Therapeutic Alternatives in Hypertension*

Albert N. Brest, M.D., F.C.C.P., and Nicholas Ruggiero, M.D.

The traditional therapeutic approach to essential diastolic hypertension consists of adjunctive measures (ie, dietary salt restriction, weight reduction, elimination of smoking and anxiety factors) plus antihypertensive drug regimens. Contrariwise, the management of secondary hypertension customarily centers on the direct approach to the underlying disorder, whenever possible (eg, renal revascularization or surgical excision of pheochromocytoma). During the past decade, however, it has become increasingly apparent that alternative therapies are sometimes feasible, occasionally with dramatic beneficial results.

Renal Arterial Hypertension

Renal arterial hypertension emerged during the late 1950s as an important cause of secondary diastolic hypertension. The recognition that renal artery stenosis could generate hypertension, via the renin-angiotensin-aldosterone system, seemed to invoke surgical revascularization (or, less preferably, nephrectomy) as the logical therapeutic approach. During the ensuing years, however, it has become apparent that renal revascularization is not inevitably successful, ie, does not always reduce the blood pressure to normotensive levels, nor indeed is it technically possible to revascularize in every instance. Furthermore, the attendant surgical morbidity and mortality as well as the long-term prognosis are adversely affected by coexistent cardiovascular disease or other infirmities.

From the technical standpoint, it may not be possible to repair or bypass the stenotic renal arterial segment if the arterial lesion is located distally at the bifurcation of the main renal artery or if the primary branches are involved or both. Regarding age, it is generally agreed that young patients warrant special consideration for surgery because they have the potential for long-term benefit from surgery, without the specter of prolonged drug therapy. In contrast, older patients (whose renal arterial stenotic lesion is usually atherosclerotic in type) frequently have coexistent atherosclerotic lesions in the coronary and cerebral vessels, and these lesions greatly enhance the risk of a surgical procedure. Mild to moderate renal functional impairment may sometimes be improved by renal revascularization, whereas advanced renal impairment is unlikely to remit. Thus, technical considerations related to the underlying pathology, the age of the patient, the coexistence of vascular disease in other arteries, and the degree of renal impairment play important roles in deciding whether to treat surgically.

However, another important consideration in the decision to treat renal arterial hypertension surgically is the response per se to antihypertensive drug therapy. That is, if the hypertension responds favorably to drug therapy, the need for surgical treatment is less compelling.

Sheps and co-workers1 undertook medical treatment of hypertension in 54 selected patients with arteriographically proved stenosis of the renal artery (32 with atheromatous and 22 with fibromuscular lesions). At follow-up study (average, 20.3 months), 65 percent of 49 surviving patients were normotensive on a regimen of common antihypertensive drugs in usual doses. There also was improvement in the optic fundus. It is noteworthy, however, that renal function deteriorated in three instances in spite of effective control of the blood pressure. Accordingly, the authors emphasized the need for close observation for progression in severity of the stenosis or deterioration of renal function among patients treated medically, even though the blood pressure may be controlled satisfactorily.

*From the Division of Cardiology, Jefferson Medical College and Hospital, Philadelphia.
Reprint requests: Dr. Brest, Jefferson Medical College, 1025 Walnut Street, Philadelphia 19107
Dustan and co-workers\(^5\) also stressed the excellent control of blood pressure that can be achieved with the usual antihypertensive drugs. Of ten patients who were followed closely and who took blood pressure measurements at home, only one had continued hypertension. Follow-up in this group ranged from six months to 2\(\frac{1}{2}\) years. In none of these patients was there major loss of renal excretory function.

Similar favorable experiences have now been reported from many other centers. Accordingly, medical management of renal arterial hypertension is a valid therapeutic alternative.

Medical (drug) therapy should be considered especially when the situation technically demands nephrectomy (ie, renal revascularization is not feasible) or when there is associated severe symptomatic cardiovascular disease, old age, or other important infirmities.

**RENAL PARENCHYMAL HYPERTENSION**

The traditional management of hypertension related to bilateral renal parenchymal disease includes careful attention to fluid and electrolyte balance as well as prudently selected antihypertensive drug therapy. When marked deterioration of renal function supervenes, maintenance dialysis is often needed to ensure reasonable blood pressure control (and, of course, to control uremia also). In some patients with renal failure, however, hypertension is resistant to the restoration of normal water and sodium balance as well as to the addition of antihypertensive drugs. Several authors have found that control of blood pressure in these cases may be obtained by bilateral nephrectomy.\(^3\)\(^4\)

Inherent in the importance of blood pressure reduction in such patients is the clinical recognition that prognosis is related not only to the reversal of uremia but also to the concomitant control of hypertension.

Donohue and co-workers\(^5\) described 18 patients with hypertension and coexistent end-stage renal failure. Twelve appeared to have salt-and-water dependent type hypertension which persisted despite chronic dialysis and careful salt, water, and medical management. All 12 patients had a sustained reduction in blood pressure following bilateral nephrectomy. Six others had malignant hypertension with rapid progression despite all medical measures. These six patients had renin-dependent type hypertension, and all six had a dramatic reduction in their severe hypertension in the immediate postnephrectomy period and subsequently.

Weidmann and associates\(^5\) opined that moderately to markedly increased plasma renin activity clearly distinguishes those patients whose hypertension will likely remit with bilateral nephrectomy, in contrast with those individuals whose hypertension is treatable by dietary restrictions and hemodialysis. Seventeen of their 18 renal failure patients with uncontrollable hypertension had high plasma renin activity, and in each of the 17, bilateral nephrectomy was followed by a prompt and significant blood pressure reduction. The other patient with uncontrollable hypertension had normal plasma renin activity and did not benefit from nephrectomy.

Additional information is needed regarding the genesis of hypertension in end-stage renal failure. Nonetheless, it is abundantly clear that bilateral nephrectomy is a valid therapeutic alternative in carefully selected patients with terminal renal failure whose hypertension is resistant to conventional measures.

**PHEOCHROMOCYTOMA**

Surgical excision of the tumor has been the treatment of choice for pheochromocytoma, ever since the first successful operation in 1927. Nonetheless, there are patients with pheochromocytoma who refuse surgery or have medical contraindications to surgery. There are others in whom the tumor cannot be located, and those with metastatic pheochromocytoma which is not resectable. Such patients require alternative medical therapy.

Engelman and Sjoerdsma\(^6\) described four patients with pheochromocytoma who were successfully treated on a chronic basis with oral phenoxybenzamine (Dibenzyline), a long-acting alpha-adrenergic blocking drug. One patient was treated for longer than six months in preparation for subsequent curative surgery, while the other three cases—of which two were malignant—were treated for longer than one year. The effects of therapy included control of both the physiologic and the metabolic alterations caused by the increased catecholamine production in these patients.

Other reports indicate similar beneficial effects of drug therapy in cases of nonsurgical or unresectable pheochromocytoma. Bellas\(^7\) described the medical management of a case diagnosed eight years earlier, in which the patient had refused operation. He found that the regular administration of phenolamine (Regitine) controlled most of the disturbing symptoms over a period of eight years. Similarly, Simanis and co-workers\(^8\) reported a pregnant patient at 24 weeks gestation who was found to have an unresectable pheochromocytoma. The administration of alpha (phenoxybenzamine) and beta (propranolol) adrenergic blocking agents was started at that time and continued through a successful delivery by cesarean section at 32 weeks.
Subsequently the patient was maintained on phenox-
ybenzamine and propranolol for more than three
years, and she remained both normotensive and
asymptomatic.

Medical (drug) management is an acceptable
therapeutic alternative in patients with proved
metastatic pheochromocytoma and those with be-
ign tumors who cannot tolerate the surgical pro-
cedure. Alpha-adrenergic blocking drugs, eg, phe-
noxybenzamine or phenolamine, may be used to
reduce blood pressure, ameliorate sweating, and
prevent hypertensive episodes. The beta-adrenergic
agent, propranolol, is particularly valuable in the
control of catecholamine-induced arrhythmias.

PRIMARY ALDOSTERONISM

There are two basic forms of primary aldoster-
nism. One is caused by functional adenoma within
one or both adrenal glands; the other is due to
bilateral micronodular adrenal hyperplasia. Both
types qualify as varieties of primary aldosteronism
because the syndrome they produce is related to ex-
cessive aldosterone production in the absence of
known stimuli. The adenomatous type is usually
handled surgically, whereas the hyperplastic type
responds poorly to surgery and is better managed
medically. Nonetheless, the hypertension associated
with adenomatous as well as hyperplastic primary
aldosteronism may at times be successfully con-
trolled with large doses of spironolactone.

Short-term responses to spironolactone have been
reported by several authors. Gwynup and Steinberg6
have described the beneficial effects of 200 mg of
spironolactone daily for ten weeks or more on the
blood pressure of four patients with primary aldo-
steronism and have contrasted that with the pa-
tient's poor response to thiazides. Similarly, Crane
and Harris16 reported that 400 mg of spironolactone
daily resulted in normotension within three weeks in
seven of ten patients with primary aldosteronism.

Brown and co-workers11 described a case of
adenomatous primary aldosteronism in which ad-
ministration of spironolactone for a period of 10%
months corrected the electrolyte abnormalities, in-
creased the plasma renin concentration to normal,
and lowered the blood pressure, although the raised
aldosterone secretion was unchanged. Subsequently,
Brown and associates12 reported their findings in 45
patients with primary aldosteronism treated with
oral spironolactone in doses ranging from 150 to 400
mg per day for periods ranging from one month to
6% years. Spironolactone corrected the electrolyte
abnormalities in every patient, and produced a
marked fall in blood pressure in most (to 150/90
mm Hg or less in 24 cases). In most instances the
hypotensive effect of spironolactone was similar to
that obtained by subsequent adrenal surgery; in
eight cases spironolactone did not cause satisfac-
tory lowering of blood pressure, and five of these were
subsequently submitted to adrenal surgery without
any effect on blood pressure.

Spironolactone therapy may provide efficient al-
ternative therapy in patients with adenomatous pri-
mary aldosteronism. Furthermore, drug treatment is
preferred in the hyperplastic form of this disorder.

ESSENTIAL HYPERTENSION

Control of blood pressure elevation can be
achieved with available antihypertensive drugs in
most instances of essential hypertension. Nonethe-
less, there are occasional patients with drug-resistant
hypertension, and many others who will not adhere
to complicated and expensive multiple-drug regi-
mens for prolonged intervals. Accordingly, there is a
recognized need for alternative approaches in the
management of essential hypertension.

The surgical treatment of hypertension was ini-
tiated in this country in 1925 when Rowntree and
Adson13 reported a hypertensive patient for whom
bilateral lumbar sympathectomy was done. During
succeeding years, a host of other inventive but in-
creasingly radical surgical approaches were intro-
duced. Included were subdiaphragmatic splanchni-
cectomy, supradiaphragmatic splanchnecetomy,
thoracolumbar splanchnecetomy, "total sympathe-
tomy," denervation of the adrenal glands, partial
adrenalectomy, and finally total adrenalectomy
alone or in combination with sympathectomy. De-
spite occasional beneficial results, the overall re-
sponse to these various surgical maneuvers has been
broadly disappointing and they have been virtually
abandoned.

More recently, bilateral carotid sinus nerve stimu-
lation (BCSNS) has been introduced as a thera-
peutic alternative for hypertensive patients who are
poorly responsive to combination antihypertensive
drug therapy or others in whom blood pressure
reduction is achieved with drug treatment but at the
expense of serious untoward effects.

Schwartz14 reported long-term results (20 months
to 4% years) in eight hypertensive patients who
were either not responsive to medication or could
not tolerate the side-effects of drugs. Six of the eight
achieved significant blood pressure reduction with
BCSNS alone. The two remaining patients, who had
previously been refractory to all medication, had
minimal response to carotid sinus nerve stimulation
alone but reinstitution of medication resulted in a
marked reduction in blood pressure.

Brest and co-workers15 studied the clinical effec-
tiveness of BCSNS in eight patients with drug-resistant essential hypertension. Significant blood pressure reduction was achieved in each of the eight. Normotension was obtained in five of the six patients with nonmalignant hypertension while the sixth patient in this category had significant blood pressure reduction, albeit without achievement of normotension. The two patients with malignant hypertension also obtained a significant antihypertensive response; however, despite the blood pressure reduction, both experienced a rapidly deteriorating clinical course and ultimately succumbed to renal failure. It is noteworthy that each of the five patients who achieved normotension, continued to sustain this effect for periods ranging from 18 to 24 months and thus denied the theoretical consideration that chronic carotid sinus nerve stimulation might lose its effectiveness.

The ultimate therapeutic role of BCSNS in essential hypertension must await additional investigations. Nonetheless, the procedure exemplifies the continuing search for alternatives in the management of the various (primary and secondary) hypertensive disorders.

REFERENCES