SEVERE HYPERTENSION:
PROGNOSTIC DETERMINANTS AND THEIR PHARMACOLOGIC ALTERATION

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Medical Grand Rounds
March 1, 1979

The University of Texas
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Dallas, Texas

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Prior to 1950, accelerated and malignant hypertension ran a relentless course resulting in 80-90% mortality within the first year after diagnosis (1-3). During the 1950's, ganglionic blocking drugs and orally active diuretic agents were found to prolong survival and to protect against the progression of renal disease even though side effects were severe and drug administration was inconvenient (2-6). Further prognostic improvement was achieved in the 1960's with addition of the peripheral sympathetic neuron blocking agent guanethidine and more widespread use of hydralazine and reserpine.

According to the current computer printout, the 1970's belong to minoxidil and very aggressive control of elevated blood pressure in severely hypertensive patients. During these three decades the characteristics of severely hypertensive patients changed in that the incidence of malignant and accelerated hypertension decreased. Consequently, our reference points from which comparisons between treated patients today and untreated patients prior to 1950 are even less valid than they were in the 1950's. For example, the use of weak antihypertensive drugs which only partially control high blood pressure can reverse or prevent the malignant phase of hypertension. With widespread use of antihypertensive drugs the incidence of hypertensive papilledema or malignant hypertension has diminished considerably. However, the other vascular complications in partially treated patients continues to progress resulting in advanced renal and heart disease, strokes and possibly in the so-called refractory hypertensive which we see fairly frequently at Parkland.

I will now review some of the factors determining prognosis in severely hypertensive patients. These include retinal lesions, degree of renal disease, blood pressure level, sex, age, previous stroke and surprisingly to a relatively minor extent, heart disease.

Retinal lesions were a far more important determinant of prognosis before therapy was available. Keith, Wagner, and Barker (1) followed 146 patients at the Mayo Clinic with malignant hypertension during a 5-year interval and compared their survival with those having lesser degrees of hypertension (Figure 1).

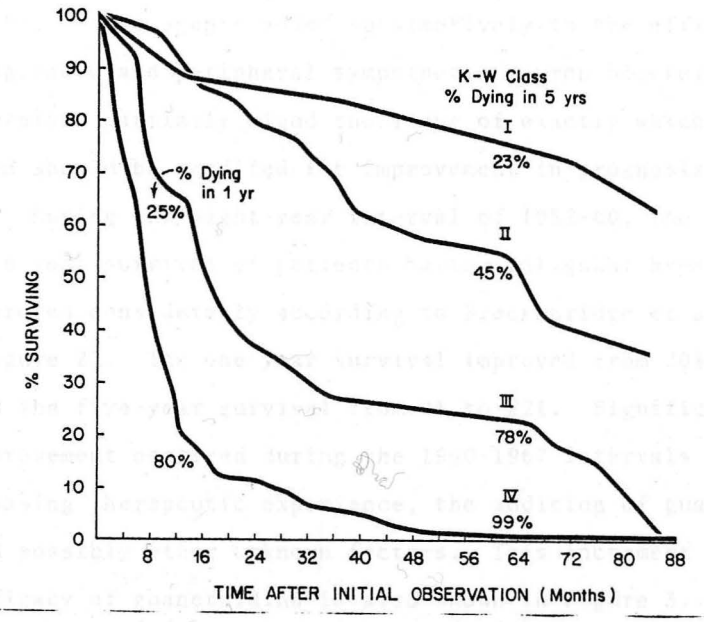


Figure 1. Keith-Wagner-Barker retinal classification of hypertensive patients. Class I patients had mild arteriolar narrowing. Class II had A-V crossing defects, irregular arteriolar narrowing and increased arterial light reflex. Class III had retinal edema, cotton-wool patches, hemorrhages and usually old sclerotic lesions. Class IV had edema of the nerve head resulting in elevation and blurring of the lateral disc margin usually accompanied by findings of the first three classes (1).

"Malignant" hypertension in the pre-drug era was appropriately named with a one-year survival of approximately 20% and essentially zero survival after five years. Nearly identical survival percentages were published for untreated malignant hypertensives by Harrington et al. (2) and other groups (3,4).

The prognosis of malignant hypertension was markedly improved (in those patients who would use these drugs) with the introduction of ganglionic blocking drugs and later peripheral sympathetic neuron blocking agents such as guanethidine. Superimposed on these major "new" entities were the orally active thiazide diuretics, reserpine preparations and hydralazine. These agents added substantively to the efficacy of ganglionic and peripheral sympathetic neuron blockers and therefore partially cloud the issue of exactly which intervention should be credited for improvement in prognosis.

During the eight-year interval of 1952-60, the one- and five-year survival of patients having malignant hypertension improved considerably according to Breckenridge et al. (5) (Figure 2). The one year survival improved from 20% to 50% and the five-year survival from 0% to 22%. Significant further improvement occurred during the 1960-1967 intervals with increasing therapeutic experience, the addition of guanethidine and possibly other unknown factors. This increment in apparent efficacy of guanethidine is also shown in Figure 3.

With control and prevention of papilledema and retinal hemorhages and exudates by antihypertensive drugs, renal disease and the degree of blood pressure elevation has become the predominant risk factors in determining prognosis. Malignant

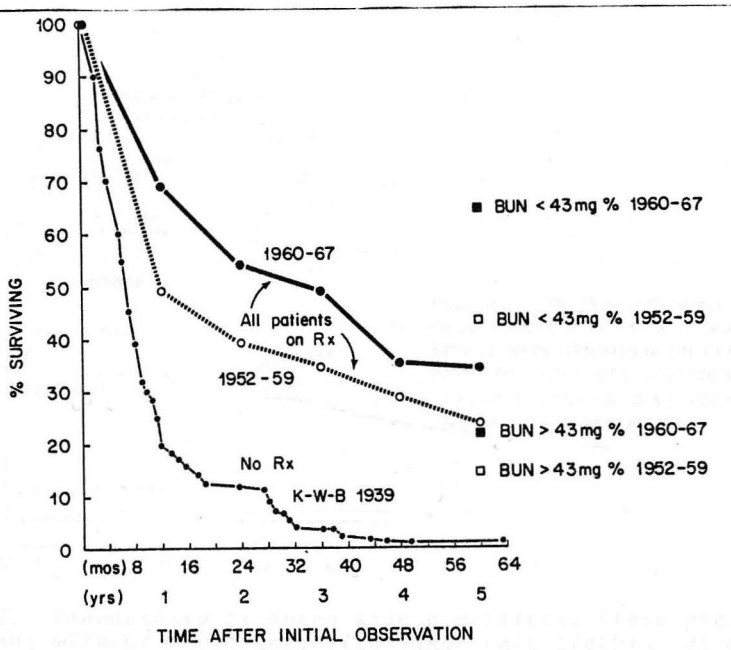
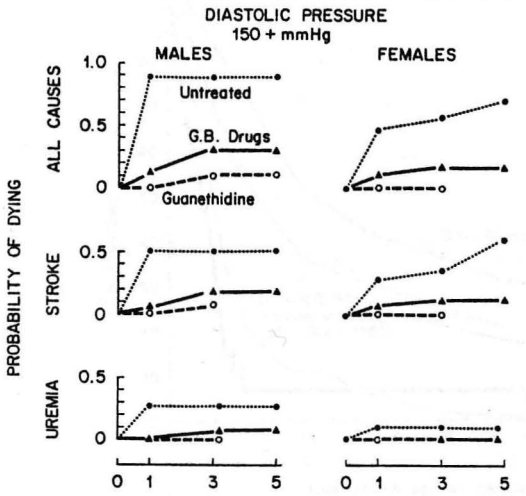


Figure 2. Survival of treated malignant hypertensive patients during the 1952-59 and 1960-67 intervals at Hammersmith compared with the untreated group at Mayo (K-W-B). Five-year survival of the Hammersmith patients according to the BUN level is shown on the right (5).

hypertensive patients, for example, in Breckenridge's clinic having BUN < 43 mg% in the 1952-59 interval had a 28% better prognosis at five years then those with BUN > 43 mg%. An even greater increment in prognosis was associated with better renal function during the 1960-67 interval (Figure 2).

The extremely poor prognosis of maligant hypertensives with renal failure is illustrated by Harrington et al. (2) in Figure 3. If the initial BUN was > 60 mg% the survival was as poor as in untreated malignant hypertensives.



PROBABILITY OF DYING FROM ALL CAUSES, FROM STROKE, AND FROM UREMIA , IN SEVERE HYPERTENSION IN UNTREATED PATIENTS, AND THOSE TREATED WITH GANGLION-BLOCKING (G.B.) AGENTS, AND/OR WITH GUANETHIDINE

Figure 3. Probability of dying from a diastolic blood pressure > 150 mmHg without treatment, with ganglionic blocking drugs and with guanethidine. Reduction of the probability of dying from stroke and from uremia is impressive (3).

The magnitude of blood pressure elevation is a major determinant of prognosis. In untreated men, Leishman (3) reported greater than 80% mortality in patients with diastolic pressures > 150 mmHg who did not have malignant hypertension (Figure 5). Survival of men having diastolic pressures of 130-149 mmHg were as poor as patients with K-W-B Class IV retinopathy. For a given blood pressure elevation, untreated men have a significantly worse prognosis than women (3) (Figure 6).

In the studies of Breckenridge et al. (5), the degree of blood pressure elevation was a determinant in treated hypertensive patients only when the initial diastolic pressure was 140 mmHg or greater (Figure 7). This observation indicates

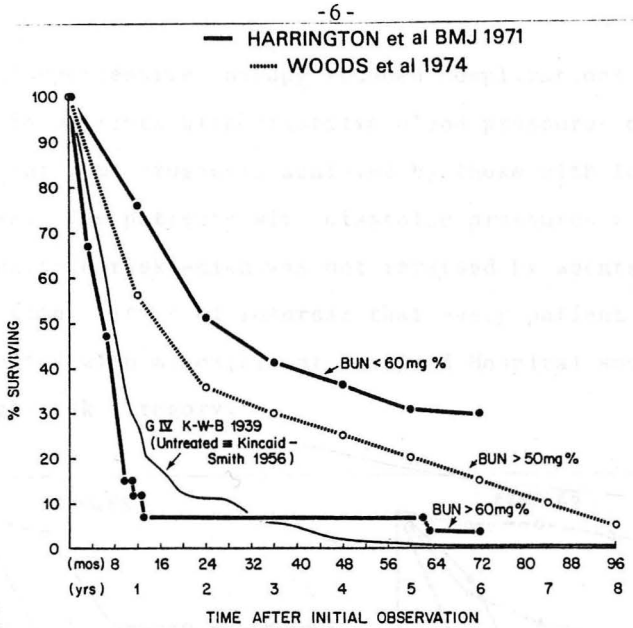


Figure 4. Survival in treated malignant hypertensives with renal failure. Harrington (2) & Woods (7). Thin wavy line (Keith-Wagner-Barker) - survival of untreated patients with malignant hypertension (1).

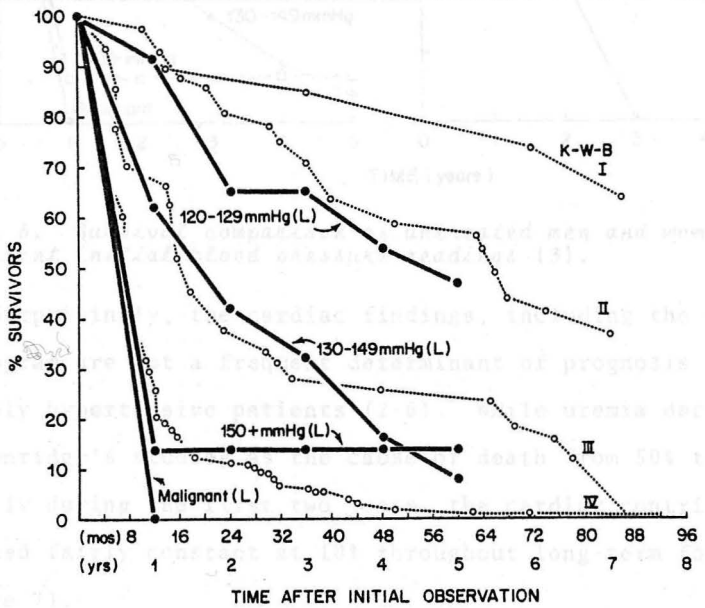


Figure 5. Survival comparison according to initial blood pressure reading (3) and retinopathy (1) in untreated hypertensive patients. The data here for blood pressure is from men which are contrasted with women in Figure 6.

that antihypertensive therapy reduced complications of hyper tension in patients with diastolic blood pressures of 120-140 mmHg to the same prognosis achieved by those with lower initial pressures. The patients with diastolic pressures > 140 mmHg had a built-in risk which was not reversed by agents available at that time. It is of interest that every patient that we have treated with minoxidil at Parkland Hospital would fit into this high-risk category.

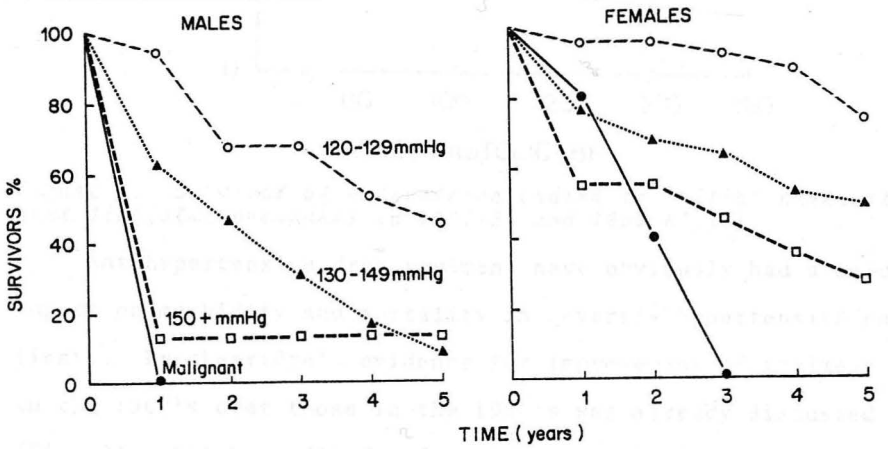


Figure 6. Survival comparison of untreated men and women at equivalent initial blood pressure readings (3).

Surprisingly, the cardiac findings, including the electrocardiogram are not a frequent determinant of prognosis in the severely hypertensive patients (2-6). While uremia declined in Breckenridge's studies as the cause of death from 50% to 10% annually during the first two years, the cardiac contribution remained fairly constant at 10% throughout long-term follow-up (Figure 7).

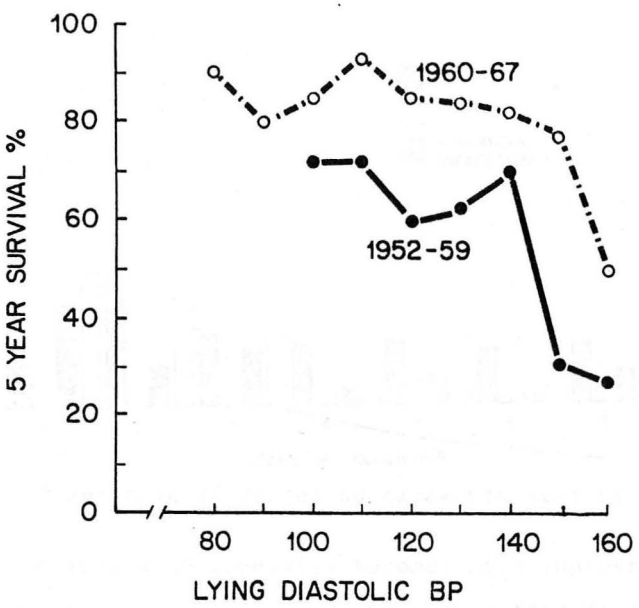


Figure 7. Survival of patients according to initial pretreatment diastolic pressures in 1952-59 and 1960-67 (3).

Antihypertensive drug regimens have obviously had a major impact on morbidity and mortality in severely hypertensive patients. Breckenridge's evidence for improvement of regimens in the 1960's over those in the 1950's was already discussed (Fig. 2). Leishman (3) found a clear superiority of guanethidine over ganglionic blocking drugs in preventing deaths due to the most frequent lethal mechanisms (stroke and uremia) in severely hypertensive patients (Figure 8).

The prospective randomized controlled VA cooperative study (8) involving patients with diastolic pressures of 115-129 mmHg was originally planned as a five-year project. However, the morbidity and mortality in the "control" group was so tragic that the study had to be discontinued in two years for ethical reasons. As the severity of the hypertension increases, the beneficial effects of antihypertensive drugs during the first

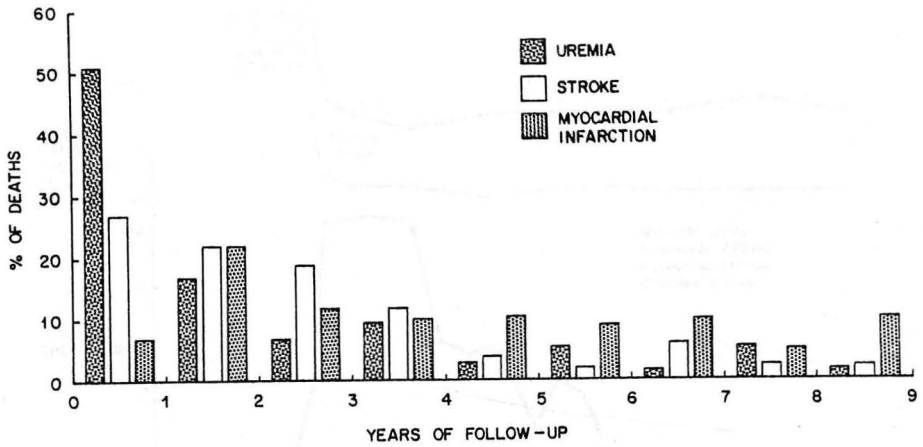


Figure 8. Proportion of deaths by cause per year of follow-up (5).

2-3 years of follow-up generally becomes more impressive. However, as Breckenridge et al. had shown from 1952-67 (5), there was a marked fall-off in survival in treated patients with pretreatment diastolic pressures over 140 mmHg (Fig. 7).

Azotemia in patients with malignant hypertension can occasionally be reversed as shown in Figure 9. This patient is 38 years of age and has sporadically used antihypertensive drugs for ten years. She was first seen in the Parkland outpatient clinic in December 1976 with serum creatinine of 3.9 mg% and BUN of 50 mg%. Cl_{Cr} was 21 ml/min. Methyldopa and hydrochlorothiazide were prescribed. She was admitted 1/6/77 with blurred vision and vomiting. Blood pressure was 260/162 and papilledema was present. BUN was 62 and creatinine 6.4 mg%. She was treated with standard medications and serum creatinine increased to 12.2 mg% on 1/20/77. On 1/21/77, treatment with minoxidil was initiated and hemodialysis was started on 1/25/77. On 2/4/77,

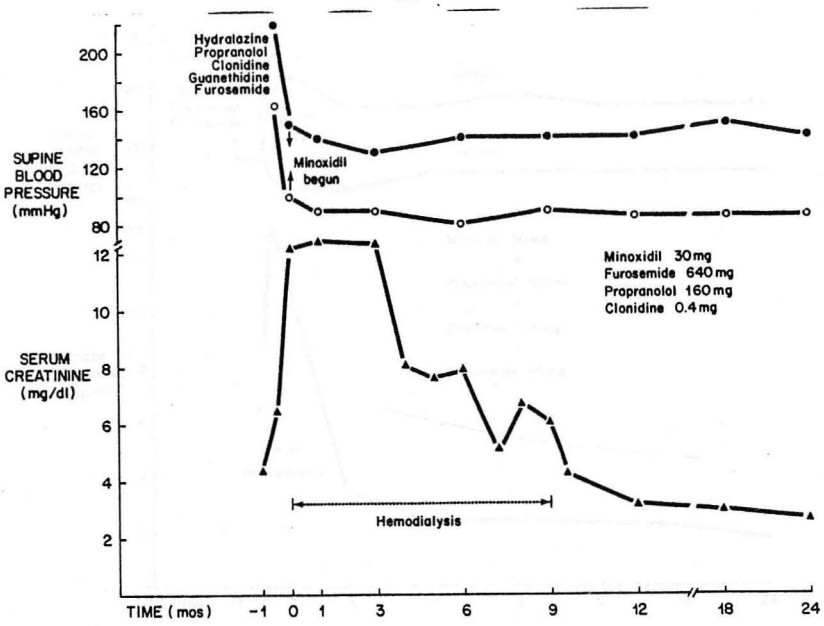


Figure 9. Patient #1 - Reversal of apparent end-stage renal disease by blood pressure control and hemodialysis for nine months. (Hemodialysis data courtesy of Dr. Alan Hull).

chronic dialysis was stopped but uremia recurred. After nine months on chronic hemodialysis this procedure was stopped and she returned for follow-up to our hypertension clinic. This chronology with follow-up data are summarized in Figure 9. Therapy currently consists of minoxidil 30 mg, propranolol 160 mg, clonidine 0.4 mg, and furosemide 640 mg daily.

A second patient with malignant hypertension (Figure 10) also shows reversal of apparent end-stage renal disease by controlling elevated blood pressure using minoxidil and temporary hemodialysis.

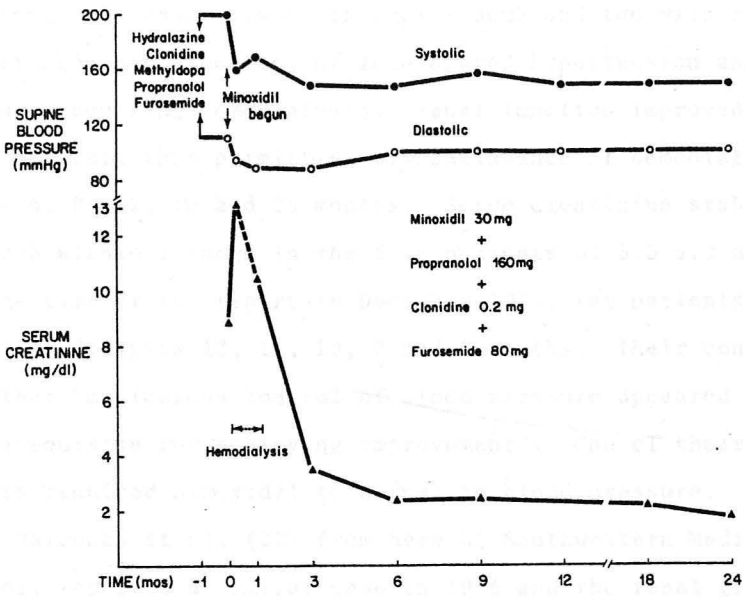


Figure 10. Patient #2 - Reversal of apparent end-stage renal disease by control of blood pressure with minoxidil and short-term hemodialysis.

Prior to 1973, several centers were doing bilateral nephrectomy sometimes as an emergency procedure for controlling accelerated hypertension in patients approaching end-stage renal disease (8-14). However, our experience here at Southwestern Medical School with minoxidil indicated that most patients previously refractory to antihypertensive drugs would respond to minoxidil (15). In the meantime, other investigators have had similar results (16-19) and now emergency nephrectomy is seldom indicated (20).

There are other examples of substantive improvement of renal function occurring with aggressive blood pressure control with or without hemodialysis. In 1974, Mamdani et al. (21)

reported five cases, two with papilledema and two with retinal hemorrhages and exudates, of accelerated hypertension and renal failure requiring hemodialysis. Renal function improved in each patient, thus permitting discontinuance of hemodialysis after 6, 9, 12, 16 and 25 months. Serum creatinine stabilized in each within a range in the five patients of 3.3-5.0 mg/dl. At the time of the report in December 1974, the patients had been off dialysis 12, 11, 10, 7 and 5 months. Their conclusion was that "meticulous control of blood pressure appeared to be a prerequisite for achieving improvement". One of their patients required minoxidil to normalize blood pressure.

Barcenas et al. (22) from here at Southwestern Medical School, reported a similar case in 1976 and the renal group is now preparing a report on a larger series.

Interestingly, hemodialysis can improve blood pressure control. Our patients who have had dialysis have required less minoxidil and occasionally have required no antihypertensive drugs at all.

Aggressive antihypertensive therapy using primarily diazoxide intravenously has been reported to improve renal function in azotemic severely hypertensive patients (21). Mroczek (23) gave diazoxide intravenously as necessary, along with furosemide for approximately two weeks to control diastolic blood pressure below 110 mmHg in 25 severaly hypertensive azotemic patients. Temporarily, serum creatinine and BUN increased 17 and 19% respectively because of the lowered renal perfusion pressure. However, after three months, the average reductions of BUN

and creatinine were 24 and 2.8 mg/dl respectively. Similar results were recently reported by Mutterperl using minoxidil (24).

In a prospective controlled study, Woods et al. (5) aggressively treated 20 azotemic malignant hypertensives beginning with a period of prolonged hospitalization. With essentially no dialysis, he was able to substantively improve the dismal prognosis of this fragile group. Whether he could have further improved the prognosis with better blood pressure control using minoxidil (as he suggested) is of course, unknown.

This next case (Figures 11 and 12) illustrates the extreme difficulty in controlling refractory hypertension, even with minoxidil, as well as the potential for arresting progression

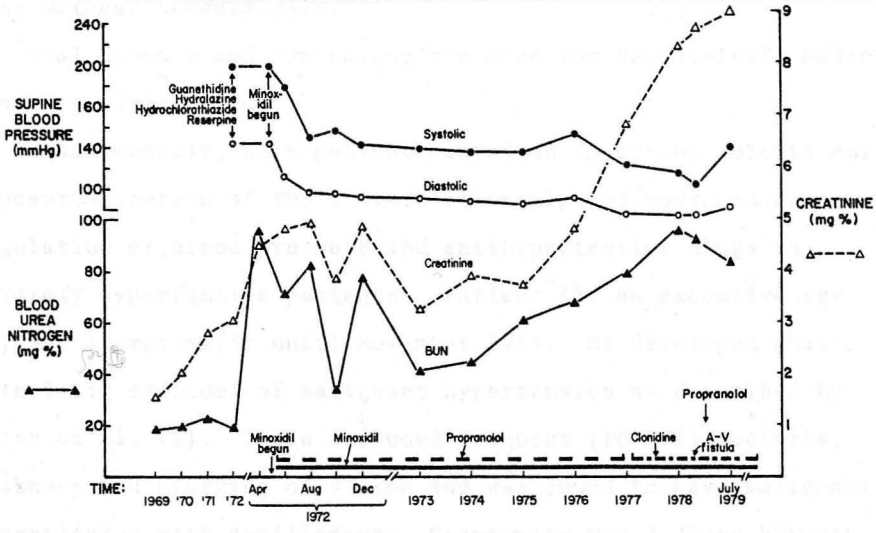


Figure 11. Partial reversal of progressive renal failure and stabilization of renal function by normalization of blood pressure without hemodialysis. Late progression of renal disease with recurrent pyelonephritis.

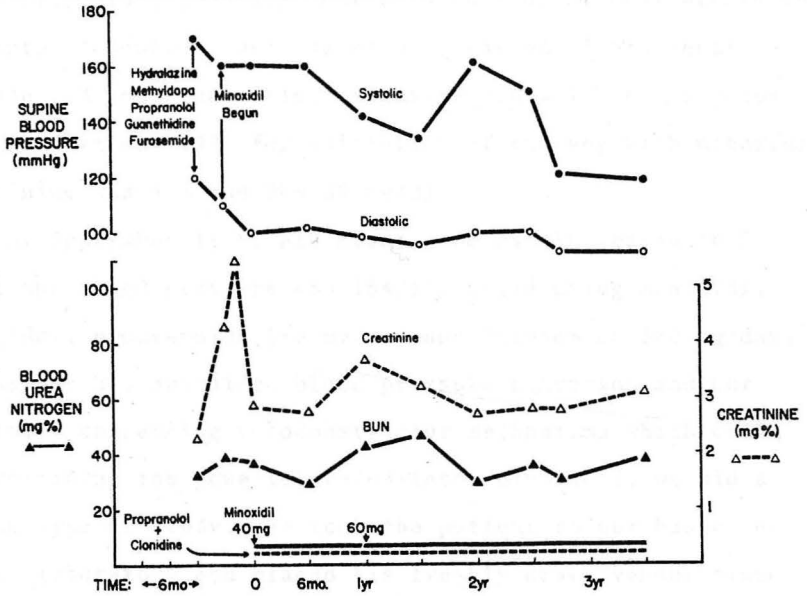


Figure 12. Partial reversal of progressive renal failure and stabilization of renal function by normalization of blood pressure without hemodialysis.

of renal disease and preventing the need for hemodialysis and/or renal transplantation.

Additionally, this patient played an important role in our conceptualization of the interrelationships of neuroendocrine regulation of blood pressure and antihypertensive drugs in severely hypertensive patients. Patient #3, an executive age 40, was asymptomatic until November 1974. He developed characteristic symptoms of malignant hypertension as described by Keith et al. (1). These included frequent (10-12X) nocturia, weakness and blurring of vision and was found to have malignant hypertension with papilledema. Creatinine was 2.3 and BUN was

33 mg/dl. Blood pressure control with conventional agents was attempted. However, because of progression of his renal disease and inadequate blood pressure control, he was rehospitalized in May 1975 for initiation of therapy with minoxidil. Creatinine was 4.3 and BUN 39 mg/dl.

By September 1975, his creatinine had increased to 5.5 mg/dl and blood pressure was 164/110 while using minoxidil 40 mg/day, propranolol 180 mg/day and furosemide 360 mg/day. Because of his sustained blood pressure elevation and our curiosity concerning vasoconstrictor mechanisms which could be overriding the powerful vasodilator minoxidil, we did a unique type of study. We took the patient to our basic research laboratory and placed his freshly drawn venous blood samples onto a cascade of tissues each having smooth muscle which contract characteristically to different hormones. The rabbit aorta contracted intensely and this could be blocked with the alpha-adrenergic blocking drug phentolamine. These results suggested that his circulating catecholamines were high and stimulated us to set up the techniques for measuring plasma epinephrine and norepinephrine. We confirmed that his circulating norepinephrine was markedly elevated and that it is elevated in most of our minoxidil-treated subjects (25), as shown in Figure 13. Of particular interest is the fact that the high circulating norepinephrine levels are normal in minoxidil-treated patients given clonidine. These recent data thus confirm the neuroendocrine-antihypertensive drug interrelationships as shown in Figure 14.

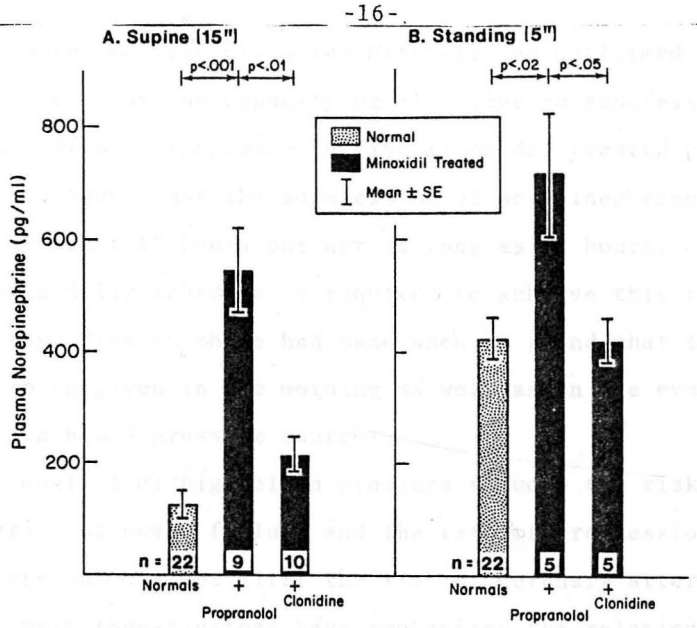


Figure 13. Supine (A) and standing (B) plasma norepinephrine levels in 22 normal subjects and in minoxidil-treated patients. Nine of the minoxidil-treated subjects were using propranolol without clonidine. Eight of the minoxidil-clonidine-treated patients were also using propranolol (25).

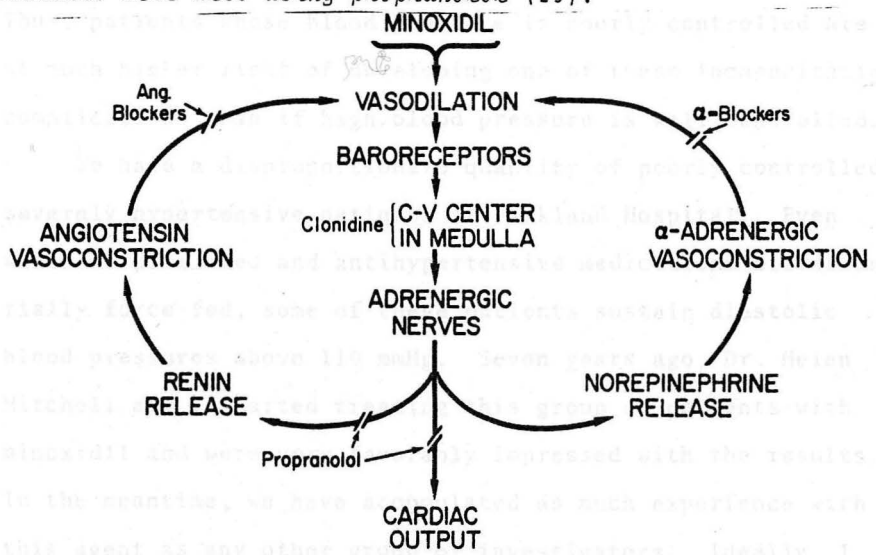


Figure 14. Neuroendocrine interrelationships of antihypertensive drugs and blood pressure regulation. Propranolol lowers blood pressure in minoxidil-treated patients and in animal models by inhibiting reflex-mediated renin release. Clonidine activates an α-adrenergic receptor in the medullary cardiovascular control center which suppresses the sympathetic nerves to the cardiovascular system.

More recently Dr. Helen Mitchell has confirmed in a prospective study the capacity of clonidine to suppress the high levels of norepinephrine in five minoxidil-treated patients. She has found that the suppression of norepinephrine continues for at least 12 hours but not as long as 24 hours. Therefore, a twice daily schedule is required to achieve this reduction, an assumption which we had made when we found that the drug had to be given in the morning as well as in the evening to sustain blood pressure control.

Control of high blood pressure reduces the risk of stroke, severity of heart failure and the rate of progression of renal disease but may not alter the risk of coronary artery thrombosis.

Most investigators have emphasized the relationship between quality of blood pressure control and the reduction of risk of these tragic events in severely hypertensive subjects. Thus, patients whose blood pressure is poorly controlled are at much higher risks of developing one of these incapacitating complications than if high blood pressure is well controlled.

We have a disproportionate quantity of poorly controlled severely hypertensive patients at Parkland Hospital. Even while hospitalized and antihypertensive medications are essentially force-fed, some of these patients sustain diastolic blood pressures above 110 mmHg. Seven years ago, Dr. Helen Mitchell and I started treating this group of patients with minoxidil and were very favorably impressed with the results. In the meantime, we have accumulated as much experience with this agent as any other group of investigators. Ideally, I would like to report to you that all patient's blood pressure can be normalized without symptoms using this drug and that

all complications of hypertension could be prevented. However, our report to you this morning, while it is quite favorable, still falls short of this goal. Nevertheless, most of our patients have had good quality of blood pressure control and their quality of life has generally improved with minoxidil.

While some of you may have one or two patients at this time who might be candidates for minoxidil, the things which we have learned in these investigations are frequently applicable to the management of patients with less severe hypertension using similar drugs. Whether minoxidil will be advantageous in the treatment of patients with less severe hypertension is now under investigation here and in several other centers.

Incidentally, we and others presented our experience with minoxidil to the Food and Drug Administration in November 1978. As a result minoxidil is expected to be formally approved in May. It should be available for your use on special request from the Upjohn Company in June of 1979 and generally available through the usual channels by October or November of this year. During the remainder of this session I will review the information set which should contribute to your decisions concerning the use of this drug.

Minoxidil is a very potent long-lasting systemic vasodilator which is used in the treatment of severely hypertensive patients or in those patients in which other antihypertensive drugs cannot be used because of toxicity or side effects. Because of reflex activation of the compensatory mechanisms shown

in Figures 13 and 14, sympathetic suppressant or blocking drugs are required, particularly during the first few months of treatment.

We generally prefer propranolol as the sympathetic blocking agent because of fewer unpleasant side effects. However, clonidine can be substituted for propranolol as shown in Figure 15 for the mechanistic reasons illustrated in Figures 13 and 14.The antihypertensive activities of clonidine or methyldopa from their central nervous system site of action, or phenoxybenzamine acting peripherally are additive to the propranolol-minoxidil combination and are used in patients in whose further blood pressure lowering is desired.

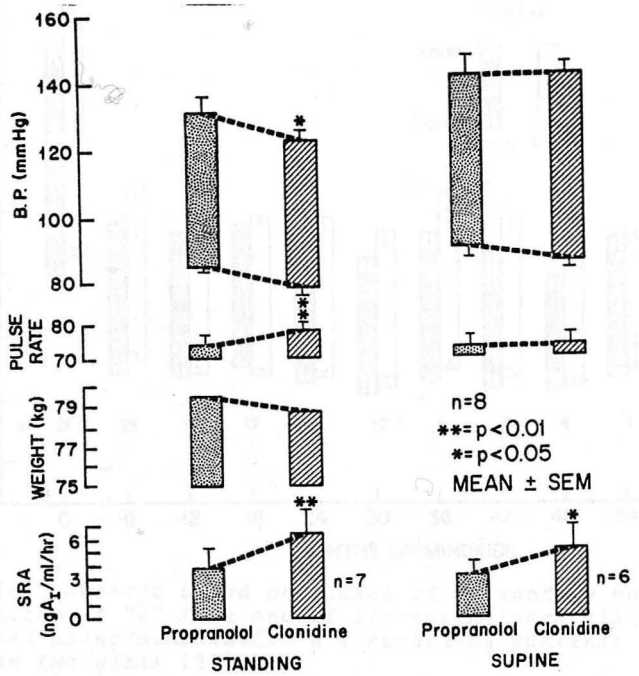


Figure 15. Substitution of clonidine for propranolol in minoxidil-treated ambulatory patients (29).

With blood pressure reduction there is a tendency for renal retention of salt and water with edema formation. Nearly all of our minoxidil treated patients have sustained diastolic pressures above 160 mmHg while not taking medications. Thus, the decrement in renal perfusion pressure contributes in a major way to edema. Interestingly, approximately two-thirds of our patients require more than 100 mg hydrochlorothiazide daily. Additional diuresis is achieved by substituting furosemide for thiazides. If large doses of furosemide are required (i.e. > 300 mg daily) this dose is reduced to 120-160 mg and thiazides included for an additive effect (15).

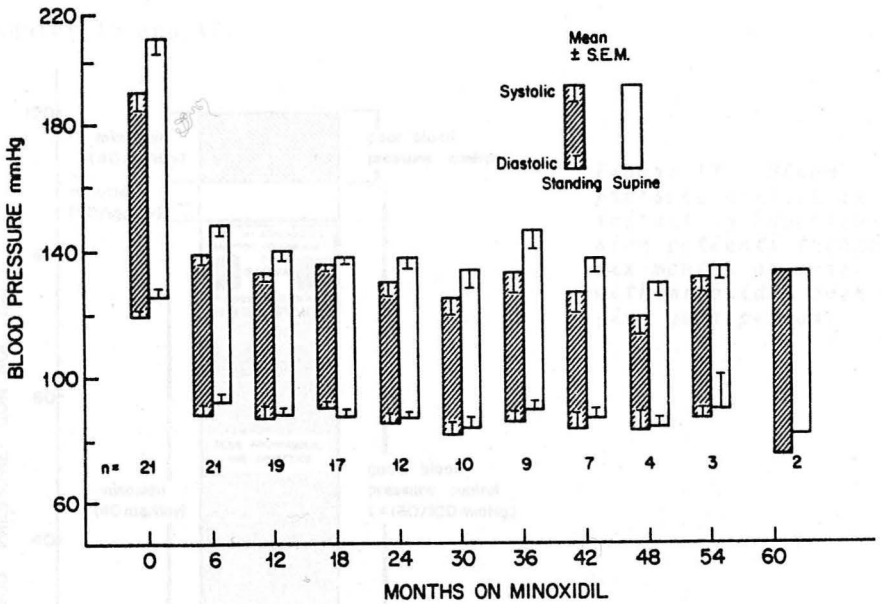


Figure 16. Average blood pressures of refractory hypertensives hospitalized at "0" time and at six-month intervals while ambulatory and using minoxidil. n = number of patients followed more than two years (25).

The mean blood pressure response has not diminished over a five-year period (Figure 16). The average diastolic blood pressure in these patients while hospitalized was 125 mmHg supine and 120 standing. In order to be considered for the minoxidil program, they had to sustain average diastolic pressures above 100 mmHg while hospitalized and using diuretics, hydralazine, propranolol and usually one other drug in maximal or optimal doses. Since ambulatory outpatient blood pressures are 10-30 mmHg higher than while patients are hospitalized this study-design tends to diminish the apparent efficacy of the drug. However, blood pressure control was achieved and maintained in the majority of these patients as shown in Figures 16 and 17.

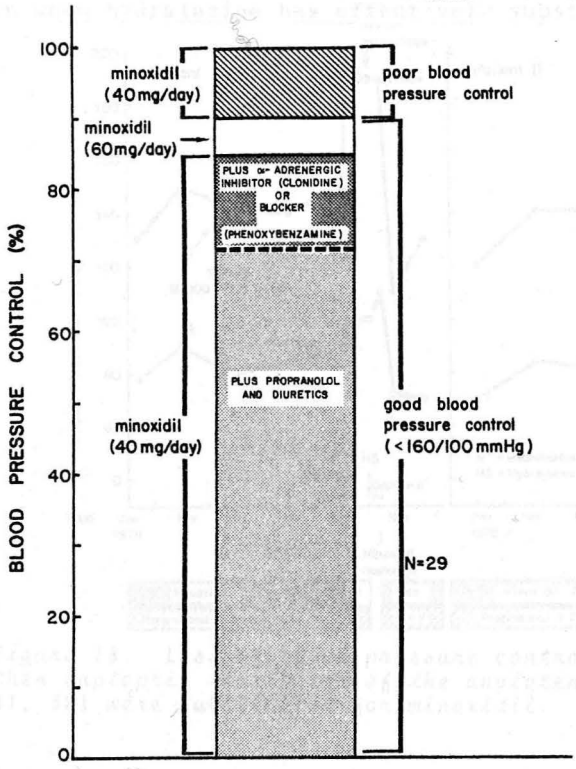


Figure 17. Blood pressure control in refractory hypertensive patients treated six months or more with minoxidil over a five year period.

Perry et al. (30) reported decreased drug requirements during chronic therapy of severely hypertensive patients with ganglionic blocking agents. We have occasionally been able to reduce the drug dosages but generally not. The tendency to marked elevation of the blood pressure persists as shown in Figure 18. When hydralazine was substituted for minoxidil in these two patients, severe hypertension recurred resulting in retinal hemorrhage in patient A with temporary loss of macular vision. Rapid escalation of captopril (an inhibitor of the angiotensin converting enzyme) dosage did not control blood pressure in contrast to the experience reported by others (31, 32). Similar patterns of loss of blood pressure control have occurred on withdrawal of minoxidil except for two patients in whom hydralazine has effectively substituted for minoxidil.

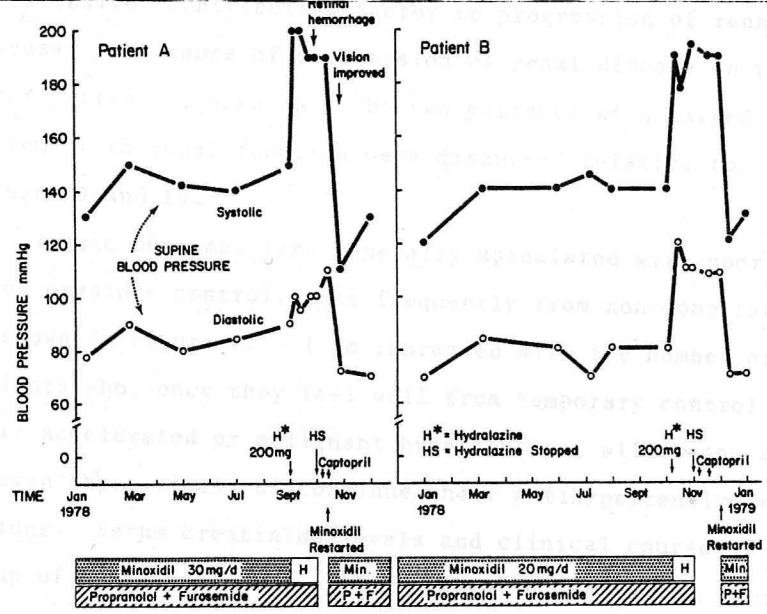


Figure 18. Loss of blood pressure control when hydralazine, then captopril (inhibitor of the angiotensin converting enzyme, 31, 32) were substituted for minoxidil.

Renal function has been maintained in most patients in whom the blood pressure was adequately controlled and who did not have intrinsic renal disease as shown in Figures 19 and 20. Three patients requiring only minoxidil, propranolol and diuretics have had progression of renal disease. Patient #1 has a 20-year history of diabetes mellitus and could thus have a non-hypertensive basis for the renal disease. Patient #2 had recurrent pyelonephritis and #10 extended periods of non-compliance.

The patients in Figure 20 have generally had more severe hypertension and required the addition of sympathetic blockers or suppressants. One of the two patients having progression of renal disease has chronic glomerulonephritis as a "non-hypertensive" contributing factor to progression of renal disease. The cause of progression of renal disease in the other patient is unknown. The two patients with marked improvement in renal function were discussed relative to Figures 9 and 10.

Tragic outcomes were generally associated with poor blood pressure control, most frequently from non-compliance, as shown in Figure 21. I am impressed with the number of our patients who, once they feel well from temporary control of their accelerated or malignant hypertension, will once, twice or even three times, discontinue their antihypertensive medications. Serum creatinine levels and clinical course of a group of these patients is illustrated in Figure 21. Each time that these patients have recrudescence of signs and symptoms the potential for return of renal function diminishes.

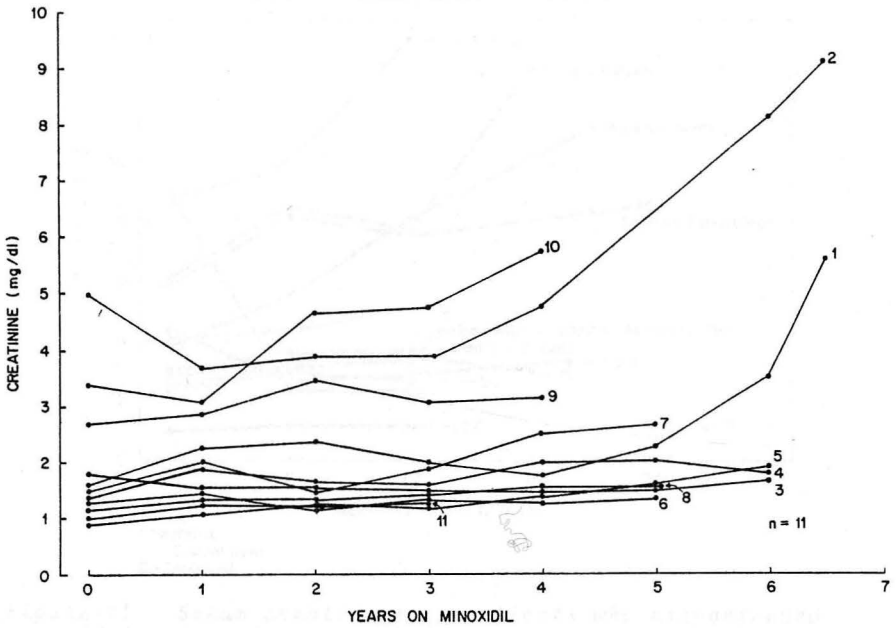


Figure 19. Serum creatinine levels in patients followed more than two years and who responded to the combination of propranolol, minoxidil and diuretics.

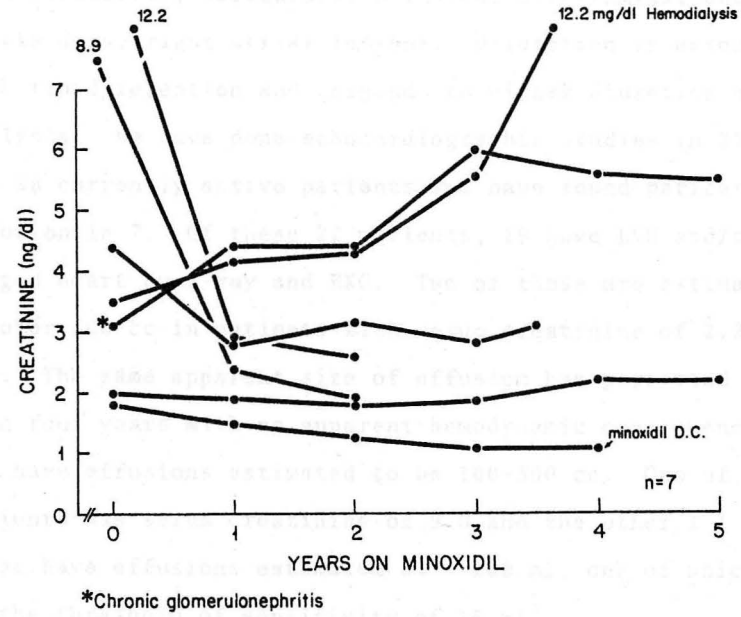


Figure 20. Serum creatinine levels in patients followed more than two years who required addition of sympathetic depressants or blockers other than propranolol.

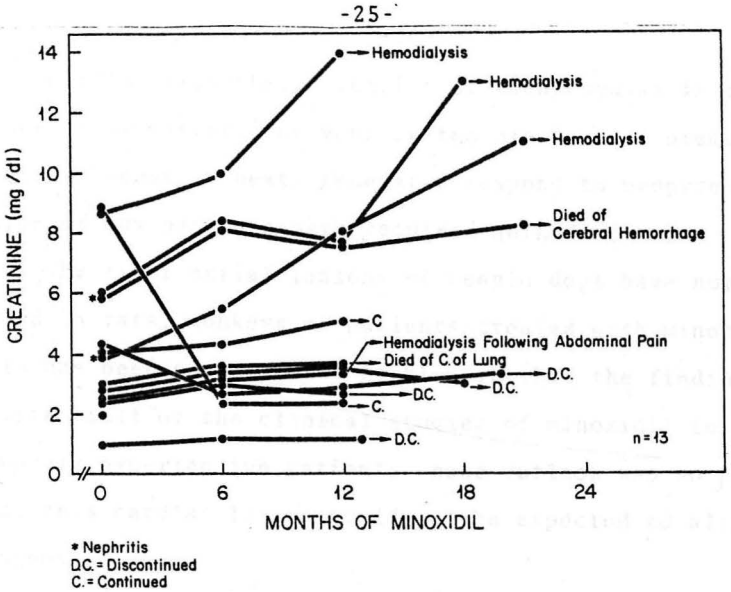


Figure 21. Serum creatinine in patients who discontinued minoxidil after six months but before two years.

Cardiac findings associated with minoxidil usage have been dilatation, pericardial effusion, arrhythmias, and in beagle dogs, right atrial lesions. Dilatation is associated with fluid retention and responds to either diuretics or to dialysis. We have done echocardiographic studies in 22 of the 28 currently active patients and have found pericardial effusion in 7. Of these 22 patients, 19 have LVH and/or enlarged heart by x-ray and EKG. Two of these are estimated to be over 300 cc in patients with serum creatinine of 2.2 and 3.1. The same apparent size of effusion has persisted more than four years with no apparent hemodynamic consequences. Two have effusions estimated to be 100-300 cc. One of these patients has serum creatinine of 9.0 and the other 1.1 mg%. Three have effusions estimated at < 100 ml, one of which is at the threshold of sensitivity of 15 ml.

Cardiac arrhythmias consist of tachycardias in the absence of sympathetic nervous system blockers or premature beats. Premature beats generally respond to propranolol but three of our patients have required quinidine.

The right atrial lesions of beagle dogs have not been found in rats, monkeys or patients treated with minoxidil. This has been an important problem in that the finding has limited most of the clinical studies of minoxidil to very severely hypertensive patients whose outlook was so poor that this cardiac lesion would not be expected to alter the prognosis.

Pulmonary hypertension was reported from two centers (19,34) in minoxidil-treated patients. However, this finding appears to be a function of patient selection since increased systemic vascular resistance is associated with increased pulmonary vascular resistance (35). Minoxidil is a pulmonary artery dilator (36) and would thus be expected to decrease pulmonary vascular resistance as suggested by Atkins et al. (35). In a prospective study, Klotman et al. (37) found no increase in pulmonary vascular resistance when minoxidil was used in treating severely hypertensive patients.

Our position on this problem is to use minoxidil very carefully in patients with advanced pulmonary disease for the following reasoning. Minoxidil increases cardiac output. If there is a fixed resistance to blood flow in the lung, as occurs in advanced pulmonary disease, marked elevation of pulmonary artery pressure could occur with right heart failure.

Increased hair growth is a major problem in young women and has been the factor leading to early death in two renal patients, one age 19 and the other age 23. Both patients had marked body hair growth during the first 2-3 months of minoxidil therapy. They found this sufficiently unacceptable to discontinue use of the drug and both died within four months from the renal disease and hypertension management problems.

Older women have each felt better using minoxidil than when using their previous regimens. Consequently, they have readily accepted use of depillatories and/or intermittent shaving of exposed areas. Mixed reactions to the excess hair growth have occurred in men. However, the reaction to increased scalp hair growth has been greeted enthusiastically by bald headed men.

We have two research projects involving minoxidil at this time. One is to evaluate its use in patients who sustain average diastolic pressures above 96 mmHg while using 100 mg of hydrochlorothiazide and 160 mg of propranolol daily. These patients have less severe hypertension than the refractory patients currently under treatment with minoxidil. A second project involves a trial of a few patients having Raynaud's syndrome to test the hypothesis of whether a long-acting potent vasodilator can alleviate the symptoms in this vasospastic syndrome. If you have patients who are potential candidates for these studies, please contact me or Dr. Mitchell at 688-2287.

Finally, I would like to illustrate the use of minoxidil in acute circumstances in which you would like to discontinue nitroprusside, nitroglycerin, ganglionic blocking and other antihypertensive agents.

This 86 year old woman was admitted to Parkland on 6/11/77. She had had acute onset of mid-thoracic back pain while out plowing a field. Hydrochlorothiazide, 50 mg daily, had been used for treating her hypertension.

She was a muscular elderly woman. The blood pressure was 150/100. The fundi were K-W Grade II. The neck veins were distended, the heart was enlarged and there was dullness to percussion over the lower left thorax. There was an 8 cm pulsating aortic aneurism in the abdomen. The chest x-ray confirmed a massive left effusion which on tap was found to be grossly bloody. Serum creatinine was 1.0 mg% and circulating hemoglobin was 8.5 gm%. She was transfused with three liters of blood and antihypertensive drugs were used for blood pressure control as summarized in Figure 22.

We first saw the patient on the 17th day of hospitalization. She was nearly comatose from reserpine and methyldopa. Minoxidil was started and sodium nitroprusside, hydralazine, reserpine and guanethidine were discontinued. The methyldopa dose was decreased by one-half. As usual in this circumstance of extensive polypharmacy, the blood pressure was well controlled by minoxidil 5 mg bid, tid or qid within 30 hours and the patient awoke. Several weeks after discharge, she was doing well except for occasional diarrhea. This symptom was alleviated by discontinuing Aldomet.

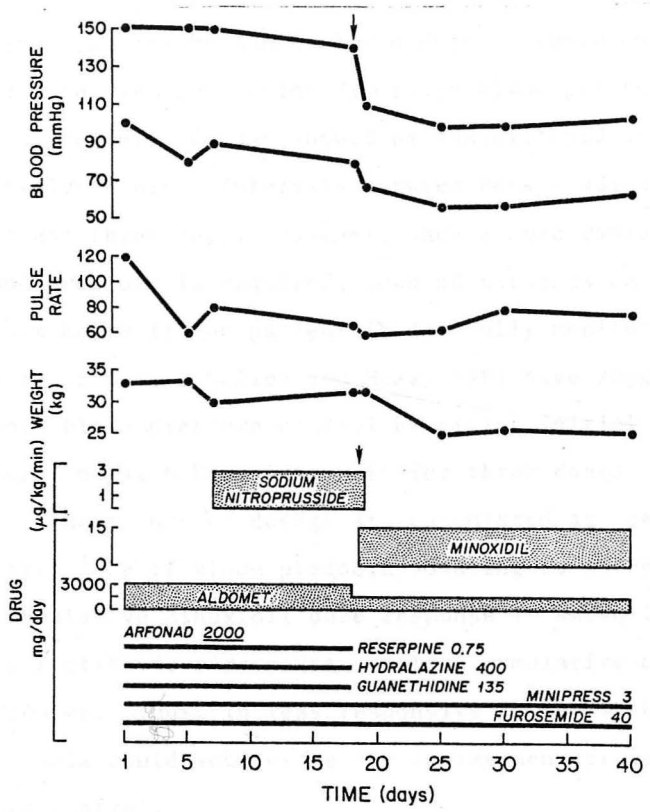


Figure 22. Eighty-six year old woman with a dissecting aneurism and extremely high blood pressure. Each time nitroprusside was discontinued, the blood pressure went above 200/130 until minoxidil was administered.

This case illustrates the remarkable potency of minoxidil in substituting for nitroprusside and other agents. Also, it is relatively easy to use and the patients wake up within 48-hours of discontinuing these other drugs. This case also illustrates the complexity of circumstances in which the drug has been used and the difficulty faced by investigators at the Upjohn Company in developing a new drug application for Food and Drug Administration approval for marketing.

Minoxidil may be administered once or twice daily. If minoxidil has reduced supine diastolic blood pressure 30 mmHg or more, the daily dosage should be administered in equal doses every twelve hours. Intervals between dosage adjustment should be at least three days. However, when a more rapid reduction of blood pressure is required, dose adjustments can be made every six hours if the patient is carefully monitored.

For example, O'Malley and McNay (38) have suggested achieving rapid blood pressure control by giving initial minoxidil doses of 5 mg at 6 hour intervals for three doses. Subsequent six-hour increments of dosage are calculated as one-half the cumulative dose if blood pressure lowering is suboptimal. Their cumulative minoxidil dose response is shown in Figure 23. Their effective dose-response covers a cumulative dose range of 15-100 mg. Thus, in less responsive patients the use of this formula could accelerate the achievement of ideal blood pressure control.

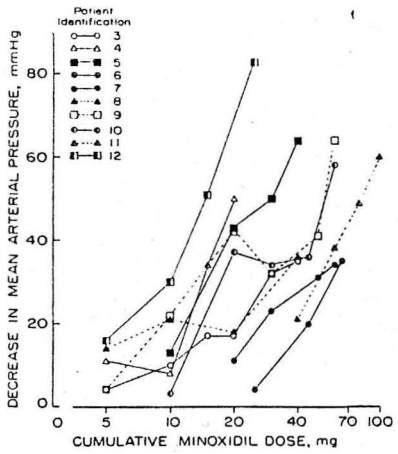


Figure 23. Cumulative minoxidil dose-response in severely hypertensive patients. (Taken from O'Malley & McNay, 38).

In conclusion, retinal findings, renal disease, blood pressure, age, sex, previous stroke, and cardiac status were prognostic determinants, in this order decrementally, in hypertensive patients prior to the era of antihypertensive drugs. Retinal findings of papilledema hemorrhages and soft exudates from severe hypertension are readily reversed by control of elevated blood pressure. In patients with advanced renal disease these retinal findings in fact indicate potential for recovery of renal function if blood pressure is well controlled. The degree of elevated blood pressure is certainly a determinant but the quality of control achieved by the patient and physician is probably a more important determinant of prognosis.

Minoxidil is clearly an advantage in achieving this quality of control in the more severely hypertensive patients. We are pleased that this powerful new drug will be available for your use this year.

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