variables may be slightly smaller because of missing data.

Table 7. Analysis of Age at Onset of Hypertension and Age at Death of the Entire Population at the University of Virginia Hospital.

Age in Years	Death from Renal Failure		Death from Other Causes	
	Age at Onset (Sample Size=26)	Age at Death (Sample Size=36)	Age at Onset (Sample Size=84)	Age at Death (Sample Size=138
20-29	1		1	1
30-39	7	4	9	1
40-49	6	11	18	20
50-59	10	12	28	38
60-69	2	7	21	37
70-79		2	4	33
80-89			3	7
90-99				1

Table 8. Analysis of Heart Weight of the Entire Population at the University of Virginia Hospital.

Heart Weight (Gms.)	Death from Renal Failure (s.s. 34)	Death from Other Causes (s.s.138)
200-299	0	4
300-399	2	29
400-499	5	34
500-599	12	34
600-699	5	19
700-799	7	13
800-899	2	4
900-999	1	1
Mean Wt. (Gms.)	607.1 ± 136.4	503.2 ± 137.3
Mean Wt. (Gms.) of Entire Population = 523.8 ± 142.9		

Table 9. Means ± Standard Deviations of Clinical Data for the Entire Population at the University of Virginia Hospital.

	Death from Renal Failure			Death from causes other than Renal Failure		
	Entire Group	10* Whites	26* Negroes	Entire Group	74* Whites	64* Negroes
	Means ± SD (Sample Size)	Means	Means	Means ± SD (Sample Size)	Means	Means
Age at Onset (yrs.)	46.2±9.3 (26)	48.3	45.6	54.4±12.0 (84)	54.7	54.1
Initial Systolic B.P. (mm.Hg.)	211.8±44.3 (28)	222.8	208.2	190.3±30.8 (77)	189.2	191.2
Initial Diastolic B.P. (mm.Hg.)	118.5±20.6 (28)	122.6	117.2	113.1±16.4 (77)	113.1	113.0
Initial Cardiac-Thoracic Ratio(%)	58.4±6.7 (17)	54.3	59.7	53.4±6.8 (36)	50.2	55.0
Initial Urea Level (mg/100 ml)	135.2±105.6(27)	189.7	116.2	45.1±40.2 (65)	47.4	43.7
Highest Urea Level (mg/100 ml)	488.6±173.4(30)	508.7	483.5	94.4±73.2 (100)	86.1	101.9
Last Urea Level (mg/100 ml)	465.1±181.7(30)	498.0	456.9	71.8±49.3 (108)	68.2	75.3
Initial Blood Creatinine(mg/100 ml)	7.8±5.6 (18)	9.0	7.3	2.3±1.2 (9)	2.6	2.0
Highest Blood Creatinine(mg/100 ml)	20.7±7.2 (18)	22.5	20.2	2.7±1.7 (36)	2.6	2.8
Last Blood Creatinine(mg/100 ml)	18.4±8.3 (18)	21.8	17.4	2.3±1.4 (36)	2.2	2.4
Ponderal Index	12.0±0.8 (25)	12.2	11.9	12.1±1.1 (74)	12.3	11.9
Duration (yrs.)	5.0±3.6 (26)	2.3	5.8	7.5±5.8 (84)	7.4	7.6

* Sample sizes for individual variables may be smaller because of missing data.

Table 10. Analysis of Some of the Clinical Variables by Race and Sex for the Entire Population at the University of Virginia Hospital.

Clinical Variables	Race				Sex			
	White		Negro		Male		Female	
	Sample Size	Mean ± S.D.	Sample Size	Mean ± S.D.	Sample Size	Mean ± S.D.	Sample Size	Mean ± S.D.
Initial Systolic B.P. (mm Hg)	(41)	194.6±34.1	(64)	196.8±37.4	(57)	191.7±30.2	(48)	201.2±41.6
Initial Diastolic B.P. (mm Hg)	(41)	112.8±19.7	(64)	114.4±18.0	(57)	113.8±16.8	(48)	115.5±18.7
Initial Cardiac-Thoracic Ratio (%)	(16)	51.2± 6.5	(37)	56.7± 6.7	(26)	52.4± 6.7	(27)	57.6± 6.6
Initial Blood Urea (mg/100 ml)	(32)	78.6±102.2	(60)	67.8±61.3	(47)	84.9±87.1	(45)	57.7±64.4
Duration (yrs.)	(44)	6.7± 5.6	(66)	7.1± 5.4	(63)	7.0± 5.3	(47)	6.8± 5.8

Table 11. Discriminant Analysis based on Initial Clinical Findings of the Population at the University of Virginia Hospital.*

Variables	Age at Onset (yrs.)	Initial Cardiac-Thoracic Ratio (%)	Initial Systolic BP (mm Hg)	Initial Blood Urea (mg/100 ml)
Mean Values				
14 dying of renal failure	46.7	58.9	214	106
35 dying of other causes	53.9	53.5	196	37
Significance Tests				
Discriminant coefficient	-0.0015	0.0031	0.00047	0.0011
t test on coefficient	-1.77	2.13	1.65	5.25
Probability (44 df)	< 0.05	< 0.025	< 0.1	< 0.001

* Analysis of variance for discrimination: $F_{4,44}$ ratio = 12.02, $p < 0.001$

Table 12. Regression Analyses of Kidney Weight Versus Other Initial Clinical Variables in 101 Cases of Primary Hypertension at the University of Virginia Hospital.

Regression Equation: Kidney Weight = a + b (variable).

	Variables	Systolic BP (mm Hg)	Pulse Pressure (mm Hg)
Kidney Weight	Regression Coefficient (b)	-0.435	-0.480
	Intercept (a)	217.3	174.5
Significance Tests	$F_{1,99}$ Ratio	12.25	8.56
	p	< 0.001	< 0.005

Table 13. Regression Analyses of Kidney Weight versus Other Initial Clinical Variables in a Population of Patients with Primary Hypertension at the University of Virginia Hospital.

Regression Equation: Kidney Weight = a + b (variable)

Variables	Diastolic Blood Pressure (mm Hg)	Mean Arterial Pressure (mm Hg)	Blood Urea (mg/100 ml)	Cardiac-Thoracic Ratio (%)	Duration (yrs.)
Kidney Weight					
Regression coefficient (b)	-0.254	-0.356	-0.123	-1.54	-0.057
Intercept (a)	161.1	191.2	137.6	213.3	136.9
Significance tests					
F Ratio	$F_{1,104}$ .91	$F_{1,99}$ 4.13	$F_{1,91}$ 3.77	$F_{1,52}$ 2.46	$F_{1,94}$ 0.005
Probability	> 0.05	< 0.05	> 0.05	> 0.05	> 0.05

Table 14. Regression Analyses of Heart Weight versus Other Initial Clinical Variables in a Population of Patients with Primary Hypertension at the University of Virginia Hospital.

Regression Equation: Heart Weight = a + b (variable)

Variables	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Pulse Pressure (mm Hg)	Mean Arterial Pressure (mm Hg)	Blood Urea (mg/100 ml)	Cardiac-Thoracic Ratio	Duration (yrs.)
Heart Weight							
Regression coefficient (b)	0.431	1.276	0.199	0.860	0.270	3.833	-0.628
Intercept (a)	461.9	399.7	530.3	413.1	528.6	361.5	548.1
Significance tests							
F Ratio	$F_{1,102}$ 1.22	$F_{1,102}$ 2.76	$F_{1,98}$ 0.13	$F_{1,98}$ 2.30	$F_{1,89}$ 2.04	$F_{1,50}$ 1.69	$F_{1,94}$ 0.063
Probability	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Table 15. Characteristics of the Hypertensive Population at the Yale-New Haven Hospital - Those who died from Renal Failure (9) and Those who died from Other Causes (19).

Race	Sex	Death from Renal Failure	Death from Other Causes
White	Male	1	9
	Female	3	7
Negro	Male	4	2
	Female	1	1

Table 16. Causes of Death among the 19 Patients of the Comparison Group at the Yale-New Haven Hospital.*

Causes of Death	Total		Race	
	No.	%	White	Negro
Cerebrovascular Accident	5	26.3	3	2
cerebral hemorrhage	2		1	1
cerebral infarction	3		2	1
Myocardial Infarction	4	21.1	4	
Pneumonia	2	10.5	2	
Pulmonary Embolus	2	10.5	1	1
Congestive Heart Failure	1	5.3	1	
Cardiac Arrhythmia	1	5.3	1	
Emphysema & Cor Pulmonale	1	5.3	1	
Mesenteric Artery Thrombosis	1	5.3	1	
Tuberculosis	1	5.3	1	
Aspiration Pneumonitis	1	5.3	1	
Hemorrhagic Enteritis	1	5.3	1	
Drug Overdose	1	5.3	1	

* In 2 cases, 2 causes of death were recorded in this group so that the total number of causes of death is greater than 19 and the total percentage is greater than 100%.

Table 17. Means ± Standard Deviations of Clinical Data for the Entire Population at the Yale-New Haven Hospital.

Clinical Variables	Death from Renal Failure (Sample Size = 9) Means ± S.D.	Death from Other Causes (Sample Size = 19) Means ± S.D.
Initial Systolic Blood Pressure (mm Hg)	212 ± 30	183 ± 19
Age at Onset (yrs.)	44.9 ± 8.8	66.3 ± 10.7
Initial Urea Level (mg/100 ml)	99.5 ± 83.2	35.3 ± 16.0
Initial Cardiac-Thoracic Ratio (%)	53.1 ± 2.7	51.3 ± 3.9

Table 18. Discriminant Scores and Means and Standard Deviations for those Dying of Renal Failure and those Dying of Other Causes at the Yale-New Haven Hospital.

DISCRIMINANT SCORES

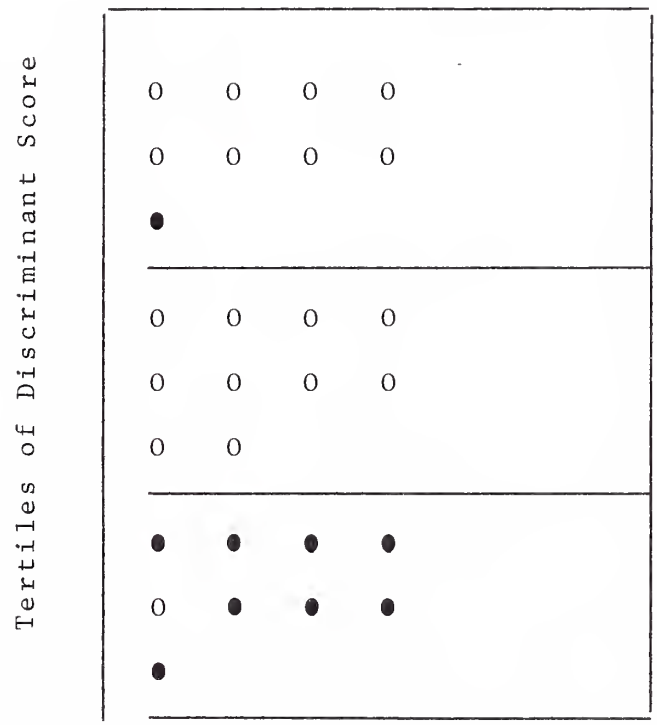
Dying of Renal Failure (9 cases)		Dying of Other Causes (19 cases)	
Subject	Score	Subject	Score
(1)	176.5*	(1)	144.2
(2)	224.0*	(2)	156.5
(3)	249.9	(3)	158.8
(4)	251.2	(4)	161.3
(5)	264.3	(5)	164.1
(6)	301.4	(6)	165.3
(7)	354.5	(7)	169.4
(8)	401.0	(8)	170.7
(9)	456.0	(9)	177.1
		(10)	177.3
		(11)	177.6
Mean 297.6	S.D.± 89.9	(12)	179.8
		(13)	185.4
		(14)	188.3
		(15)	191.1
		(16)	191.9
		(17)	206.6
		(18)	208.2
		(19)	273.0*
		Mean 181.4	S.D.± 27.7

* Denotes that cases would be misclassified according to the following criterion: classify the subject as "dying of renal failure" if $D > 249$, and classify the subject as "dying of other causes" if $D \leq 249$.

Table 19. False Negative and False Positive Ratios for Discriminant Function Analysis of the Population at the Yale-New Haven Hospital.

	Dying of Renal Failure	Dying of Other Causes
Actually Observed	9	19
Correctly Predicted	7	18
	False Negative Ratio 2/9	False Positive Ratio 1/19

Table 20. Analysis of Those Dying of Renal Failure and Those Dying of Other Causes at the Yale-New Haven Hospital by Tertiles of Discriminant Score.



	Dying of Renal Failure	Dying of Other Causes
	1	8
	0	10
	8	1
Total	9	19

● Patients dying of renal failure

0 Patients dying of other causes

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