Editorial

Hypertension and Unilateral Renal Disease. The Usefulness of Modified Intravenous Urography

THERE IS little doubt of existence of the clinical counterpart of Goldblatt hypertension. But, there is great uncertainty about its incidence. When Smith reviewed the situation in 1956, he decided that curable hypertension due to unilateral renal disease was extremely rare. It was most often a result of unilateral pyelonephritis. Subsequently, the application of differential renal function tests, such as that first described by Howard and co-workers, has made it possible to identify a physiologic defect closely associated with occlusive renal arterial disease. Demonstration of such disease also has been facilitated by improved technics of renal angiography.

As a consequence of these two developments, a host of enthusiastic reports has appeared that claim correction of hypertensive disease by vascular repair or nephrectomy. In view of the natural history of hypertensive disease, these reports might be premature. On the strength of such reports, numbering only a few hundred "cures," it has been claimed that from 5 to 15 per cent of the hypertensive population (two to six million people in the United States) have renal artery stenosis as the cause of their hypertension. Time will tell whether there is truth in this apparently extravagant estimation. Follow-ups are short, and it is especially difficult to evaluate the so-called improved categories. Validation or refutation of this claim places a new and important responsibility on all physicians involved in the study of hypertensive disease.

Before considering the application of screening procedures and of more complex diagnostic technics to this large patient population, it must be emphasized that the mechanisms involved in hypertension of renal origin are still incompletely understood. The following considerations may caution the reader to recommend surgery only after a measure of circumspection: (1) Though there is much evidence for the possible importance of renin and angiotensin in renal hypertension, in the chronic stage of experimental Goldblatt hypertension it has not been possible to demonstrate consistently increased blood levels of these substances. Furthermore, in some species, after a time, removal of the original ischemic kidney does not correct the hypertension. (2) Renal artery stenosis seen on arteriography or at postmortem examination may be incidental. Similar lesions are often seen in normotensive individuals. (3) Renal functional involvement in essential hypertension may be unequal, a phenomenon that might occasionally give rise to false "positive" results on differential renal function tests. (4) The correlative studies of Vertes, Grauel, and Goldblatt, utilizing bilateral renal biopsies, indicate that failure of corrective surgery may often be due to inability to recognize, either by clearances or angiography, occult bilateral intrarenal disease, especially arteriolar nephrosclerosis. These workers believe that nephrectomy may be quite deleterious in patients with bilateral renal disease in which functional inequality, perhaps compounded by a main renal artery obstruction, mimics the syndrome of pure unilateral renal disease. In a number of patients, they have found that surgical correction of unilateral main renal artery obstruction did not improve ipsilateral renal functional capacity. (5) The natural history of untreated renovascular hypertension and the usefulness of purely medical therapy have not been fully evaluated. The latter approach may be indicated in the elderly and particularly in those with known coronary or cerebral vascular insufficiency. (6)
Finally, surgical cure rates in many large series are no higher than 50 per cent, and the average mortality is in the range of 8 per cent. Furthermore, the relapse rate in the initially successful surgically treated cases is something of an unknown quantity.

Meanwhile, how does the practicing physician identify and manage the possibly large numbers of patients who might have surgically correctable renal disease as the basis for their hypertension? Unilateral renal disease can be more strongly suspected on clinical grounds when the hypertension is of recent onset, is more severe, and develops at an age when essential hypertension is unlikely or when an abdominal bruit is detected. These signs, however, are not always present. Two screening tests, the radioisotope renogram and the modified intravenous urogram, are available to aid in dealing with the problem.

The radioisotope renogram is a simple and innocuous test. With $^{131}$I-labeled hippurate, the renogram affords a sensitive means for detecting certain differences between the two kidneys. Unfortunately, these differences are difficult to quantitate, and the interpretation is quite subjective, despite much effort devoted to correlating the parameters of the renogram with conventional renal function tests. Though probably few cases of unilateral renal ischemia are missed, up to 25 per cent of patients examined will have a false-positive test. The cost or unavailability of the special equipment and personnel required to perform the examination and the lack of demonstration of renal morphology are other disadvantages. Recently, radioactive mercury-203 or 197-labeled neohydrin has been used in conjunction with renogram and renal scanning technics in order to provide additional information. These isotope methods are in a state of incomplete development. It is hoped that they will prove valuable in the future.

In recent years, the intravenous urogram has become increasingly important in the detection of patients with potentially curable renovascular hypertension. This is because of the radiologist's better understanding of the urographic changes associated with significant renal artery obstruction. Renal ischemia has both morphologic consequences, mainly renal atrophy, and functional consequences, increased reabsorption of urinary sodium and water by the renal tubules resulting in a reduced output of more concentrated urine by the ischemic kidney. To better identify these changes, the intravenous urogram as applied to hypertensive patients has been modified by the use of rapid-injection technic, the elimination of abdominal compression, and the addition of minute sequence films. Observed differences in the appearance time of the radiopaque contrast material in the renal pelves and differences in its density reflect inequalities in urine output and concentration by the two kidneys. Significant unilateral obstructions of the main renal artery are seldom exactly symmetrical, and so these, too, usually produce an abnormal urogram. Segmental renal artery occlusions, which have not produced gross morphologic changes, may not be detected except by aortography. Nevertheless, utilizing this rapid-sequence type of intravenous urography, in a recent series of 200 hypertensive patients we have been able to suspect renal ischemia with greater than 90 per cent accuracy in patients with significant major renal artery obstruction as shown by subsequent aortography and other function tests in the same group of cases. Similar experiences have been reported by other clinics.

This modification of the urogram is safe. It requires the same time as an ordinary intravenous urogram. It can be performed in any radiology department without special equipment. With experienced interpretation it yields relatively few false-positive results, and it will often demonstrate the reason for a false-positive renogram. We consider the modified intravenous urogram our most important screening test for unilateral renal ischemia. The radioisotope renogram is regarded as nonessential and a less useful test. When the modified intravenous urogram is positive, when the renogram is positive in a
manner not explained by the urogram, or when both tests are positive, further more elaborate study of the patient in the hospital is usually worth while.

Divided or split renal function tests, requiring bilateral ureteral catheterization, though cumbersome, costly, and not without morbidity and mortality, provide the only available quantitative measure of renal dysfunction and of the functional adequacy of the opposite kidney. However, the findings on the modified intravenous urogram may be so impressive, when taken in conjunction with the clinical considerations and the renal arteriographic studies, that divided renal function tests are often not necessary prior to corrective renovascular surgery. In certain instances, further elaboration of the modified intravenous urogram by repeat examination of the patient under conditions of oral water hydration or urea-saline diuresis, as advocated by Amplatz and associates, may so exaggerate differences in renal function as to supplant the necessity for separate ureteral catheterization studies. These tests are promising and warrant continued study. Aortography is helpful in equivocal cases, and, of course, it is essential in virtually all patients who are ultimately regarded as candidates for surgical treatment.

Because mechanisms remain in doubt, we cannot be sure of the true specificity of any diagnostic test. The characteristic abnormality of reduced sodium and water excretion as demonstrable on differential clearances often can suggest the presence of a pressor kidney. But, neither this procedure nor angiography are applicable to widescale screening of the hypertensive population. Renal biopsy, to be meaningful, should probably be done bilaterally. Even then, sampling may be inadequate. More important, none of these procedures are without risk. Bilateral renal vein catheterization, recently reported by a number of groups, has revealed a most striking correlation between an elevated renal venous renin or angiotensin content and the subsequent success of surgery. This procedure seems simple and safe, and may prove more meaningful than either clearances or angiography. Theoretically too, it puts the long suspected renal humoral mechanism for hypertension on firmer ground. However, only a few laboratories can now perform these bioassays.

As long as the true nature of renal hypertension remains obscure, the specificity of all diagnostic procedures will remain uncertain. In the meantime, the rapid-sequence intravenous urogram provides the physician with a valuable screening test for the presence of significant major renal artery occlusive disease. Our observations to date convince us that, given an unsuggestive clinical picture plus a negative rapid-sequence pyelogram, further testing for unilateral renal disease causing hypertension is not warranted.

The rare situation of bilateral vessel disease may escape detection. However, in our present state of knowledge we believe that this approach can identify nearly all of the probably few per cent or less of the hypertensive population who have correctable renal hypertension. It will spare the great majority unnecessary procedures.

Richard J. Fleming, M.D.
Kent Ellis, M.D.
Jay I. Meltzer, M.D.
John H. Laragh, M.D.

References
6. Taplin, G. V., Meredith, O. M., Jr., Kade, H., and Winter, C. C.: Radioisotope renogram. External test for individual kidney function

NEW MANUSCRIPTS

Authors are requested to send all new manuscripts for CIRCULATION to:

Howard B. Burchell, M.D.
CIRCULATION
Plummer Building
200 First Street SW
Rochester, Minnesota 55902

Please note that correspondence concerning manuscripts sent to CIRCULATION before July 1, 1965 should be addressed to Herrman L. Blumgart, M.D., 330 Brookline Avenue, Boston, Massachusetts 02215.