Arterial Pressure Responses to Discontinuing Antihypertensive Drugs

By Harriet P. Dustan, M.D., Irvine H. Page, M.D., Robert C. Tarazi, M.B., M.D., and Edward D. Frohlich, M.D.

SUMMARY
A wide spectrum of arterial pressure responses to discontinuing long-term antihypertensive drug treatment was found in 65 patients. In five, spontaneous pressure variations prevented judging effects of drug discontinuance. Of the remaining 60, pressure returned to pretreatment levels in 21, and rose toward control levels in 37; while in two, diastolic hypertension did not reappear in more than 8 years. Rate of rise of arterial pressure seemed related to type of hypertension and to height of diastolic pressure and severity of vascular disease before treatment. In six of nine patients who had had malignant hypertension and six of nine with renal arterial disease, pressure rose promptly and treatment was restarted within a month. Among essential hypertensive patients, those who remained off treatment for 2 to 6 months had significantly lower pretreatment pressure than those whose hypertension returned in less than 2 months. The two whose diastolic hypertension seemed "cured" had no distinguishing features.

These results suggest that most hypertensive patients require continuous treatment for good pressure control; downward resetting of pressure by treatment is rare.

Additional Indexing Words:
Hypertension Renal arterial disease Essential hypertension
Malignant hypertension Renal parenchymal disease Pressor mechanisms
Baroceptor resetting Placebo therapy

ANTIHYPERTENSIVE drug treatment has become effective and practical during the 17 years since the first potent drugs were introduced. Accordingly, there is an increasing number of hypertensive patients in whom arterial pressure is maintained at normal, or near normal, levels. This ability to reduce arterial pressure for prolonged periods has suggested the possibility that in some patients pressure might be reset at a lower level, so therapy would no longer be necessary.1 Alternatively, drug treatment might serve only to suppress pressor mechanisms constantly present and would be required continually for control of hypertension.

This report describes arterial pressure responses to discontinuing antihypertensive drug treatment in 65 hypertensive patients. It extends our earlier observations1 and, by including a comparison of pressure responses to placebo therapy and to discontinuing all medication, provides validation of an experimental design that includes active patient participation through daily arterial pressure measurements.

Plan of Study
The period of this study extended from early 1951, when drugs were first used, to June 1967. All patients were admitted to the hospital for investigation of known causes of hypertension. Insofar as possible, this was done prior to the beginning of drug treatment, but for patients in the earlier years of the study, investigations were limited and as new techniques became available they were applied whenever feasible. For instance, renal arteriography, not available

---

From the Research Division, Cleveland Clinic Foundation, Cleveland, Ohio.
Supported in part by Grant HE-6835 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.
at the beginning of the study, was performed in all but eight of the 65 patients. Hypertension was classified as essential or malignant, or associated with renal arterial stenosis or parenchymal disease—pyelonephritis or polycystic disease (table 1). Patients with pheochromocytoma or primary aldosteronism were not included.

All patients were taught how to use a sphygmomanometer and measured blood pressures at home twice daily, while they were lying and standing. Weekly averages of supine readings were used in assessing effects of treatment and its discontinuance. During the earlier years, drug treatment was begun after an appropriate period of hospital observation (2 or 3 weeks), but more recently control readings have usually been obtained at home if supine diastolic pressure during the hospital investigations averaged less than 110 mm Hg.

Values for arterial pressure, given in the tables as representative of levels achieved during treatment, were means of many weeks’ or months’ readings prior to the stopping of treatment. When more than one study without therapy was carried out, subsequent “treatment” values were obtained from readings taken during sequential treatment periods. The levels of arterial pressure reported as occurring during periods without treatment depended on the length of time without drugs. When this was 3 months or longer, the blood pressure given usually represented the last month’s average; during shorter periods, when blood pressure rose rapidly, the value used was often the average obtained during the week before treatment was restarted.

Arterial pressure responses during periods without treatment were graded under the headings of “increase,” “return to control levels,” and “no change.” In the first two categories, the decision was often arbitrary. For example, if arterial pressure during the control period had averaged 228/126 mm Hg and that without treatment, 184/124 mm Hg, arterial pressure was considered to have increased; in contrast, if the pressure without therapy rose to 228/120 mm Hg, it would be judged as having returned to control levels.

Severity of hypertensive cardiovascular disease before treatment was estimated by use of a severity index, which assigns a numerical grading to the level of supine diastolic arterial pressure and to evidence of hypertensive cerebral, retinal, cardiac, and renal disease.

The antihypertensive drugs used most frequently were hydralazine, ganglion-blocking agents (hexamethonium, pentolinium, mecamylamine, and chlorisondamine), reserpine, chlorothiazide and hydrochlorothiazide, guanethidine, and methyldopa. One drug was used initially, and to this, one or two additional drugs were added, if indicated. Care was taken to establish the response to any drug or combination before another agent was added.

At some time during treatment, drugs were either discontinued or replaced by an appropriate placebo (table 2). For the most part, treatment was begun again whenever arterial pressure returned to pretreatment levels or was considered to have risen sufficiently to eliminate the possibility of spontaneous variation. For the purpose

* We are indebted to the following pharmaceutical companies for generous supplies of drugs: CIBA Pharmaceutical Company for hydralazine, reserpine, chlorisondamine, hydrochlorothiazide, and guanethidine; E. R. Squibb and Sons for hexamethonium; Merck, Sharpe and Dohme for mecamylamine, chlorothiazide, and methyldopa; and Wyeth Laboratories for pentolinium.

Table 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>M</th>
<th>F</th>
<th>Range</th>
<th>Age</th>
<th>Median</th>
<th>Length of study (years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension</td>
<td>39</td>
<td>29</td>
<td>10</td>
<td>18-60</td>
<td>45</td>
<td></td>
<td>3-22 8</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td>28-44</td>
<td>38</td>
<td>5-15</td>
<td>9</td>
</tr>
<tr>
<td>Renal arterial stenosis</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>41-59</td>
<td>47</td>
<td>3-16</td>
<td>5</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>15-58</td>
<td>28</td>
<td>2-20</td>
<td>6</td>
</tr>
</tbody>
</table>

*Indicates length of observation, and not treatment; some patients had been followed for several years before potent drugs became available.
Table 2
Arterial Pressure Responses to Discontinuing Antihypertensive Drug Treatment*

<table>
<thead>
<tr>
<th>Patient numbers</th>
<th>Sex</th>
<th>Diagnoses†</th>
<th>Study period</th>
<th>Arterial pressure (mm Hg)</th>
<th>Arterial pressure (mm Hg)</th>
<th>Arterial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>Control</td>
<td>Range</td>
</tr>
<tr>
<td>A. Comparison of placebo and “no treatment” periods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-17</td>
<td>9-S</td>
<td>EH (13), RAD (2), RPD (2)</td>
<td>pl</td>
<td>188/115</td>
<td>S</td>
<td>147-242</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Placebo periods only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-26</td>
<td>7-2</td>
<td>EH (6), MH (1), RAD (2)</td>
<td>pl</td>
<td>180/113</td>
<td>S</td>
<td>152-209</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. “No treatment” periods only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27-60</td>
<td>23-11</td>
<td>EH (15), MH (8), RAD (5), RPD (6)</td>
<td>0</td>
<td>195/123</td>
<td>S</td>
<td>158-235</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. Spontaneous variations in arterial pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61-65</td>
<td>3-2</td>
<td>EH (5)</td>
<td>pl</td>
<td>168/108</td>
<td>S</td>
<td>144-182</td>
</tr>
</tbody>
</table>

*An expanded table is available, which gives information for each patient, including duration of drug treatment before discontinuing, arterial pressure averages, length of time without treatment, age, duration of hypertension before treatment was begun, and a numerical estimate of the severity of hypertensive disease. This information may be obtained on request.

†Diagnoses: EH, essential hypertension; RAD, renal arterial disease; RPD, renal parenchymal disease; MH, malignant hypertension. Bracketed numbers refer to numbers in each diagnostic group.

S, systolic arterial pressure.
D, diastolic arterial pressure.
Table 3
Arterial Pressure Responses During Periods Without Drugs in 60 Hypertensive Patients

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Number of patients</th>
<th>Arterial pressure responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Increase</td>
</tr>
<tr>
<td>Placebo vs. “no treatment”</td>
<td>17</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“no treatment”</td>
</tr>
<tr>
<td>Placebo</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>“No treatment”</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

of this discussion, “no treatment” refers to discontinuing any medication considered by the patient as treatment for hypertension. Placebo periods or periods of “no treatment” ranged from 2 weeks to more than 10 years, with a median length of 4 months.

Table 2 lists the types of treatment changes carried out in these 65 hypertensive patients. In 17, effect of placebo therapy was compared with effect of discontinuing all drugs. Nine patients were given placebos only, while in 34, the effect of “no treatment” was studied. An additional five patients treated with placebos are presented as a separate group because arterial pressure seemed to vary spontaneously in such a fashion that effect of placebo therapy could not be assessed adequately.

Twenty-two of the 30 patients reported originally 1 are included in this study. Three could not be considered because although the potent antihypertensive drugs had been stopped, treatment with hydrochlorothiazide was continued. Five were excluded because subsequent experiences suggested that either their arterial pressure responses during periods without treatment may have been spontaneous variations or their concern over the pressure changes prevented their reporting them reliably.

Results
Arterial Pressure Responses During Placebo and “No Treatment” Periods

To assess the validity of the study design, which included home blood pressure readings, arterial pressure responses during placebo periods were compared with “no treatment” periods in 17 patients. Table 2A gives the group means for the two periods, as well as the pretreatment blood pressure levels. In some, the placebo trial was carried out first, followed many months later by discontinuing therapy; in others, the sequence was reversed. Arterial pressures were equally well controlled by therapy during the months prior to placebo and “no treatment” periods and rose to the same level during times without therapy (tables 3 and 4), with the exceptions that in one patient pressure returned to control levels during placebo treatment and did not rise so high when all drugs were discontinued, whereas in another the opposite response occurred. The only group difference was that placebo periods were longer: 3 months versus 1.7 months. Individually considered, the placebo period was longer than the “no treatment” period in 13 patients, of equal length in one, and shorter in three.

Nine patients were studied during placebo therapy only for periods ranging from 3 to 15 months (table 2B). Arterial pressure rose in all (tables 3 and 4); in five, it returned to control levels, and in four, somewhat lesser increases occurred.

In 34 patients, all treatment was stopped for periods ranging from 2 weeks to more than 10 years (table 2C). Arterial pressure rose in most (tables 3 and 4); in 10, it returned to pretreatment values, and in 22, it increased, but not so much. In two patients, drug treatment was not restarted. One (no. 39), a man with essential hypertension, who was 60 years old when treatment was begun,
Table 5
Arterial Pressure Responses to Discontinuing Antihypertensive Drugs in Various Types of Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Patient no.</th>
<th>Time off drugs (mo)</th>
<th>Duration Rx (mo)*</th>
<th>Severity index†</th>
<th>Arterial pressure responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>A. Malignant hypertension:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.3</td>
</tr>
<tr>
<td>Periods without drugs of 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>207/143</td>
</tr>
<tr>
<td>or less—6 patients—Means</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>190/130</td>
</tr>
<tr>
<td>Individual patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>182/122</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>182/130</td>
</tr>
<tr>
<td>B. Renal arterial stenosis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.7</td>
</tr>
<tr>
<td>Periods without drugs of 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>189/122</td>
</tr>
<tr>
<td>or less—6 patients—Means</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>162/96</td>
</tr>
<tr>
<td>Individual patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>205/110</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>69</td>
</tr>
<tr>
<td>C. Essential hypertension:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.3</td>
</tr>
<tr>
<td>Periods without drugs of 2 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>179/110</td>
</tr>
<tr>
<td>or less—14 patients—Means</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>218/122</td>
</tr>
<tr>
<td>Periods without drugs from 2.5 to 6 months—15 patients—Means</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>202/110</td>
</tr>
<tr>
<td>Individual patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>210/112</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>180/124</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>210/108</td>
</tr>
</tbody>
</table>

*Refers to months of drug treatment before discontinuing it.
†Represents the total severity index, as given in table 2.

received drugs for 14 months only, and even after more than 8 years without treatment, diastolic hypertension had not returned; he died of a myocardial infarction 99 months after treatment was discontinued. The other patient (no. 55), a girl with chronic pyelonephritis, was 15 years of age when treatment with hydralazine was begun because of mild hypertension (hospital blood pressures averaged 144/97 mm Hg). Arterial pressure became normal when hydralazine was given and did not rise when the drug was stopped 4 years later, nor has it risen above normal in the 10 years since.

In patients who had more than one period without drug treatment, response of arterial pressure was similar each time. This is shown not only by comparing pressure changes in the 17 patients during placebo and “no treatment” periods (tables 2 and 3), but also by the responses during additional periods without drugs in four of the 17 and in another nine patients from the placebo or “no treatment” groups. Some patients had as many as four periods of drug discontinuation, separated by many months, and similar responses occurred each time.

Arterial Pressure Responses in the Various Types of Hypertension

The rate of blood pressure rise during periods without antihypertensive drug treatment seemed related, in part, to the type of hypertension and to the height of diastolic arterial pressure and severity of hypertensive cardiovascular disease prior to therapy (table 5). Neither age at the start of treatment nor duration of treatment seemed important.

Treatment was discontinued in the nine patients with malignant hypertension. In six, blood pressure rose promptly, so that drugs were begun again in 4 weeks or less (table 5A) (fig. 1). Pretreatment arterial pressure average for the six was 207/143 mm Hg; during treatment, the average was 159/101 mm Hg, and without treatment, 190/120 mm.
ARTERIAL PRESSURE RESPONSES

Hg. These patients had severe vascular disease, as expressed by a severity index for the group of 10.3. They had been treated an average of 52 months before drugs were discontinued. The courses of the other three patients with malignant hypertension were different, although pretreatment diastolic pressure and vascular disease were similar. In one (no. 45), pressure rose slowly over a period of 2 months and did not reach levels found in the six. The other two patients discontinued treatment, but returned for medical care, 5 and 30 months later; both again had malignant hypertension.

Six of the nine patients with renal arterial stenosis also had responses similar enough to classify them as a group (table 5B). Like the patients with malignant hypertension, arterial pressure rose so promptly when drug therapy was discontinued that treatment was restarted within a month. The rate of blood pressure rise and duration of treatment prior to stopping drugs (47 versus 52 months) were the same as in the malignant hypertensive patients, but, in contrast, the average pretreatment pressure was not so high (189/122 versus 207/143 mm Hg), hypertensive vascular disease was less severe (severity index 4.7 versus 10.3), and arterial pressure control during treatment was better (148/95 versus 159/101 mm Hg). In the three other patients with renal arterial stenosis, arterial pressure rose more slowly during periods without treatment. One patient (no. 26) had only very mild hypertension, but with that exception there were no features that distinguished these patients from the other six.

Most of the patients with essential hypertension could be divided into two groups, depending on whether periods without drugs were shorter than 2 months or ranged from 2 to 6 months (table 5C). The first group, in contrast to the second, had been treated longer (69 versus 50 months), had higher arterial pressure pretreatment (195/120 versus 179/110 mm Hg, P < 0.05) and poorer arterial pressure control during treatment (158/99 versus 142/86 mm Hg). The remaining five essential hypertensive patients were without treatment longer than 6 months; in four, treatment was begun again after periods ranging from 7 to 27 months (fig. 2), but one (no. 39) remained nearly normotensive until his death, 99 months after medication had been discontinued. These patients did not have any features that set them apart from the rest of the patients with essential hypertension.

Figure 1

A summary of the course of arterial pressure during 6 years of a man (no. 46) treated originally because of malignant hypertension, showing the good blood pressure control accomplished with drugs and the prompt increase in arterial pressure during two of the four times that treatment was stopped. "Months" refers to months of known hypertension. Arterial pressure was taken in the supine position; the values graphed here represent weekly averages of either hospital readings (circles), taken four times daily, or home averages (triangles), taken twice daily. Arrows indicate treatment: (1) guanethidine and hydrochlorothiazide begun, (2) both drugs discontinued, (3) guanethidine treatment begun again, (4) guanethidine discontinued, and (5) guanethidine treatment restarted.

Figure 2

A summary of the course of arterial pressure throughout 9 years of observation of a woman with essential hypertension. "Months" refers to months of known hypertension. Supine arterial pressure readings are given; the values represent weekly averages of either hospital readings (circles) or home readings (triangles). Arrows refer to treatment changes: (1) hydralazine treatment started, (2) hydrochlorothiazide added, (3) both drugs discontinued, and (4) treatment begun again. It shows the arterial pressure control achieved by hydralazine alone and in combination with hydrochlorothiazide, and the gradual return of hypertension during the 2 years without treatment.

Circulation, Volume XXXVII, March 1968
The effectiveness of drug treatment in controlling hypertension may have been a determinant of the rate of arterial pressure rise when therapy was discontinued, but the data are not sufficient to establish this. Although the 15 essential hypertensive patients who were without drugs for the longest periods had had the best blood pressure control, they also had the mildest hypertension and least severe vascular disease before treatment.

Of the eight patients with renal parenchymal disease, six had pyelonephritis; two, polycystic renal disease. In all except one, arterial pressure rose toward (five), or to, control (two) levels in 3 weeks to 6 months without antihypertensive drugs, but the rates of rise were too variable to permit separation of any homogeneous subgroups. The remaining patient (no. 55) was the 15-year-old girl with pyelonephritis who has remained normotensive during more than 10 years without drugs.

Spontaneous variations in arterial pressure during placebo, “no treatment,” and treatment periods were large enough in five patients (table 2D) that the effects of treatment changes could not be assessed with assurance. These patients have been included to point up the necessity for long-term observations in hypertensive patients, because two of them were reported initially,1 one as an example of modification of arterial pressure level by long-term antihypertensive drug treatment.

Mortality of Hypertensive Patients During Long-Term Observation

An analysis of the mortality among these patients indicates the safety of this type of study. Thus, although 14 patients have died, only one death occurred when drug treatment was not being given. This was the death of the patient (no. 39) whose hypertension did not return during the 99 months without treatment that preceded his death. Of the remaining 13, five patients died following cerebrovascular accidents; six, of coronary heart disease; one, with slowly progressing uremia; and one, following rupture of an abdominal aortic aneurysm. In none was hypertension uncontrolled at the time of the fatal illness. Neither these nor the patients now living suffered nonfatal complications of hypertension during periods without therapy.

Discussion

Long-term drug therapy of any illness carries with it the potential of unavoidable late side effects; fortunately, antihypertensive drugs have been relatively free from such difficulties. Although hexamethonium produced a fatal pneumonitis3 and mecamylamine, a serious neurological disorder,4 they were long ago supplanted by safe drugs that more effectively suppress sympathetic nervous activity. Further, we now know that the lupoid illness produced by hydralazine5 can usually be prevented by using small doses of the drug and that reserpine's potential for causing severe depression can be practically eliminated by reducing dosages.

In spite of the apparent safety of the truly effective antihypertensive drugs, it should be established whether patients require continuation of drug therapy after many years of treatment. Currently, it is not feasible to perform such a study without having patients participate actively by recording their own arterial pressures. Yet this aspect of experimental design puts in doubt the validity of the results, because the increases in blood pressure that can occur when treatment is stopped are often accompanied by varying degrees of anxiety, which might, of themselves, be pressor. However, home readings are necessary because as many measurements as possible must be obtained to establish the changes that may result from treatment manipulations. Office readings cannot be performed often enough to yield reliable information, particularly in patients with reversed malignant hypertension or renal arterial stenosis, whose pressures tend to rise sharply over short periods of time. For this type of investigation, an apparatus is needed for home use that automatically records readings without the patient's knowledge. A semiautomatic, portable blood pressure recorder6,7 with a
magnetic tape-recording device has been developed, but is not yet available for wide use.

Although the design of our study may be questioned because the patients knew their blood pressure levels, its validity seems established by the similarity of arterial pressure responses during placebo and "no treatment" periods. That placebo periods were longer than periods without treatment does not necessarily indicate a slower rise in pressure when placebo was given, because moderately elevated pressures were sometimes allowed to persist longer during placebo periods than when all treatment was stopped.

Most of our patients required drugs for continuing blood pressure control. Although some remained nearly normotensive for several months after drugs were stopped, pressure eventually rose and treatment was begun again; only two appeared to have been "cured." Perry and associates\(^8\) have also suggested that drug treatment is usually required over a long time by showing the large mortality from hypertensive complications (as opposed to atherosclerotic ones) in patients whose diastolic pressures after stopping treatment were 120 mm Hg or above. Similar indications of need for long-term treatment come from the reports of Schroeder and Perry\(^9\) and Hood and associates.\(^10\)

Our two patients, apparently "cured," were among the nine we reported in 1962\(^1\) whose hypertension seemed to have been greatly modified, or "cured," by long-term treatment. In six of the nine (nos. 27-29, 38, 57, and 60), treatment was subsequently restarted, and in one (no. 63), pressure was found to vary enough spontaneously that effects of discontinuing drugs could not be assessed. Two other studies have described patients whose hypertension was "cured," or greatly modified, by long-term drug therapy. Perry and associates\(^8\) reported 16, from a group of 316, who remained normotensive for prolonged periods after treatment was stopped, but Thurm and Smith\(^11\) found in 16 of their 69 patients that arterial pressure remained down for 10 to 42 months without drugs.

The small numbers of "cured" patients in our study and that of Perry and associates\(^8\) are in sharp contrast to the experience of Thurm and Smith.\(^11\) This difference is probably based on differences in severity of hypertension and hypertensive vascular disease among the patients studied. Many of those included in this and Perry's report had high diastolic pressure and severe vascular disease, while those of the Thurm and Smith study were mildly hypertensive, as shown by a group average for mean arterial pressure of 122 mm Hg. The results reported here also show that patients with mild essential hypertension maintained reduced pressure for much longer periods without drugs than did the essential hypertensive subjects with higher diastolic pressures or than those with malignant hypertensive or renal arterial stenosis.

McCubbin and associates\(^12\) showed that chronic renal hypertension in dogs was associated with upward resetting of carotid sinus baroreceptor function, so that a neurogenic factor helped to maintain elevated pressure. This finding suggested the possibility that downward resetting might occur in hypertensive patients if arterial pressure could be kept at near-normal levels by prolonged drug treatment. However, the results of the present study do not indicate resetting of a degree sufficient to maintain arterial pressure at wholly normal levels, and this is not surprising considering the mosaic of factors that determine the pressure level.\(^13\) The differing responses of patients with various types of hypertension to discontinuing drugs support the evidence for several factors as important in clinical hypertensions; those now recognized are adrenal, renal, and neural.

In untreated malignant hypertension, increased aldosterone secretion\(^14\) and elevated plasma renin activity\(^15\) have been found consistently. The most effective drugs for treatment of malignant hypertension are those that suppress sympathetic nervous function, and since nervous activity influences renin release,\(^16\) these drugs may suppress, but not eliminate, a renal factor. In our patients with
renal arterial stenosis, suppression of a neurogenic factor in renin release may also have been important in control of hypertension, because of the six whose pressures rose quickly when treatment was discontinued, four had been taking guanethidine, and one, reserpine.

In contrast to the findings in the patients with malignant hypertension and those with renal arterial disease, responses of patients with essential hypertension suggest some modification of the arterial pressure level by long-term treatment. Particularly was this so in patients who were able to go without drugs for 2 to 6 months. Their pretreatment arterial pressure levels were significantly lower than those without treatment for 2 months or less. Recently, we have found that it is the mild essential hypertensive subjects in whom evidence for increased neurogenic activity can be demonstrated by exaggerated pressor responses to head-up tilt and the Valsalva maneuver and depressor responses to intravenously administered trimethaphan. Perhaps it is in these patients that neurogenic influences can be modified by maintenance of arterial pressure at normal levels for prolonged periods.

Spontaneous variations in arterial pressure level, large enough to vitiate conclusions concerning effects of treatment manipulations, were found in five patients. Although the variability of arterial pressure throughout a 24-hour period or from one office visit to another is well recognized, there is little information concerning the course of arterial pressure through months or years. Brown, in 1930, reported a patient who measured blood pressure at home, three times daily, for over 2 years, and described the same sort of long-term variations that we encountered in these five patients.

Acknowledgment

We wish to thank Dr. Roland Schneckloth and Dr. Richard Hurley for their help in part of this study, and acknowledge the participation of Drs. A. C. Corcoran and R. D. Taylor (now deceased) as these investigations were being initiated.

We also wish to thank Miss Enid Davy, R.N., Miss Rosemarie Horvath, Miss Christine Monroe, Miss Patricia Oberle, and Mrs. Aldona Raulnaititis for skillful assistance.

References

12. McCubbin, J. W., Green, J. H., and Page, I. H.:

Hypothesis Defined

... In a modern professional vocabulary a hypothesis is an imaginative preconception of what might be true in the form of a declaration with verifiable deductive consequences. It no longer taws 'gratuitous,' 'mere' or 'wild' behind it, and the pejorative usage ('evolution is a mere hypothesis,' 'it is only a hypothesis that smoking causes lung cancer') is one of the outward signs of little learning. But in the days of Travellers' Tales and Marvels, when (as John Gregory contemptuously remarked) philosophers were more interested in animals with two heads than in animals with one, 'hypothesis' carried very strongly the connotation of the wantonly fanciful and above all (we read it often) the gratuitous; nor was there any thought that a hypothesis need do more than explain the phenomena it was expressly formulated to explain. The element of responsibility that goes with the formulation of a hypothesis today was altogether lacking. ... – P. B. Medawar: The Art of the Soluble. London, Methuen & Co. Ltd., 1967, p. 138; also distributed by Barnes & Noble, Inc., New York.
Arterial Pressure Responses to Discontinuing Antihypertensive Drugs
HARRIET P. DUSTAN, IRVINE H. PAGE, ROBERT C. TARAZI and EDWARD D. FROHLICH

Circulation. 1968;37;370-379
doi: 10.1161/01.CIR.37.3.370

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/37/3/370