Studies on the Control of Hypertension. VII. Effects of Ganglionic Blockade Combined With Hydralazine on the Malignant Stage Complicated by Renal Azotemia

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The malignant stage of arterial hypertension complicated by azotemia is usually a rapidly fatal disorder. The elevated blood pressures of 82 patients in this stage were chronically lowered by the regular, continued use of oral ganglionic-blocking agents and hydralazine hydrochloride in doses sufficient to control their hypertension without provoking dangerous hypotension or further azotemia. By careful administration of these potent antihypertensive drugs the mortality rate of azotemic patients was significantly reduced. The malignant stage of hypertension that has progressed to moderate renal insufficiency is no longer a rapidly fatal disease when properly treated, while that which has progressed further is usually uninfluenced.

The oral administration of frequent variable doses of an autonomic-blocking agent and hydralazine has been shown to lower the blood pressure of hypertensive patients as long as the drugs were given. Moreover, their use has been accompanied by an increased period of survival for patients with malignant stages of hypertension as compared to untreated patients with similarly severe disease. The toxicities of both types of drugs have been discussed together in general terms and separately in more detail. In an attempt to define the limitations of treatment, data are presented for all of our patients who had malignant stages of hypertension that had progressed to the point of nitrogen retention before the inception of drug therapy. The initial severity of the disease, the antihypertensive regimen, the changes following therapy, the period of survival, and the cause of death have been tabulated.

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Methods

Of the patients admitted to Barnes Hospital between August 1, 1951, and August 1, 1955, with malignant stages of hypertension and renal azotemia, 82 were treated with a combination of ganglionic blockade and oral hydralazine under the direct supervision of one of the authors. In this paper malignant stages of hypertension, or more simply malignant hypertension, is a clinical diagnosis that makes no prediction about the presence of renal arteriolar necrosis. As used here malignant hypertension is characterized by a persistent elevation of diastolic pressure at rest in the hospital above 120 mm. Hg, hemorrhagic and exudative retinitis with papilledema, proteinuria, and markedly diminished renal function. In addition, all the patients considered had nitrogen retention that failed to disappear after the correction of heart failure. Thirty-nine of the 82 patients were female, 28 were Negro, and 45 were ward patients. Therapy was begun for 21 during the first year of the study, for 18 during the second, for 22 during the third, and for 21 during the fourth. On admission to the hospital 8 patients were believed to have hypertensive encephalopathy, manifested by confusion or coma; 7 others had pulmonary edema, and 12 more showed significant signs of left ventricular failure. Five patients had histories suggesting that they had suffered apoplectic strokes, and 2 had electrocardiographic evidence of previous myocardial infarction; 4 had had surgical sympathectomies.

* Some patients previously reported are not included, since the authors did not actually supervise therapy although they were consulted.
Control data included each patient’s mean pretreatment blood pressure, which was calculated by averaging all values determined by nurses at four hour intervals in the hospital with the patient in a supine position. The mean number of such determinations was 10, the maximum was 37, and, except in the case of the 15 acute emergencies, the minimum was 6. None of the 16 sodium amytal release tests that were performed produced diastolic normotension. In every case the ocular fundi were examined, and at least one hemogram and a pair of urinalyses were obtained. Except for the 7 patients who had pulmonary edema, the degree of azotemia was measured in the absence of evident cardiac failure and before antihypertensive therapy. Everyone with an initial level of nonprotein nitrogen below 31 mg./100 ml. plasma was excluded from the series, although 25 mg. is the upper limit of normal in the Barnes Hospital Laboratories; the unusually low values are due to precipitation of the protein by zinc hydroxide, which removes glutathione, ergothioneine, uric acid, and perhaps other substances that are not precipitated by the more usual phosphotungstic acid procedure.\(^\text{11}\) In 67 patients renal function was measured by the urinary excretion of phenol red within 15 minutes of its intravenous injection. Cardiac status was evaluated by physical, electrocardiographic, and roentgenologic examination, as well as by symptomatology.

The method of administering a constant dose of hydralazine and a simultaneous, variable dose of autonomic-blocking agent depending on the systolic pressure of the seated patient has previously been reported.\(^\text{2}\) All medication was oral except in an initial emergency situation. Every patient who went home was instructed to continue the antihypertensive regimen worked out for him in the hospital. In only 1 case did this include salt restriction, and in only 6 was digitalis prescribed. Each patient was given a sphygmomanometer and adequate instructions in its use. The follow-up data involving blood pressure and medication were determined on readmission to the hospital, by careful interrogation on return visits, and from the continuous charts that each patient was requested to fill out daily and hand in at regular intervals. During treatment the blood pressure was ordinarily taken five times a day with the subject in a sitting posture in order to gage the required amount of autonomic blocking agent; hence the weekly pressure and dosage for each individual patient were the averages of approximately 35 recordings. For purposes of simplicity these individual means were frequently further consolidated into group means. At intervals reexaminations were made by the original physician and in the same laboratories to reevaluate cardiac and renal status as well as the general condition of the patient. Close questioning of each individual about his activities permitted a subjective estimate of rehabilitation. A continuing effort was made to follow all patients, and whenever possible survival time and cause of death were ascertained. The study was closed in August 1955.\(^*\)

**Results**

Of the 82 patients with malignant hypertension and pretreatment renal azotemia, 66 continued therapy. Of these, 28 are alive after an average of 21.4 months and 38 died after an average of 4.7 months. The 66 were arbitrarily divided on the basis of the extent of nitrogen retention before treatment. Twenty-seven of the 46 patients with less than 61 mg. nonprotein nitrogen per 100 ml. of plasma are being successfully maintained on therapy; whereas only 1 of 20 patients with more marked azotemia has survived. Table 1 indicates survival time as a function of pretreatment azotemia. Figure 1 indicates the length of time that each living patient has followed an antihypertensive regimen. Figure 2 presents similar data for patients who have died.

The remaining 16 patients discontinued therapy; all had less than 61 mg. nonprotein nitrogen per 100 ml. of plasma before treatment. Four, including 2 private patients, were lost to follow-up immediately after discharge from the hospital and presumably are dead. The other 12 are known to have died within a month of discontinuing antihypertensive drugs. Eight of these died with uremia less than 60 days after starting therapy, half in 1951 and half

\(^*\) Slow increases in nitrogen retention that were persistent and significant have only been observed in case 1, and in 2 other patients of our series of over 500 under treatment. A 34-year-old man with probable chronic glomerulonephritis and formerly in the malignant stage of hypertension was normotensive under therapy for 30 months until he developed a severe upper respiratory infection in November 1955 after this study was closed. Subsequently his nonprotein nitrogen, which had remained between 50 and 70 mg./100 ml. blood, increased to 118 mg. in April 1956. He is normotensive and working at the time of writing. A 52-year-old malignant hypertensive woman, who was not included in the study because she was not azotemic when first treated in October 1951, developed slowly progressive nitrogen retention after 40 months of therapy and died with uremia in March 1956. Chronic pyelonephritis was found at autopsy. In these 2 cases the underlying renal diseases not dependent upon nephrosclerosis were unaffected by control of blood pressure.
since; in each instance therapy was stopped after a marked increase in nitrogen retention coupled with complete prostration and often with confusion. The remaining 4, including 2 private patients, died 3, 6, 9, and 15 months after treatment was begun: the first following an episode of hypertensive encephalopathy; the second and third after cerebral hemorrhage, and the last as a result of progressive malignant hypertension when hydralazine was discontinued because of disseminated lupus erythematosus.

During the inception of therapy, azotemia increased in the surviving patients by an average of 18 mg. nonprotein nitrogen per 100 ml. of plasma, with the maximum rise being 54 mg.; however, by the time of their discharge from the hospital the mean level was 6 mg. below its original value. Figure 3 indicates the relationship of blood pressure, medication, and azotemia (as blood urea nitrogen) during the initial hospitalization of an 18-year-old white man with acute malignant hypertension and polycystic kidneys. The patient, who has continued almost normotensive on medication, is asymptomatic and working full-time; he is not included in the series because he was treated at another hospital. Figure 4 gives similar data for an older Negro man who also had malignant hypertension and pretreatment

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**Table 1. Mortality as a Function of Nitrogen Retention in 66 Patients Who Continued Therapy**

<table>
<thead>
<tr>
<th>Pretreatment Nonprotein Nitrogen mg. %</th>
<th>No. of Patients</th>
<th>Av. No. of Months Lived</th>
<th>Mortality Per cent</th>
<th>Surviving Patients</th>
<th>No.</th>
<th>Av. No. of Months Lived</th>
<th>Deceased Patients</th>
<th>No.</th>
<th>Av. No. of Months Lived</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>31</td>
<td>19.3</td>
<td>42</td>
<td>18</td>
<td>28.1</td>
<td></td>
<td>13</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>10</td>
<td>4.1</td>
<td>50</td>
<td>5</td>
<td>2.2</td>
<td></td>
<td>5</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>5</td>
<td>14.4</td>
<td>20</td>
<td>4</td>
<td>17.6</td>
<td></td>
<td>1</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>46</td>
<td>15.5</td>
<td>41</td>
<td>27</td>
<td>21.8</td>
<td></td>
<td>19</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>60-79</td>
<td>12</td>
<td>3.7</td>
<td>92</td>
<td>1</td>
<td>11.0</td>
<td></td>
<td>11</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>80-99</td>
<td>1</td>
<td>0.5</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>&gt; 100</td>
<td>7</td>
<td>2.7</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>20</td>
<td>3.3</td>
<td>95</td>
<td>1</td>
<td>11.0</td>
<td></td>
<td>19</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>11.6</td>
<td>58</td>
<td>28</td>
<td>21.4</td>
<td></td>
<td>38</td>
<td>4.6</td>
<td></td>
</tr>
</tbody>
</table>

* 8 died with fibrinous pneumonitis in the absence of uremia.

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**Fig. 1.** Post-treatment survival time of 28 living patients who had malignant hypertension. The open bars indicate patients who had 30 to 60 mg. nonprotein nitrogen/100 ml. plasma before antihypertensive therapy. The cross-hatched bar indicates the patient with 64 mg. nonprotein nitrogen/100 ml. plasma before therapy.

**Fig. 2.** Post-treatment survival time of 38 deceased patients who had malignant hypertension and who continued therapy. The open bars indicate patients who had 30 to 60 mg. nonprotein nitrogen/100 ml. plasma before antihypertensive therapy. The cross-hatched bars indicate those with greater degrees of nitrogen retention before therapy. Of the 13 patients in the former group who died within six months of instituting therapy, 7 had the marked tachypnea and anatomic lesions of fibrinous pneumonitis.
azotemia. He is not included in the series either, because he was discharged from the hospital too recently. Another example of the reciprocal relationship between hypertension and nitrogen retention has been published.4

Table 2 indicates the blood pressure before and after therapy as well as the amount of drug necessary to maintain the antihypertensive effect for the 28 living patients who had malignant hypertension and pretreatment azotemia. The values one month after discharge from the hospital are included for comparison with those occurring at yearly intervals. The pretreatment blood pressure is a measure of the severity of the hypertensive process, and the post-treatment levels indicate how well the original control of blood pressure has been maintained. In terms of hexamethonium chloride* the azotemic patients

* Except for brief transition periods two or more autonomic blocking agents were not simultaneously administered. Fifty-six patients received only hexamethonium chloride, 15 both hexamethonium chloride and pentolinium tartrate, 7 only pentolinium tartrate, 3 both hexamethonium chloride and 4,5,6,7-tetrachloro-2-(2-dimethylaminoethyl)-isoindoline dimethochloride (Ecolid, Ciba Su-3088), and 1 all 3 ions. All dosages cited are in terms of oral hexa-
ingested an average of 2.42 Gm. of ganglionic-blocking agent per day after a month at home. The decreased requirement of the drug at two years is not real, since the 13 patients who have been treated that long were initially ingesting an average of 1.86 Gm. of hexamethonium chloride a day. Although the mean daily intake of oral hydralazine exceeded 0.5 Gm. for a considerable period in many, only 4 patients developed any signs of hydralazine toxicity.†

Table 2 also lists laboratory data for the 28 living patients. The disappearance of hemorrhages and exudates from the ocular fundus may indicate a generally improved condition of the small afferent vessels. The diminished albuminuria contrasts with the persistent azotemia and the continued inability to concentrate urine or excrete phenol red. Although cardiomegaly was absent roentgenologically and electrocardiographically in only 2 after a year of therapy, the status of the heart appeared objectively improved in most instances. There was no significant change in the mild anemia during three years of treatment.

Few patients were doing any work before therapy or within a month of hospital discharge. By the end of the first year of treatment, however, most of the survivors had returned to some job. After two and three years the percentage of those gainfully employed had increased (table 2). Several have

methenonium chloride. When necessary the dose of oral pentolinium tartrate has been multiplied by 5 in order to render it comparable. 12

† Among the 28 patients who survived a year of therapy, 4 who had achieved good control of their blood pressures had manifestations of delayed hydralazine toxicity. Two white women developed arthritides, an increased cephalin-cholesterol flocculation of their serum, and circulating lupus erythematosus cells. A Negro woman with clinical findings characteristic of infectious hepatitis was found to have many lupus erythematosus cells in her peripheral blood. She is one of the 16 patients listed as having discontinued therapy, although she continued only hydralazine. Despite 1 gram of oral Ecolid daily her diastolic pressure averaged more than 160 mm Hg in the sitting position during the six months before she died of progressive malignant hypertension terminating in renal failure. Another Negro woman, whose case is reported in detail as an example of "fibrinous pneumonitis" resulting from ganglionic-blocking agent, 10 was suspected of showing toxicity to hydralazine as well.

![Fig. 4. Medication, blood pressure, and nitrogen retention during hospitalization. The solid bars represent oral hydralazine. The open bars represent oral mecamylamine (Inversine, Sharpe & Dohme). Each of the points on blood pressure curve is the average of at least six, and initially as many as 24, determinations. All were made with the patient supine. In addition to the medication shown, 513 mg. of intramuscular hexamethonium chloride were administered on November 22 without any effect on the blood pressure. Except for probable pyelonephritis 10 years previously, followed by the discovery of high blood pressure, this 45 year old Negro policeman was essentially asymptomatic until six months before he entered Barnes Hospital. Progressive asthenia and increasingly frequent periods of syncope associated with vertigo and amblyopia were followed by urinary frequency and dyspnea, and finally nausea and vomiting. There was hemorrhagic retinitis with bilateral papilledema. Cardiomegaly was present, the lung fields were clear to percussion and auscultation, and there was no edema. There were cylindruria and 3 plus albuminuria; 100 ml. of blood contained 10 Gm. of hemoglobin. Electrocardiograms and roentgenograms of the chest indicated left ventricular enlargement. Azotemia and blood pressure decreased following the institution of oral mecamylamine and hydralazine therapy. The patient was discharged from the hospital with a regular diet without digitalis. He had no symptoms except amblyopia referable to his hypertension or to his therapy, and he returned to work three weeks later. There were 67 mg. nonprotein nitrogen/100 ml. plasma on January 20, 1956, and 71 mg. on February 24, 1956.

been able to resume moderately hard manual labor such as farming or truck driving; whereas others, like the subject of the second case report, have adopted less strenuous occupa-
STUDIES ON CONTROL OF HYPERTENSION

TABLE 2.—Blood Pressure, Dosage, and Laboratory Data in 28 Surviving Patients with Malignant Hypertension and Pretreatment Azotemia

<table>
<thead>
<tr>
<th></th>
<th>Before therapy</th>
<th>1 month*</th>
<th>1 year*</th>
<th>2 years*</th>
<th>3 years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>28</td>
<td>28</td>
<td>23</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Systolic pressure, mm. Hg.</td>
<td>223</td>
<td>160</td>
<td>162</td>
<td>161</td>
<td>162</td>
</tr>
<tr>
<td>Diastolic pressure, mm. Hg.</td>
<td>142</td>
<td>99</td>
<td>102</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>Blocking agent, † Gm./day orally</td>
<td>0</td>
<td>2.42</td>
<td>2.50</td>
<td>1.94</td>
<td>1.93</td>
</tr>
<tr>
<td>Hydralazine, Gm./day orally</td>
<td>0</td>
<td>0.54</td>
<td>0.51</td>
<td>0.34</td>
<td>0.31</td>
</tr>
<tr>
<td>Hemorrhagic and exudative retinitis with papilledema</td>
<td>100</td>
<td>—</td>
<td>0$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Albuminuria, graded 0 to 4+</td>
<td>2.5</td>
<td>—</td>
<td>1.0</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Nonprotein nitrogen, mg. %</td>
<td>39</td>
<td>40</td>
<td>38</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>Maximum urinary specific gravity</td>
<td>1.013</td>
<td>—</td>
<td>1.015</td>
<td>1.012</td>
<td>1.014</td>
</tr>
<tr>
<td>Phenolsulfonphthalein, % excreted in 15 minutes</td>
<td>7</td>
<td>—</td>
<td>10</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Cardiomegaly by x-ray, % improved</td>
<td>93†</td>
<td>—</td>
<td>52</td>
<td>62</td>
<td>78</td>
</tr>
<tr>
<td>Electrocardiographic abnormalities, % improved</td>
<td>100†</td>
<td>—</td>
<td>57</td>
<td>54</td>
<td>67</td>
</tr>
<tr>
<td>Hemoglobin, Gm. per 100 ml.</td>
<td>12.5</td>
<td>—</td>
<td>11.9</td>
<td>12.1</td>
<td>11.6</td>
</tr>
<tr>
<td>Working, %</td>
<td>8</td>
<td>5</td>
<td>68</td>
<td>78</td>
<td>91</td>
</tr>
</tbody>
</table>

* After discharge from the hospital
† Calculated as oral hexamethonium
‡ Per cent with abnormalities
§ 6 patients exhibited hard exudates without hemorrhages or papilledema

TABLE 3.—Postmortem Findings in 32 Patients

<table>
<thead>
<tr>
<th>Pretreatment Nonprotein Nitrogen mg. %</th>
<th>Total No.</th>
<th>No. Dead</th>
<th>No. of Autopsies</th>
<th>Fibros pneunmonitis</th>
<th>Cerebral vascular accident</th>
<th>Myocardial infarction</th>
<th>Cardiac failure</th>
<th>Pneumonitis</th>
<th>Renal failure (%)</th>
<th>Renal arteriosclerosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who continued treatment</td>
<td>31–60</td>
<td>46</td>
<td>19</td>
<td>11</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patients who continued treatment</td>
<td>61–137</td>
<td>20</td>
<td>19</td>
<td>13</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Patients who discontinued treatment</td>
<td>31–60</td>
<td>16</td>
<td>12</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>50</td>
<td>32</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>15</td>
<td>4</td>
<td>21</td>
<td>13</td>
</tr>
</tbody>
</table>

tenmias. The 9 patients treated three years initially had severe symptoms of autonomic blockade; however, all were doing some work within a year of discharge from the hospital and now none has symptoms referable to his drugs.

Of the 50 patients known to be dead, autopsies were performed in 32 of the 34 who died in the hospital. Some postmortem findings are summarized in table 3. Fibros pneunmonitis was found anatomically in 9 of 11 patients without excessive pretreatment azotemia who continued their therapy. Of these only 1 had renal failure (case report 1); whereas 8 died with less than 60 mg. nonprotein nitrogen per 100 ml. of plasma, with the terminal tachypnea that has been associated with large doses of ganglionic blocking agents, and with no other obvious reason for demise. Six of the 8 died during 1951 and 1952. One of the 2 patients without fibros pneunmonitis died of an apoplectic stroke and the other with heart failure.

Among the patients who discontinued
therapy and among those who initially had more than 60 mg. nonprotein nitrogen per 100 ml. of plasma, renal and cardiac failures were the rule; moreover fibrinous pneumonitis was not found without uremia. In the entire 32 autopsies significant pyelonephritis was found only 4 times; recent myocardial infarction and cerebral vascular accident were each discovered once. Renal arteriolar necrosis was most common in the group with the greatest pre-treatment nitrogen retention; however, it was present in 3 of 11 patients who had less than 60 mg. nonprotein nitrogen at the time of death.

Two illustrative cases, one of a living and one of an expired patient, are reported accompanied by graphs indicating medication, mean blood pressure, and azotemia before and during treatment.

REPORTS OF CASES

Case 1. This 40 year old white man was first admitted to Barnes Hospital in February 1952 with paroxysmal frontal headaches that had begun two years previously. These increased in severity and became associated with emesis and syncope, making the patient permanently bedfast nine months prior to hospitalization. Systolic pressure varying between 180 to 240 mm. Hg and 4 plus albuminuria were present during this period. In the two months immediately before he entered the hospital, he lost 11 Kg. of weight; in addition amaurosis, asthenia, and hematuria appeared. There was no history suggestive of renal or cardiac failure. Except for a supine blood pressure of 286/180 mm. Hg, his vital signs were within normal limits when he was admitted to the hospital. He was asthenic but alert and cooperative. There was papilledema as well as hemorrhagic and exudative retinitis. The lungs were clear to percussion and auscultation. Cardiomegaly and an apical systolic gallop were present. No peripheral edema nor abnormal abdominal findings were noted. There were 14.0 Gm. hemoglobin per 100 ml. blood; urinalyses revealed 3 plus albuminuria, cylindruria, and microscopic hematuria. The determination of fecal blood by guaiac was 3 plus. There were 38 mg. non-protein nitrogen per 100 ml. plasma. Less than 8 per cent of intravenously injected phenol red was excreted in 120 minutes. Urine cultures were repeatedly negative. The circulating electrolytes were within normal limits. Electrocardiograms and roentgenograms of the chest revealed cardiomegaly. Roentgenologic air-contrast studies made in search of a pheochromocytoma revealed only bilaterally small kidneys. Neither benzodioxane nor sodium amytal lowered the diastolic blood pressure below 180 mm. Hg.

As shown in figure 5 the blood pressure was initially lowered with oral hexamethonium chloride. When tolerance appeared within a few days, it was quickly overcome by the addition of hydralazine; however, with normotension disorientation had appeared and only gradually resolved. During a stormy 10 weeks in the hospital ganglionic blockade produced urinary retention and the resultant catheterization led to infection of the genitourinary tract with a strain of Escherichia coli that proved resistant to all available antibiotics. His nonprotein nitrogen level increased to 108 mg./100 ml. of plasma. Two months after the patient had returned home, taking 500 mg. of hydralazine and 375 mg. of hexamethonium chloride a day, he had regained his mental facilities and 15 Kg. of weight; moreover there were only 48 mg. nonprotein nitrogen per 100 ml. plasma. Slowly both his strength and his azotemia increased, but his nutritional and mental status remained unaltered, and his blood pressure was unchanged.

In May 1954, he first began to complain of vague abdominal pain. At this time 1 plus albuminuria was found without other urinary abnormalities. There were 6300 leukocytes per cu. mm. blood, 10.5 Gm. hemoglobin/100 ml. blood, and 110 mg. nonprotein nitrogen, 84 mg. cholesterol, 5.6 Gm. albumin, and 1.9 Gm. globulin/100 ml. plasma. No circulating lupus erythematosus cells were seen, and the sedi-
neous, eosinophilic material. There were also cardiac hypertrophy and mucosal ecchymoses in the rectosigmoid colon. Pulmonary congestion and fibrinous pneumonitis were prominent. In some areas of the lung there was dense homogeneous material in the alveolar spaces that stained deeply with eosin and resembled a hyaline membrane; into it infrequent fibroblasts were growing; intra-alveolar hemorrhage associated with focal necrosis was present.

**Case 2.** This 49 year old white man was operating his own steam shovel until he first entered Barnes Hospital in August 1952, with a history of hypertension for 11 years. His initial symptom was a "slight stroke" without residual six weeks before admission. The only other complaints were amblyopia and nocturia, which appeared soon thereafter. In the hospital his blood pressure was 215/145 mm. Hg; temperature, pulse, and respirations were normal. Hemorrhagic and exudative retinitis associated with papilledema was seen. Save for cardiomegaly the rest of the physical examination was normal. There was 3 plus albuminuria; 13.2 Gm. hemoglobin/100 ml. blood and 48 mg. nonprotein nitrogen/100 ml. plasma were present. Only 2 per cent of intravenously injected phenol red was excreted within 15 minutes. Both electrocardiogram and roentgenogram of the chest indicated left ventricular enlargement. Other laboratory studies were not remarkable. Oral hexamethonium chloride and hydralazine were instituted according to the previously described regimen with minimal side effects. After a month he went home with the medications and blood pressure indicated in figure 6.

He reentered Barnes Hospital 45 days later because of dysuria, anorexia, weight loss, and intermittent diarrhea and constipation without nausea or vomiting. His blood pressure was 160/90 mm. Hg; "hard" exudates but neither papilledema nor hemorrhages were observed in the ocular fundi; otherwise the physical signs were unchanged. There was 1 plus albuminuria and 40 mg. nonprotein nitrogen/100 ml. plasma. Since considerable infected residual urine was found, transurethral prostatectomy was performed, following which the nonprotein nitrogen rose to 82 mg./100 ml. plasma. After six weeks of supportive therapy the azotemia returned to its previous level, and he returned home with little improvement in his gastrointestinal symptoms. Six months later these had diminished considerably and he had returned to full-time office work.

Azotemia, blood pressure, and intake of antihypertensive agents during the fourth admission to Barnes Hospital in May 1954 are indicated in figure 6. He reentered because of continuing minimal anorexia and constipation. The blood pressure was 170/100 mm. Hg. Funduscopic examination revealed no hemorrhages, exudates, or papilledema. The lungs were clear, and the heart did not seem to be enlarged; the liver was felt 3 cm. below the costal margin, but peripheral edema was not found. There were 12 Gm.

*Fig. 6. Case 2. Medication, blood pressure, and azotemia are indicated on the same time axis for three different periods. The figures for blood pressure and medication are weekly averages and represent 35 recorded values at home and 42 in the hospital; the pressure readings were taken with the patient in a sitting position. The oral dosage of hexamethonium chloride is represented by solid bars and that of pentolinium tartrate by cross-hatched ones.*
hemoglobin/100 ml. blood and 8000 leukocytes per cu. mm. blood. A trace of albuminuria persisted and many leukocytes were found in the urine. There were 52 mg. nonprotein nitrogen/100 ml. plasma, but the concentrations of circulating proteins were normal. Cephalin-cholesterol flocculation and thymol turbidity of the serum were within normal limits, and no lupus erythematosus cells were seen in peripheral blood. The electrocardiogram was markedly improved in comparison to the original record, and the chest film substantiated the decrease in cardiac size. When the autonomic-blocking agent was changed from hexamethonium to pentolinium ion, the blood pressure fell to unusually low levels and the non-protein nitrogen immediately rose to 94 mg./100 ml. plasma. Despite this he was sent home, where his blood pressure returned to its usual level and his nitrogen retention decreased.

Another prostatectomy was performed in February 1955, following intermittent bouts of pyuria and the discovery of 200 ml. of residual, infected urine. At this time his blood pressure was 155/95 mm. Hg. The physical examination was unchanged. There were 11 Gm. hemoglobin/100 ml. blood. A trace of albumin persisted. There were 69 mg. nonprotein nitrogen/100 ml. plasma; this value rose to 85 mg. following surgery but fell to 61 mg. before discharge. Since discharge he has had no further complaints, and he continues to work a full day running his own construction business.

Discussion

The patients considered here were all in the final stages of a rapidly progressive fatal disease. With antihypertensive regimens, some have lived and worked for years. The 12 patients who are known to have died within a month of discontinuing therapy indicate the severity of the disease. The fact that only 8 discontinued therapy without our consent is a measure of how well patients accepted such a regimen. Cardiac status gradually improved with tension sustained near normal but renal function changed little. In consideration of the prognosis without treatment, the hazards of therapy are slight. The danger of acute renal failure following relative hypotension can be largely obviated by carefully titrating blood pressure against nitrogen retention. Delayed toxicity to hydralazine, which may simulate disseminated lupus erythematosus, vanished upon cessation of the offending drug. Reactions to ganglionic blockade, although less readily reversible, have become increasingly rare as the drugs are more effectively used.

Summary

A combination of ganglionic blocking agent and 1-hydrizinophthalazine was given orally to 82 patients with malignant hypertension and nitrogen retention. Of 46 who had between 30 and 60 mg. nonprotein nitrogen per 100 ml. plasma and who continued on adequate therapy, 27 are alive and working after an average of 21.8 months; almost half have been treated for two years. Only one of 20 patients with more severe initial azotemia is living. The survivors have maintained near normotension; for them cardiac function has improved, but renal function has not changed. Heart failure occurred 15 times and kidney failure 21 times in the 32 autopsied patients. The major post-mortem diagnoses were fibrinous pneumonitis in 18, renal arteriolar necrosis in 13, pyelonephritis in 4 and myocardial infarction and cerebral vascular accident in one each; however, in the 11 cooperative patients with initially mild azotemia, uremia occurred only once and fibrinous pneumonitis eight times.

Summario in Interlingua

Le combination de un agente ganglioblocante con 1-hydrizinophthalazina eseva administrate oralmente a 82 patientes con hypertension maligne e retencion de nitrogeno. Inter le 46 patientes, qui habeva inter 30 e 60 mg nitrogeno nonproteincic per 100 ml plasma e qui continuava reciper un adequate therapia, 27 vive e labora post un intervallo median de 21,8 menses; quasi 50 pro cento ha essite sub trattamento durante duo annos. Un sol paciente ex le gruppo de 20 subjectos con plus sever azotemia initial es ancora inter le viventes. Le superviventes ha mantenite un tension quasi normal. In illes le function cardiac se ha meliorate, sed le function renal ha remanite inalterate. Disfallimento cardiac occurreva 15 vices e disfallimento renal 21 vices in le 32 patientes autopsiate. Le principal diagnoses post morte eseva pneumonitis fibrinose (18 casos), necrosis reno-arteriolar (14), pyelonephritis (4), infarcimento myocardial (1), e accidente cerebro-vascular (1). Tamen, in le 11 patientes cooperative con initialmente leve grados de azotemia, uremia
occurreva solmente un vice e pneumonitis fibrinose 8 vices.

REFERENCES


The first case, an apparently normal 28-year-old woman without previous complaints, developed numerous episodes of syncope during the third month of a second pregnancy. The electrocardiogram showed a wide QRS with a separate slow initial component as in the Wolff-Parkinson-White syndrome, but the P-R was never less than 0.12 sec. The episodes could not be influenced by atropine or ephedrine, but ceased as soon as complete A-V block with a typical left bundle-branch block pattern appeared. Death occurred suddenly during the eighth month of pregnancy. In a second similar case, the syncope appeared during the fifth month of pregnancy, followed by normal delivery. It reappeared during the following year, especially in the premenstrual period, but disappeared as soon as complete A-V block set in. The ventricular complex at this time as well as previously, showed deeply inverted, pointed T waves in leads I, and V₁ to V₅. Death occurred suddenly. The relation of A-V block to pregnancy and menstruation in these cases is attributed to hormonal influences.

Lepeschkin
Studies on the Control of Hypertension. VII. Effects of Ganglionic Blockade Combined With Hydralazine on the Malignant Stage Complicated by Renal Azotemia

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