Is Drug Treatment Indicated for Mild Hypertension With Diastolic Blood Pressure of 90 mmHg to 100 mmHg?

An Affirmative View

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Most physicians would agree with the available epidemiologic data on hypertension that indicate an increased risk for cardiovascular disease if blood pressure readings remain at levels of 140/90 mmHg or higher, and that patients with a diastolic blood pressure of 100 mmHg or more will benefit from a reduction of blood pressure by pharmacologic therapy. There is a difference of opinion, however, regarding the benefits of treatment on cardiovascular complications in patients with mild hypertension, that is, those with a diastolic blood pressure between 90 and 100 mmHg.[1,2]

A major argument against treatment is that many patients must be treated to benefit a few and that the adverse reactions of specific therapies may be frequent or serious enough to negate the benefits of therapy. Resistance to treatment of mild hypertension may also be based on a narrow interpretation of the major hypertension treatment trials.

There are sufficient data to indicate that less severe hypertension should be treated pharmacologically if, after a suitable period (three to four months) of observation and nonpharmacologic treatment, patients' blood pressure readings have not been reduced to below 140/90 mmHg.[3] The benefit of such treatment appears to outweigh the risk; blood pressure can be lowered in most patients with relatively few adverse reactions or metabolic changes and with little effect on lifestyle. Although the ideal pharmacologic approach to the lowering of blood pressure has not been found and, indeed, may be years from discovery, present medications, if used appropriately, will lower blood pressure levels to normal limits in approximately 85 to 90 percent of less severe hypertensive patients, with a resulting reduction in morbidity and mortality. If the suggested treatment outline herein is followed, overtreatment can be reduced to a minimum.

A persistent elevation of blood pressure should be verified. In several major treatment trials,[4,5] approximately 15 to 20 percent of patients who were initially randomized as hypertensive, with a diastolic blood pressure above 95 mmHg, noted a decrease in blood pressure to lower levels on placebo follow-up. This normalization usually occurred within three to four months. A patient's blood pressure should be rechecked, therefore, on at least two occasions over a three- to four-month period prior to beginning therapy. If the blood pressure decreases to less than 140/90 mmHg, the patient may then be followed at six-month intervals without specific therapy. Following this plan will immediately reduce the potential number of patients who may require treatment by about 15 to 20 percent.

During this initial period of observation, various nonpharmacologic methods of management should be tried. Personal results with these techniques have not been so successful as those reported by some investigators.[6] If, however, patients are able to reduce weight (if appropriate) and sodium intake to approximately 80 to 85 mEq/d, to continue on a moderate exercise program, and to decrease alcohol intake (if more than 3 or 4 oz/d), another 15 to 20 percent will become normotensive. These patients should also be followed at six-month intervals and should be treated only if their diastolic blood pressure returns to 90 mmHg or more.

HYPERTENSION TREATMENT— CLINICAL TRIALS

Clinical trials supply some, but not all, of the answers on how to manage patients whose diastolic blood pressure

TABLE 1. HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM STUDY RESULTS*

Results	Death Rate		Percent Reduction in Mortality
	Stepped-Care**	Routine Care**	Stepped-Care vs Routine Care Patients
Target organ damage present	15.6	20.0	22
Target organ damage absent	4.5	5.8	22.4
Diastolic blood pressure 90 to 94 mmHg	—	—	22
Diastolic blood pressure 95 to 99 mmHg	—	—	23

* From Hypertension Detection and Follow-up Program[7]
** Diastolic blood pressure from 90 to 104 mmHg

remains between 90 and 100 mmHg. Unfortunately, most of these trials started treatment at levels of 95 mmHg or more; the Hypertension Detection and Follow-up Program (HDFP) study[7] specifically intervened in a group of patients whose diastolic blood pressures were 90 to 94 mmHg.

TRIAL RESULTS AND TREATMENT OF LESS SEVERE HYPERTENSION

In over 40,000 patients enrolled in these studies, complications from strokes, fatal and nonfatal, and overall cardiovascular events were decreased by pharmacologic treatment in patients whose diastolic blood pressures were both above and below 100 mmHg—a strong argument for early treatment. In the HDFP study there was a reduction in deaths of 22 percent in patients with diastolic blood pressures of 90 to 94 mmHg and 23 percent in patients with diastolic pressures of 95 to 99 mmHg who were vigorously treated (stepped-care), compared with those less vigorously treated (routine care) (Table 1).[7] In the European Working Party Study on Hypertension in the Elderly (EWPHE),[8] cardiovascular events were reduced by 37 percent in treated patients, compared with patients in the placebo group who had diastolic blood pressures below 100 mmHg. Conclusions of the Australian study[5] clearly state the "benefit was achieved both above and below 100 mmHg in treated compared to placebo patients."

The EWPHE and HDFP studies reported a significant reduction in deaths from coronary artery disease in specially treated patients. There was also a trend, although not statistically significant, in some other trials[4,5] toward a reduction in coronary events. It is not surprising that coronary event rates were not universally reduced in the major trials, given that many trials included healthy individuals who were followed for a relatively short time. Unfortunately, subgroup numbers in several trials were not sufficient to calculate statistical benefit for those pa-

tients in specific categories whose diastolic pressures were between 90 and 104 mmHg. Results were recorded for this entire cohort of patients, so that a definitive answer to the question of whether patients with diastolic blood pressures of 90 to 100 mmHg should be treated cannot be obtained from some of these data.

WHY ELSE TREAT MILD HYPERTENSION?

To Prevent Progression to More Severe Disease

Most of the trials used fatal or nonfatal strokes, fatal or nonfatal coronary occlusions, or specific cardiovascular events, such as dissecting aneurysms, as end points to calculate statistical benefit of treatment. Most physicians have used these data to determine whether treatment is justified. The comparative data on progression from mild to severe hypertension in treated and untreated patients should, however, also be considered,[1] but are usually ignored when evaluating the benefits of therapy. In the five major clinical trials that employed placebos or untreated controls,[4,5,9-11] a total of 1,318 out of 11,129 subjects in the placebo or control groups became severely hypertensive with diastolic pressures in excess of 110 to 130 mmHg. In the active treatment groups, only 82 of 11,206 so progressed (Table 2). The lack of progression in treated patients suggests an important indication for early therapy.

Other factors may be ignored in evaluating clinical trials and the possible benefits of treatment of mild hypertension. No data, for example, are available to answer the question of "undetectable vascular changes" that may have occurred in the course of these short-term (three- to seven-year) trials in patients whose blood pressures remained elevated. If physicians are in agreement that prolonged hypertension increases the progression of atherosclerotic changes in blood vessel walls, presumably by damaging the endothelium and increasing cholesterol turnover, then it is possible that by keeping patients at normotensive levels, this type of clinically undetectable

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TABLE 2. WHY TREAT LESS SEVERE HYPERTENSION
(diastolic blood pressure 90 to 100 mmHg)

1. Prevent progression to more severe disease
   Clinical trials
   1,318 of 11,129 patients progressed to diastolic blood
   pressures of 110 to 120 mmHg in placebo or control
   groups
   Only 82 of 11,206 in active treatment group progressed

2. Prevent strokes and stroke deaths
   Data on diastolic blood pressure above and below 100
   mmHg are not available in all clinical trials, but a
   decrease of between 32% and 100% in strokes and
   stroke deaths has been noted in treated vs control
   patients

3. Prevent or reverse left ventricular hypertrophy and
   congestive heart failure
   Data on patients with diastolic blood pressure values
   below and above 100 mmHg are not available in all
   trials, but a significant decrease in incidence of
   congestive heart failure and a reversal of left
   ventricular hypertrophy in treated mild hypertensive vs
   control patients have been demonstrated

4. Delay or prevent nephrosclerosis and atherosclerosis
   This advantage has not been proven

5. Reduce the incidence of, and deaths from, myocardial
   infarctions (HDFP[7] and EWPHE[8] studies)
   Equivocal results in some trials may be explained by short
   duration of study and type of population studied

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change may be prevented (which, as yet, cannot be proved in humans).

Results from the clinical trials indicate that while blood pressure lowering may be beneficial, even after organ damage has occurred, complications are fewer if therapy is instituted prior to the development of target organ involvement. For example, in the HDFP study, patients without pretreatment target organ damage in the stepped-care or vigorously treated group experienced a decrease in death rate when compared with the routinely treated group (4.5 vs 5.6 percent, Table 1). There was also a significant reduction in deaths in the stepped-care group compared with the routinely treated patients when pretreatment target organ damage was present, but a higher overall mortality was noted in both groups (15.6 vs 20 percent). These facts are important to consider when deciding when to treat mild hypertension. It is also important not to wait for evidence of arteriolar involvement in the retina, the presence of left ventricular hypertrophy, or persistent elevations of diastolic blood pressure to 100 mmHg or above before considering specific therapy.

Observations Regarding Therapy

The definition of treatment in patients with less severe hypertension is important. If the patient is to be subjected to repeated office visits and given expensive medications that may be difficult to titrate, require frequent dosing, or produce subjective side effects, such treatment may not be appropriate for a person with a relatively benign disease process. On the other hand, if one or at most two tablets daily (or every other day) proves effective, is inexpensive, and has few subjective side effects, such treatment may be quite appropriate.

For patients with mild hypertension who are generally asymptomatic and whose risk for an immediate cardiovascular incidence is minimal, it is important that if pharmacologic therapy is to be used, the medications should produce the fewest number of problems. Because diuretics were the initial therapy in all of the clinical trials and are effective in most cases of mild hypertension, it is important to examine the data relating to the adverse effects of these compounds.

The interpretation of the Multiple Risk Factor Intervention Trial (MRFIT)[12] provides an example of how physicians may have been misled into believing that there was a significant risk in treating hypertension. This six- to seven-year trial involved a group of middle-aged men at high risk for cardiovascular disease.

The unexpected findings in MRFIT were that cholesterol levels, smoking rates, and blood pressure levels were lowered not only in the group of men assigned to special intervention clinics, but also in the men referred back to their own physicians for usual care; the anticipated mortality in the usual care group had not occurred, ie, deaths in both groups were similar. The results of the MRFIT study actually confirmed that, whether in a physicians office or at special centers, a reduction in risk factors reduces mortality.

In an attempt to explain the failure to demonstrate a difference in the death rates between the two groups, subgroup analyses were performed. These analyses revealed a special intervention subgroup of hypertensive patients with pretreatment abnormal electrocardiogram findings in whom the death rate was higher than in a similar, usual care cohort. It was suggested that some intervention (presumably the use of diuretics) had resulted in increased mortality. The results of this study have been analyzed elsewhere,[13] and little evidence has been found to substantiate this interpretation.

Several unexplainable findings in the MRFIT study are of interest:

1. Patients in the usual care group who had abnormal pretreatment electrocardiograms had unusually low mortality rates (Table 3). All other studies have shown that hypertensive patients with abnormal findings on pretreatment electrocardiograms have higher mortality rates than those with normal findings on electrocardiograms regardless of the type of management. The usual care group did

TABLE 3. MULTIPLE RISK FACTOR INTERVENTION TRIAL (MRFIT): SUBGROUP ANALYSES FOR DEATHS FROM CORONARY HEART DISEASE*

	Special Intervention		Usual Care	
Subgroup	Number of Study Participants	Death Rate	Number of Study Participants	Death Rate
Hypertensive				
With resting electro-cardiogram abnormalities	1,233	29.2	1,185	17.7
With no resting electro-cardiogram abnormalities	2,785	15.8	2,808	20.7

* From the Multiple Risk Factor Intervention Trial[12]

TABLE 4. MULTIPLE RISK FACTOR INTERVENTION TRIAL (MRFIT)* MORTALITY RATE AND DIURETIC DOSE

	Special Intervention Group Death Rate**	
Diuretic Dose	Abnormal Findings on Electro-cardiogram	Normal Findings on Electro-cardiogram
Chlorthalidone	3.31	2.08
<50 mg/d	4.84	1.76
>50 mg/d	1.84	2.37
Hydrochlorothiazide	7.61	2.21
<50 mg/d	7.20	2.27
>50 mg/d	8.01	2.55

* From the Multiple Risk Factor Intervention Trial[12]
** Per 1,000 patient-years

not show this pattern. Had the usual pattern been demonstrated, the difference between the special intervention and usual care groups would not have occurred.

2. Patients receiving chlorthalidone had a lower mortality than those receiving hydrochlorothiazide (Table 4), yet both in the MRFIT and previous studies, compared with hydrochlorothiazide, chlorthalidone use resulted in a greater degree of hypokalemia. If hypokalemia is an alleged factor in the increased mortality, this finding is difficult to explain.

3. Finally, in the group of men with abnormal pretreatment exercise stress test results, a group within which patients with ischemic heart disease should be found, deaths were lower, not higher, in the special intervention group. If therapy in the special intervention group had affected adversely the outcome by causing hypokalemia and ventricular arrhythmias, as has been suggested, deaths in this subset of patients should have been higher than in the usual care group.

Careful analyses have also failed to show a relationship between deaths and the dosage of diuretics. These data suggest, therefore, that the speculations arising from the MRFIT results are not justified by the facts, and that this study is a poor one to use as an argument suggesting greater risk than benefit in treating mild hypertension.

The issue of risk-benefit treatment of mild hypertensives is further confused by the hypokalemia-ectopy debate.

Several studies, apart from MRFIT, suggest an increased incidence of ventricular ectopy and the possibility of inducing sudden death in patients with diuretic-induced hypokalemia.[14-16]

Others, however, have failed to confirm these observations in hypertensive patients with or without evidence

of left ventricular hypertrophy.[17-19] Although a group of thiazide-treated patients from the Medical Research Council (MRC) study also demonstrated increased ectopy when compared with those on placebo, these patients were studied only after therapy; no baseline monitoring was undertaken. Monitoring before and after treatment in another group of MRC patients did not confirm this finding. The diuretic-induced hypokalemia-ectopy issue has not been settled and is not a valid one to invoke as a reason for nontreatment. If physicians are concerned about thiazide-induced hypokalemia, especially in the elderly, in diabetics, in patients taking digitalis, and so on, potassium-sparing agents with a thiazide diuretic can be used without complicating management or greatly adding to the cost.

Regarding the cholesterol issue, none of the diuretic-treatment-based clinical trials have demonstrated a rise in cholesterol levels over a three- to five-year period (Table 5). The studies that have shown a rise in cholesterol levels are of short term. Further, no firm evidence exists that the changes in high-density lipoprotein or triglyceride levels that may occur when β-blockers are used in the treatment of mild hypertension will negate the beneficial effect of therapy.

Therefore, the metabolic changes that may occur following the use of some of the commonly used antihypertensive drugs, ie, diuretics or β-blockers, should not deter physicians from treating mild hypertension with these agents; the risk appears to be minimal.

The beneficial effects noted above are enough to justify the treatment of the patient with mild hypertension provided that treatment is kept simple and relatively inexpensive, and that the patient remains relatively free of side effects. These goals can be accomplished by the use of medications as suggested by the Joint National Committee,[25] specifically the use of low-dose diuretics as first-

TABLE 5. EFFECT OF DIURETIC-BASED THERAPY ON SERUM CHOLESTEROL

Authors and Duration of Trial	Number	Cholesterol Levels During Treatment, mmol/L (mg/dL)	
		Control	Treated
Veterans Cooperative Study Group on Antihypertensive Agents[10]			
10-week trial	343	5.79 (224)	5.97 (231)*
58-week trial	167	5.84 (226)	5.77 (223)
Berglund and Andersson[20]			
6-year trial	49	6.90 (267)	6.59 (255)
Medical Research Council (MRC) trial[21]			
3 years on treatment			
Men	913	6.33 (245)	6.33 (245)
Women	940	6.75 (261)	6.72 (260)
3 years on placebo			
Men	1831	6.31 (244)	6.18 (239)
Women	1789	6.72 (260)	6.62 (256)
Veterans Administration–National Heart, Lung, and Blood Institute,[22]			
1 yr study			
Treatment	302	5.25 (203)	5.50 (213)
Placebo	308	5.09 (197)	5.09 (197)
Systolic Hypertension in the Elderly Program (SHEP) feasibility trial[23]			
Treatment	443	6.15 (238)	6.15 (238)
Placebo	108	6.26 (242)	6.28 (243)
Hypertension Detection and Follow-up Program (HDFP) trial[7]			
Stepped-care group, 5 years on treatment	716	6.00 (232)	5.77 (223)
Oslo study[9]			
4 years on treatment	26	7.03 (272)	7.05 (273)
Control	33	7.19 (278)	7.24 (280)
Multiple Risk Factor Intervention Trial (MRFIT)[12]			
Special intervention group, 6 years			
Nonsmokers on treatment	818	6.36 (246)	6.30 (244)
Nonsmokers not on treatment	293	6.57 (254)	5.97 (231)
Smokers on treatment	549	5.81 (225)	5.59 (216)
Smokers not on treatment	266	6.05 (234)	5.66 (219)
HAPPY trial[24]			
4 years on treatment	3272	6.26 (242)	6.26 (242)

*P < .001

step therapy in the majority of patients and β-adrenergic inhibitors as first-step therapy in some specific patient groups. Calcium entry blockers or converting enzyme inhibitors, alone or in combination with a diuretic, may be used in some patients, but such therapy becomes expensive and may be more complicated.

Titration of diuretic dosage is easy, cost is relatively low, and after blood pressure is controlled, patients may only have to be seen two or three times a year.[26] A major commitment or expense on the patient's part is not required. Most patients with mild hypertension who are treated with low-dose diuretics or low-dose β-blockers or, in a few cases, converting enzyme inhibitors, alone or in combination with a diuretic, do not experience a decrease in their quality of life. When other drugs, such as α-block-

ers or calcium entry blockers, are used as first-step therapy, however, treatment is more expensive,[27] titration to an appropriate dosage is more difficult, and especially with centrally acting drugs, such as clonidine, guanabenz, or α-methyldopa, subjective side effects are more difficult to manage.

CONCLUSIONS

Sufficient data have been accumulated to justify using specific medications to lower blood pressure in patients with persistently elevated diastolic blood pressures of 90 to 100 mmHg. Although the immediate or even short-term risk of cardiovascular complications is not great in

these patients, long-term risk is significantly increased compared with normotensive individuals. At present, it seems imprudent to await objective evidence of target organ involvement before beginning therapy.

In this relatively low-risk group, blood pressure should be measured several times over a three- to six-month period to establish the diagnosis. Nonpharmacologic methods of treatment should be attempted before specific antihypertensive drug therapy is undertaken, although subsets of patients at higher risk should be treated sooner.

If nonpharmacologic methods are successful in maintaining diastolic blood pressure at levels below 90 mmHg, they should be continued; if not, the stepped-care method of therapy, utilizing a diuretic or one of several β-adrenergic-inhibiting drugs as initial therapy, is effective in a majority of patients. The side effects and cost of therapy should not be great in these individuals. Arguments against instituting therapy at these levels of pressure are based upon theoretic implications of long-term drug toxicity, which, after 25 years of experience, has not been demonstrated.

Maintaining a goal diastolic blood pressure over the long term in patients with less severe hypertension can be expected to decrease the incidence of cerebrovascular disease and of deaths from this cause. Furthermore, it can be expected to prevent progression to more severe hypertension, prevent or reverse left ventricular hypertrophy, and produce an overall decrease in deaths from cardiovascular and coronary heart disease.

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An Opposing View

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Should drug treatment be initiated in hypertensive patients whose diastolic blood pressure responses are in the range of 90 to 100 mmHg? The answer is no because (1) beneficial results have not been convincingly demonstrated, (2) significant adverse effects may result and (3) other methods of treatment are available that do not have the disadvantages of drug therapy.

RESULTS OF DRUG THERAPY

It is difficult to interpret the published results of clinical trials of drug therapy for hypertension. Differences exist in the characteristics of the populations studied, the level of blood pressure on entry, the drugs used, the duration of follow-up, and the end points measured.

Ideally a study should be double blind, placebo controlled, and of sufficient duration to demonstrate differences in outcome. Subjects should be randomly assigned to active drug treatment or placebo. Conditions of care should be identical throughout the duration of the study except for active drug vs placebo treatment. The design and results of some of the most important or most frequently cited studies will be presented.

The Veterans Administration (VA) study[1] was double blind and placebo controlled. Subjects were stratified according to their entry diastolic pressure measurements. After 15 months of follow-up, it was clear that a significant difference in the complication rate existed in subjects whose entry diastolic pressure values were 115 mmHg or higher. That portion of the study was therefore stopped, and active drug treatment was given to the placebo subjects.

The subjects with entry diastolic blood pressures of 90 to 114 mmHg were continued for an average follow-up of 3.3 years.[2] It is important to realize that diastolic pressure in placebo subjects was permitted to range as high as 124 mmHg. Placebo subjects were not removed from the study unless diastolic pressure was 125 mmHg or higher for three consecutive visits over a one-month period. The average difference in diastolic pressure between drug- and placebo-treated subjects was 18 mmHg for the five-year study. Despite the difference in average diastolic pressure and the level of diastolic pressure permitted in the placebo subjects, there was no significant difference in complication rate for subjects with entry diastolic pressures of 90 to 104 mmHg. The VA study then showed striking benefits from drug therapy even at short term for subjects with entry diastolic pressures of 115 mmHg or above, but no benefit was observed over an average follow-up of 3.3 years for subjects with entry diastolic pressures of 90 to 104 mmHg.

The US Public Health Service study[3] was designed to determine whether subjects with mild hypertension would benefit from longer term (ten years) drug therapy. Subjects with any clinical evidence of secondary change (funduscopic, electrocardiographic, chest x-ray, renal function) were excluded. (The VA study had included some subjects with such findings). Entry diastolic pressure was 90 to 104 mmHg in 80 percent of subjects and 105 to 114 mmHg in 20 percent of subjects. Diastolic pressure was permitted to range to 130 mmHg. Placebo subjects were not withdrawn from the study unless their diastolic pressure reached 131 mmHg or above for three consecutive visits over a one-month period. Diastolic pressure averaged 10 mmHg lower in drug-treated subjects. The duration of follow-up averaged more than seven years. Despite entry diastolic pressure of 105 to 114 mmHg in 20 percent of subjects, despite permitting diastolic blood pressure levels to range as high as 130 mmHg, and despite diastolic pressure levels averaging 10 mmHg lower over a seven-year period, there was no significant difference in complication rate.

The Medical Research Council (MRC) Study of Mild to Moderate Hypertension[4] was large (17,354 subjects), placebo controlled but single-blind, and designed for five years of follow-up. Subjects had entry diastolic blood pressures of 90 to 109 mmHg, up to 9 mmHg above the range being considered in this paper (90 to 100 mmHg). There were four treatment groups: bendrofluazide or placebo, and propranolol or placebo. Drug treatment reduced stroke rate significantly but made no difference for the overall rate of coronary events or mortality from all causes. The difference in stroke rate was such that treatment of 850 patients for one year prevented one stroke.

Interesting differences were noted between the effects of the thiazide diuretic and propranolol and between smokers and nonsmokers. The stroke rate was reduced more by the thiazide diuretic than by propranolol and was reduced by propranolol only in nonsmokers. The rate of all cardiovascular events was not reduced by the thiazide diuretic but was reduced by propranolol in nonsmokers but not in smokers.

Withdrawals for the following reasons were increased significantly with drug treatment (P < .001) in men or women or both: impaired glucose tolerance, gout, impotence, Raynaud's phenomenon, dyspnea, or lethargy.[5] As a result of the study the National Health Service concluded that patients with blood pressure in the 90- to 109-mmHg diastolic range should not be routinely given drug therapy.

The Australian Therapeutic Trial in Mild Hypertension[6] was placebo controlled but single-blind. Subjects had diastolic blood pressure readings that averaged 95 to 109 mmHg during two screening visits. The duration of follow-up was planned for five years. The report concludes that drug treatment resulted in a significant reduction in mortality from cardiovascular disease and fewer cerebrovascular events. There was little overall difference in ischemic heart disease events. There were fewer deaths from ischemic heart disease in the drug-treated group, but the results were just short of significance. Again, the entry diastolic blood pressure levels were 95 to 109 mmHg vs 90 to 100 mmHg in the question under discussion. It should be noted that a member of the management committee of the Australian study[7] stated that the differences in nonfatal myocardial infarctions and total ischemic heart disease events in the drug-treated vs placebo group were neither clinically nor statistically significant.

The Hypertension Detection and Follow-up Program (HDFP)[8] compared a program of intensive care (stepped-care) with routine care of hypertension. Stepped-care subjects were followed in clinics with large, well-trained staffs. They received psychological and social support not ordinarily available: telephoned reminders of upcoming clinic visits, transportation to clinic, babysitters if necessary, excuses from work to ensure no loss of income, free care and medications, and availability of a physician at any time to answer questions. HDFP did not compare drug with placebo results. It reported a significant decrease in overall mortality and in deaths from myocardial infarction and stroke in stratum 1 (entry diastolic blood pressure 90 to 104 mmHg) but not in stratum 2 (entry diastolic blood pressure 105 to 114 mmHg) or stratum 3 (entry diastolic blood pressure 115 mmHg or above). There is no way to identify with certainty the cause of the improved outcomes in stratum 1: they cannot be attributed to drug therapy, as significant numbers of both stepped-care and routine care subjects received drug therapy; they do not seem likely to be due to the slightly lower treatment diastolic blood pressures in stepped-care vs routine care (stepped-care was from 5.4 to 4.3 mmHg lower than routine care), since such differences were much greater in the VA study (18.6 mmHg) and the Public Health Service study (10 mmHg), and these studies showed no significant difference in outcomes. It is possible that the differences in outcome are related to differences in psychological and social support. This hypothesis cannot be proven, but such findings are compatible with reports on the influence of psychosocial factors on the incidence of angina or the prevention of cardiac deaths in patients who have recovered from myocardial infarction.

The European Working Party Study of High Blood Pressure in the Elderly[9] (aged over 60 years) was multicentered and multinational. Unfortunately dropouts and subjects lost to follow-up totaled 78 percent and 74 percent in the placebo and active drug groups, respectively. Its findings are of questionable significance.

In summary, significant benefit has not been demonstrated for drug treatment of hypertension with diastolic blood pressure of 90 to 100 mmHg.

ADVERSE EFFECTS OF DRUG TREATMENT

Hypertension with diastolic blood pressure of 90 to 100 mmHg is usually asymptomatic. Drug therapy often converts asymptomatic patients into symptomatic patients. The frequency of withdrawals seen in the MRC study[5] illustrates this point. Many thiazide-treated male subjects in that study withdrew because of sexual dysfunction, which may have been due in part to hypokalemia. The European Working Party Study of Hypertension in the Elderly[10] found significant increases in fasting blood glucose and in blood glucose one hour following ingestion of 50 g of glucose and an increased blood uric acid level in thiazide-treated subjects. In other studies both thiazides and β-blockers have caused unfavorable changes in blood lipids levels.[11,12]

β-Blocker-treated patients often complain of sleep disturbances, including bad dreams and apparitions, fatigue, decreased tolerance for exercise, gastrointestinal distress including flatulence to the extent that it may be embarrassing, and cold hands and feet often resembling Raynaud's syndrome. The quality of life of drug-treated hypertensive patients may be impaired even though these patients may not complain. An interesting study related to this point was reported by Jachuck et al.[13] They asked physicians, patients, and spouses or other close observers regarding changes in the quality of life after drug therapy was established. Physicians reported that in 100 percent of patients it was improved. Patients' reports noted improvement in approximately 50 percent. Relatives reported that the quality of life was worse in 98 percent.

Does Drug Treatment Increase the Hazard of Developing Manifestations of Coronary Heart Disease?

Several studies are pertinent. The Multiple Risk Factor Intervention Trial[14] reported a higher death rate from

coronary heart disease in some special intervention subjects than in routine care subjects. Patients receiving special intervention had better educational programs to help motivate and instruct, more intensive drug treatment of hypertension, and relatively lower blood pressure goals. It was found that the death rate from coronary heart disease was 65 percent higher in special intervention subjects who had abnormal findings on electrocardiogram on entry but 24 percent lower in those with normal entry electrocardiogram findings. It has been suggested that the subjects with abnormal electrocardiogram findings might be more vulnerable because of hypokalemia. The report, however, also notes that the death rate from coronary heart disease was 45 percent higher in special intervention subjects with an entry diastolic blood pressure of 90 to 94 mmHg when compared with routine care subjects, while it was 30 percent lower in special intervention subjects than in routine care subjects with an entry diastolic blood pressure of 100 mmHg or higher. It is possible that the lower treatment pressure responses sought and attained for special intervention subjects contributed to the increased death rate from coronary heart disease.

Other evidence suggesting that lower diastolic blood pressure under drug therapy may increase the risk of coronary heart disease complications has been reported by Cruickshank et al.[15] In patients with ischemic heart disease treated for hypertension with the β-blocker atenolol, mortality from myocardial infarction followed a J-shaped curve. It was lowest at a diastolic blood pressure of 85 to 90 mmHg and increased both below and above that average. Samuelsson et al,[16] in a 12-year study of hypertensive men, found that cardiovascular morbidity was lowest at a diastolic blood pressure of 86 to 89 mmHg, and increased when diastolic blood pressure fell below 86 mmHg.

These studies suggest that a treatment diastolic blood pressure of 85 mmHg or lower may increase the risk of coronary heart disease. Patients with the lowest level of hypertension (a diastolic blood pressure of 90 to 100 mmHg) are the most likely to have blood pressure reduced to this level under treatment.

EFFICACY OF NONPHARMACOLOGIC TREATMENT

Nonpharmacologic methods of treatment are available that help patients to feel and function better, improve important clinical measures, and reduce risk factors of coronary heart disease.

Before discussing active treatment measures, it is important to point out that many patients with a diastolic blood pressure in the range of 90 to 100 mmHg become normotensive (below 90 mmHg) without treatment. Sixty-six percent of placebo-treated subjects with a diastolic blood pressure of 95 to 99 mmHg on entry to the Australian study[17] had an average diastolic blood pressure over three years of the study of 94 mmHg or lower. This lowering occurred without a program of weight reduction or dietary salt restriction. One could expect better results in subjects with a diastolic blood pressure of 90 to 94 mmHg.

Weight Loss

Reduction of body weight is a powerful tool to reduce blood pressure. Stamler et al[18] followed men with mild hypertension for five years. Average weight loss was 12 lb (5.4 kg). Blood pressure readings were reduced by 10/13 mmHg at the end of the study. MacMahon et al[19] compared an average weight reduction of 16.3 lb (7.4 kg) with drug treatment using the cardioselective β-blocker metoprolol. Blood pressure reading reduction was 13/10 mmHg in the weight-control subjects and 7/3 mmHg in the metoprolol-treated subjects. Weight-reduction subjects showed a decrease in total cholesterol and in the ratio of total to high-density lipoprotein cholesterol. The metoprolol group showed a decrease in high-density lipoprotein cholesterol and an increase in the ratio of total to high-density lipoprotein cholesterol.

Dietary Salt Restriction

Dietary salt restriction was studied in hypertension by Hunt and Margie[20] in a five-year program. Eighty-five percent of subjects with entry and diastolic blood pressures of 90 to 104 mmHg who restricted salt so that they consistently excreted 75 mmol/d (75 mEq/24 h) or less of sodium became and remained normotensive (diastolic blood pressure less than 90 mmHg). The blood pressure reduction cannot be attributed solely to the sodium restriction, since the subjects lost an average of 14 lb (6.4 kg) during the study.

Exercise

Exercise may effect a small but significant reduction in blood pressure. More important, however, exercise often brings a sense of well-being and relaxation, and it helps to reduce and control body weight. Exercise should be prescribed for the individual with emphasis on safety, starting with a program that is well within the patient's entry capacity and increasing intensity and duration

BOOK REVIEWS

Office Spirometry: A Practical Guide to the Selection and Use of Spirometers. *Paul L. Enright, Robert E. Hyatt. Lea & Febiger, Philadelphia, 1987, 250 pp., $18.50 (paper).*

Virtually every primary care physician has some experience with spirometry. This book succeeds in meeting its goals of refamiliarizing practicing physicians with the principles of basic spirometry as well as with the use and selection of the type of equipment practical for the contemporary office setting.

The paperback manual reads with exceptional ease and rapidly boosts the clinician's skill in this area by the use of multiple cases and their accompanying spirograms. Additional strengths include the text's specific organization into critical review components: indications for spirometry, interpretation of results (extensive example cases), consumers' guide to the purchase of equipment (prices, illustrations, anecdotal pros and cons about each of almost two dozen units), and a detailed section on pertinent calculation skills.

This selection is clearly not intended for the medical student in early training, as basic pulmonary physiology is not presented in great depth. Rather, the office practitioner who intends to manage pulmonary disease screening and reactive airways disease and to assess other pulmonary processes will without doubt find this an effective instrument toward establishing these services on a routine basis.

James J. Bergman, MD
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The Neurologic Examination in Primary Care. *Matthew Menken. Department of Neurology, University of Medicine and Dentistry of New Jersey, New Brunswick, New Jersey, 1986, 52 pp., (paper) price not available.*

This book is for the medical student who wants to understand what the experienced physician understands, and for the experienced physician to refresh his memory. It summarizes the author's views about a shortened (15-minute) neurologic examination: ". . . Many patients encountered in ambulatory care settings do not require a detailed examination, but rather a screening examination to determine whether any disease of the nervous system is likely to be present, and whether a more detailed evaluation would subsequently be appropriate." The idea is appealing, and the book should be of interest to primary care physicians; however, other books are available that would probably address the needs of the student and primary care physician in a more satisfactory fashion.

The book is not useful as a reference text, and is specifically not intended to provide complete coverage of neurologic examination technique. It is short, pamphlet like, has relatively little writing on each page, and has excellent graphics. There are self-assessment questions sprinkled throughout the book that help engage the reader. It is clearly written, and is easy to read.

The book is organized along the lines of the physical examination, beginning with pertinent information about the vital signs and proceeding to the reflexes and sensory examination. Useful tips are given regarding the significance of such aspects of the examination as the various types of nystagmus, the neurovascular examination, and the assessment of intellect and behavior.

Charles F. Margolis, MD
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Obstetrical Decision Making (2nd Edition). *Emanuel A. Friedman, David B. Acker, Benjamin P. Sachs (eds). B. C. Decker, Philadelphia, 1987, 320 pp., $38.*

The purpose of this useful book is to provide "clear, unambiguous clinical instruction and guidance about how to approach diagnostic and therapeutic problems." In its second edition, this book has been expanded and updated considerably. The format consists of a comprehensive series of decision trees for obstetric problems, each occupying one page. On the facing page of each tree is a concise text amplifying critical decision points and cross-referencing other topics. In addition, helpful diagrams and charts are provided throughout, as well as an up-to-date (1986) brief bibliography on each problem.

This book was left in a precepting room for two weeks to solicit comments. It was used by an obstetrician, family physician faculty, community preceptors, and residents. An impressive consensus was made about its usefulness and accessibility for rapidly providing critical information and an approach to practical problems. Thus it would be useful in similar settings, such as a busy office or in the obstetrics service. As an aid to stimulating organized thought about obstetric problems, it would also be of some benefit to medical students.

There are, however, some caveats: In presenting unambiguous decision trees, the authors rarely acknowledge the limited scientific basis for the choices made or the possibility of alternative strategies. Perhaps because of the origin of the book, the choices are more often interventionist than expectant. Providing more references, particularly of reviews, and annotating the trees to indicate the quality of scientific evidence would help address these problems. Although psychosocial aspects of obstetric care are addressed, these decision trees are less successful than those with a technical focus. Because of these limitations, I would recommend having access to at least one other obstetric reference source.

Peter Franks, MD
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complete blood count and Monostat (or Epstein-Barr virus titers), and acute and convalescent antistreptolysin O titers.

The following questions need to be answered:

1. What is the medical incidence of positive results in the healthy subjects vs the incidence in the ill subjects?

2. Does a positive result in one test influence the chance of another test being positive?

3. Is there a certain number of β-hemolytic colonies on a throat culture that can be used to separate colonization in healthy subjects from true positives in symptomatic subjects?

4. What is the rate of streptococcal colonization in those individuals with positive viral cultures?

5. How do the tests compare with the severity or type of clinical findings?

Note that this does not address the question of whether missing a single case of streptococcal pharyngitis is more dangerous than treating a case of nonstreptococcal pharyngitis.

Until such a comprehensive study of sore throat proves me wrong, I will continue to believe that an organism that produces an antibody response from its host is probably pathogenic, but an organism that grows on a given culture plate is not necessarily so.

Stephen Busek, MD
Columbus, Ohio

The preceding letter was referred to Adrienne Wright, who responds as follows:

We appreciate Dr. Bushek's interest in our study, and we agree with his recommendation that a comprehensive study of the full etiologic range of the common sore throat and the methods of testing for accurate diagnosis and treatment would be useful.

Our concern with the Culturette Brand 10-Minute Group A Strep ID kit was not based solely on its inability to identify as positive two out of four plates with fewer than ten colonies of β-hemolytic streptococci, but more important, it was also on the test's inability to classify as positive 13 of the

20 plates read as positive with greater than ten colonies. This finding suggests that a negative ten-minute test would need to be confirmed by a standard throat culture.

Because 87 percent of all of the tests in our study had negative results, nearly all patients seen would require a confirmatory throat culture. This reduces the advantage of the rapid streptococcus test in terms of efficiency and cost effectiveness. Numerous studies have reported a sensitivity range of 62 to 95 percent. Several of these studies suggest the need for confirmatory throat cultures on negative rapid streptococcus test results.

The significance of throat cultures with fewer than ten colonies of group A β-hemolytic streptococcus per plate is controversial. Some authors suggest that these patients are not truly infected but are carriers of streptococci.[1] Others suggest that the differentiation of carriers from patients with streptococcal infections cannot be based on the degree of positivity of the agar plate alone.[2]

Several studies found that the sensitivity of the Culturette Brand test increased with an increased degree of positivity of the corresponding culture plate. Gerber et al found that there was "little correlation between the degree of positivity of the throat culture and changes in streptococcal antibody titers or between the sensitivity of the Culturette Brand test and changes in streptococcal antibody titers."[3] Their findings support the concept that the diagnosis of streptococcus infection cannot be made on the basis of the degree of positivity of the culture plate alone. Further, their findings suggest that "almost half of patients with false-negative antigen detection test results for GABHS may have true streptococcal infections and were not merely strep carriers."[3]

Throat cultures have been the accepted method for accurate diagnosis of group A β-hemolytic streptococcus for three decades. Simultaneously, the incidence of rheumatic fever has declined considerably.[4] Perhaps medicine's methods of performing throat cultures and treating pharyngitis could, in part, be responsible.

In our study, final verification of throat culture results was done by St. Francis Hospital and Medical Center laboratory if the culture result was positive and the agglutination test if the result was negative. The data for comparing results with the severity or type of clinical findings have not been analyzed at this time.

Our study was conducted in a blinded fashion; therefore, it seems unlikely that a positive result in one test influenced the chance of another test being positive.

Our methods were rigorous, and we believe the results are valid. We conclude that because of the suboptimal sensitivity of the Culturette Brand 10-Minute Group A Strep ID kit in our hands, we do not wish to offer it as an alternative to the standard throat culture in our inner-city office practice.

Dr. Bushek, poses some provocative questions; his suggestions for evaluating the etiology of pharyngitis and the value of testing in determining treatment would make an interesting study. One objective of our study was to encourage primary care practitioners to do systematic assessments of office-based laboratory procedures by using simple methods that are cost effective, time efficient, acceptable to patients, and yield accurate results.

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